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THE PREPARATION AND PROPERTIES OF THE EIGHT DIASTEREOISOMERS OF 9,10,12,13-TETRAHYDROXYSTEARIC ACID

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The eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid were prepared from α-linoleic acid (cis-9-cis-12-octadecadienoic acid). A new method of preparation was developed which establishes the spacial relationships of the hydroxyl groups in each diastereoisomer.

Hazura (1) was the first to isolate a 9,10,12,13-tetrahydroxystearic acid (sativic acid) from the alkaline potassium permanganate oxidation of linoleic acid. Further study (2–6) of this oxidation reaction resulted in methods for improving the yield and it is now established that two diastereoisomers of the tetrahydroxystearic acid are formed in this reaction. The melting points of these acids are 173° (I) and 164° (II). The more soluble one has also been reported to melt at 157–159°, but according to Riemenschneider *et al.* (7) this is an eutectic mixture of the α- and β-sativic[1] acids melting at 173° and 164°. Nicolet and Cox (8) obtained two different diastereoisomers of 9,10,12,13-tetrahydroxystearic acid by treating linoleic acid with hypochlorous and hypobromous acids to form the dichloro- and dibromo-dihydroxystearic acids. Replacement of the halogen atoms by hydroxyl groups gave two tetrahydroxystearic acids melting at 145° and 135°. Later work suggests that these acids are the same as the two diastereoisomers obtained in the peracetic acid oxidation of linoleic acid (9), or the alkaline potassium permanganate oxidation of linolelaidic acid (10) which are now described as melting at 146° (III) and 126° or 122° (IV). Kass and Burr (10) prepared a third set of diastereoisomers of 9,10,12,13-tetrahydroxystearic acid by the alkaline potassium permanganate oxidation of the trans-cis or cis-trans geometric isomer of linoleic acid. The melting points of these acids are given as 156–158° (V) and 126° (VI). The melting point of the former has now been raised to 164°. A seventh diastereoisomer of tetrahydroxystearic acid was re-

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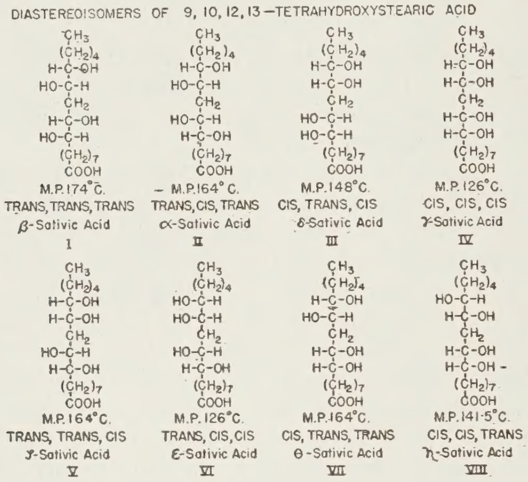
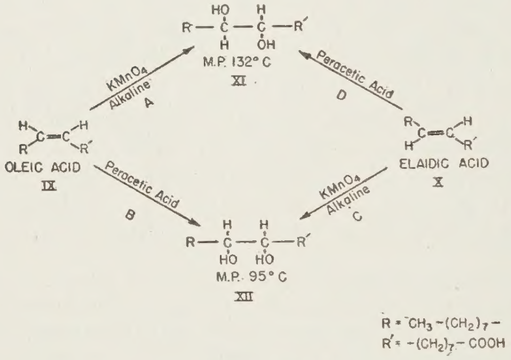
[1] The use of the name sativic acid for tetrahydroxystearic acid has led to a great deal of confusion in the study of the diastereoisomers of this acid. The main difficulty is that the terms α, β, γ etc., sativic acids give no indication of the structure of these compounds. Moreover the same Greek letters have been assigned to different diastereoisomers. Thus we propose that the system of nomenclature based on the use of the terms cis and trans be used to name these diastereoisomers. This system allows no misinterpretation of data and is more convenient for the correlation of experimental studies of these acids. In this method of naming the diastereoisomers of 9,10,12,13-tetrahydroxystearic acid three combinations of cis and trans are used *e.g.*, α-sativic acid becomes trans, cis, trans-9,10,12,13-tetrahydroxystearic acid. The first trans refers to the spacial relationship of the C_9 and C_{10} hydroxyl groups, the cis refers to the relative configuration of the C_{10} and C_{12} hydroxyl groups and the final trans to the spacial interrelationship of the C_{12} and C_{13} hydroxyl groups. The eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid are given in formulas I–VIII, with this proposed system of nomenclature together with the sativic acid system.

ported by McKay, Jones, and Sinclair (11), which also melts at 164° (VII). In this report the eighth diastereoisomer (m.p. 141.5°) (VIII) is described.

If one considers the simpler case of 9,10-dihydroxystearic acid, then only two diastereoisomers are theoretically possible. 9-Octadecenoic acid exists in two geometric isomers, the cis form commonly known as oleic acid (IX) and the trans form as elaidic acid (X). The two 9,10-dihydroxystearic acids melting at 132° (XI) and 95° (XII) are formed respectively by the alkaline potassium permanganate oxidation (A) and the peracetic acid oxidation (B) of oleic acid. In antithesis to this, the alkaline potassium permanganate (C) and peracetic acid (D) oxidations of elaidic acid (X) give the dihydroxystearic acids melting at 95° and 132° respectively. Infrared studies (12), and titration with lead tetraacetate (13) show the two hydroxyl groups in the higher-melting 9,10-dihydroxystearic



Scheme A



Scheme B

acid, to be trans to each other, and in the lower-melting diastereoisomer to be cis. Thus, alkaline potassium permanganate oxidation of a double bond supporting a cis configuration gives a trans α-glycol and vice versa. The opposite is true when peracetic acid is the oxidizing reagent. With these established facts in mind the eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid were prepared.

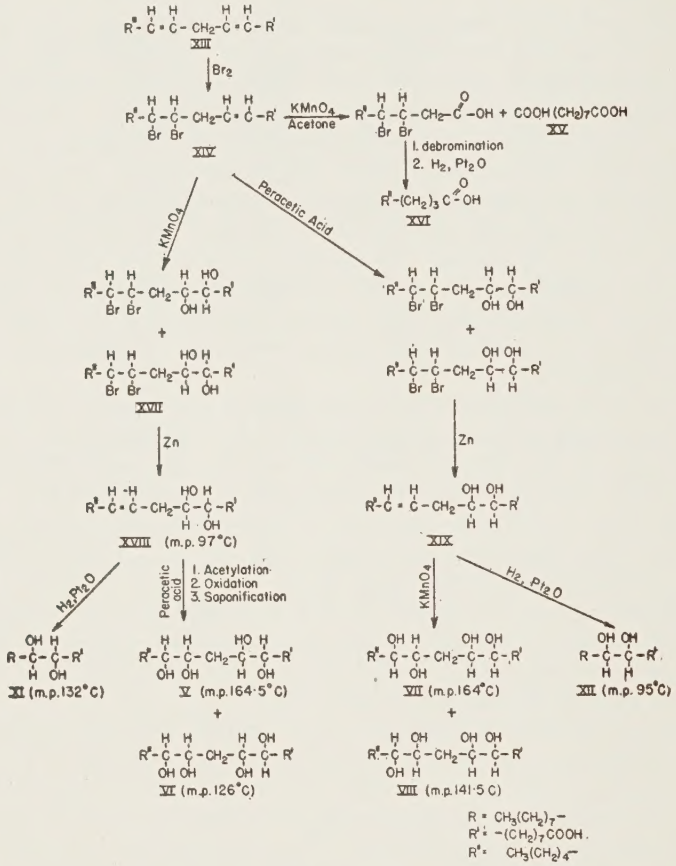
α-Linoleic acid (XIII) was brominated with slightly more than one molar equivalent of bromine at low temperatures (−15°). The desired dibromo derivative, 12,13-dibromo-9-octadecenoic acid (XIV) contained impurities of unchanged linoleic acid and 9,10,12,13-tetrabromostearic acid. The dibromination of linoleic acid and the oxidative degradation of the dibromo derivative have been reported by Toyama and Tutiya (14) without experimental details. In order to confirm the structure of 12,13-dibromo-9-octadecenoic acid, it was converted into its methyl ester (Iodine Value, 56.0), and then oxidized with potassium permanganate in acetone. The product, after debromination and hydrogenation gave azelaic acid (XV) in 78% yield and impure *n*-nonanoic acid (XVI) in 61% yield. These results prove that the double bond farther removed from the carboxyl group is preferentially brominated in the low temperature dibromination of α-linoleic acid.

Oxidation of 12,13-dibromo-9-octadecenoic acid with aqueous alkaline potassium permanganate solution gave a mixture of 9,10-dihydroxy-12,13-dibromostearic acids (XVII). Trans-9,10-dihydroxy-12-octadecenoic acid (m.p. 97°; I.V., 80.6) (XVIII) was obtained from this product on debromination. Another set of reactions, in which 12,13-dibromo-9-octadecenoic acid was oxidized with peracetic acid and the product debrominated, saponified, and then distilled, gave an oil identified as cis-9,10-dihydroxy-12-octadecenoic acid (I.V., 80.2) (XIX). The structures of both the trans and cis-9,10-dihydroxy-12-octadecenoic acids were substantiated by reduction of these compounds to the corresponding 9,10-dihydroxystearic acids melting at 132° (XI) and 95° (XII) respectively. Nearly theoretical yields were obtained in each case.

The trans-9,10-dihydroxy-12-octadecenoic acid (XVIII) was acetylated and then oxidized with peracetic acid solution. After saponification of the product and acidification of the resulting alkaline solution, the free acids were obtained. These acids, on partition by solvents, gave two racemates of 9,10,12,13-tetrahydroxystearic acid in which the C_9 and C_{10} hydroxyl groups were trans and the C_{12} and C_{13} hydroxyl groups were cis. These diastereoisomers melted at 164° (V) and 126° (VI). The isomer having the C_{10} and C_{12} hydroxyl groups cis to each other was assigned the lower melting point. It is well known that in a set of cis, trans isomers the lower-melting, more soluble member has the cis configuration.

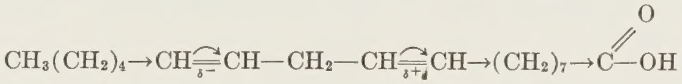
The fact that the spacial arrangement about the double bond was still cis in the trans-9,10-dihydroxy-12-octadecenoic acid was established on alkaline permanganate oxidation, when the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acids melting at 174° (I) and 164° (II) were obtained. These are the acids obtained from linoleic acid on oxidation with this reagent.

Still another set of diastereoisomers of tetrahydroxystearic acid was prepared by the alkaline permanganate oxidation of cis-9,10-dihydroxy-12-octadecenoic acid (XIX). These acids melted at 164° (VII) and 141.5° (VIII). In these acids, the C_9 and C_{10} hydroxyl groups are known to be cis to each other, and the C_{12} and C_{13} hydroxyl groups are known to be trans because of the method of preparation. If cis-9,10-dihydroxy-12-octadecenoic acid is acetylated and then oxidized with peracetic acid solution, the product on saponification gives the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acid melting at 148° (III) and 126° (IV). These are identical with the two diastereoisomers prepared from linoleic acid by peracetic acid oxidation. Therefore the previous treatment of cis-9,10-dihydroxy-12-octadecenoic acid did not alter the configuration about the remaining double bond.



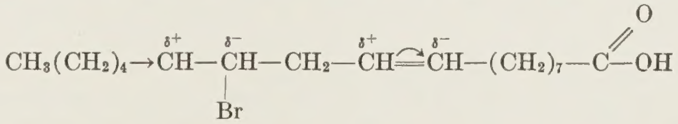
Scheme C

Riemenschneider *et al.* (7) concluded that bromination of cis-9-cis-12-octadecadienoic acid would give two racemates of 9,10,12,13-tetrabromostearic acid. This conclusion was supported by previous observations that bromine adds to a double bond exclusively by cis-addition or by trans-addition. Applying the same arguments to the oxidation of α-linoleic acid, they concluded that alkaline potassium permanganate oxidation or peracetic acid oxidation would give only two racemates of 9,10,12,13-tetrahydroxystearic acid. The present work and the earlier studies of Toyama and Tutiya (14) clearly establish that bromine adds first to the C_{12}-double bond of linoleic acid, by the isolation and identification of 12,13-dibromo-9-octadecenoic acid from the products of its partial bromination. The stepwise addition of bromine to cis-9-cis-12-octadecadienoic acid becomes clear when considered in the light of the fundamental postulates of the English school regarding rates of reactions of olefins (15). Olefins are nucleophilic in character, and any substituent which increases the electron density of the ethylenic group increases its rate of reaction with electrophilic reagents. An electron attractive group *e.g.*, $\overset{O}{\overset{/\!\!/}{C}}—OH$, $—\overset{O}{\overset{/\!\!/}{C}}—OR$, OH, $—\overset{H}{\overset{/}{C}}{=}O$ etc., will have the reverse effect. Thus, in α-linoleic acid there are present two opposing forces, the electron repulsive alkyl group attached to C_{13} and the electron attractive carboxyl group. The inductive effect of these groups may be represented as follows:



$$CH_3(CH_2)_4{\rightarrow}CH\underset{\delta-}{\overset{\frown}{=}}CH—CH_2—CH\underset{\delta+}{\overset{\frown}{=}}CH{\rightarrow}(CH_2)_7{\rightarrow}\overset{O}{\overset{/\!\!/}{C}}—OH$$

The electron attractive carboxyl group will have a greater effect on reducing the electron density of the 9-double bond than of the 12-double bond while the electron repulsive alkyl group will have a greater effect in increasing the electron density of the 12-double bond than of the 9-double bond. Both of these effects operate to increase the difference of the electron densities of the two double bonds giving the 12-double bond the stronger nucleophilic character. The $—CH_2—$ group between the two double bonds would aid in maintaining a potential difference. We have represented this by assigning the fractional charges δ^- and δ^+ to the ethylenic linkages as a whole rather than representing each ethylenic linkage as a polar entity as is general procedure, *e.g.*, $CH_3 \rightarrow \overset{\delta^+}{CH}\overset{\frown}{=}\overset{\delta^-}{CH_2}$. Thus the attack of the electrophilic reagent $:\underset{\cdot\cdot}{Br}:^+$ will be preferentially directed towards the 12-double bond. Once addition of this electrophilic reagent has occurred then the intermediate may be represented as:



$$CH_3(CH_2)_4{\rightarrow}\overset{\delta+}{C}H—\underset{Br}{\overset{\delta-}{C}H}—CH_2—\overset{\delta+}{C}H\overset{\frown}{=}\overset{\delta-}{C}H—(CH_2)_7—\overset{O}{\overset{/\!\!/}{C}}—OH$$

and the polarity between the C_{12} and C_{13} positions must be greater than the polarity between the C_9 and C_{10} positions. This would then favor the addition of the nucleophilic $:\!\ddot{\underset{\cdot\cdot}{\mathrm{Br}}}\!:^{-}$ ion to C_{13}. The over-all effect of these electron shifts causing an increased reaction rate for the C_{12}-double bond over that of the C_9-double bond. Besides the inductive effect of the carboxyl group one would expect a field effect to be operative. However, it is not possible to distinguish between the field and inductive effects.

The oxidation of linoleic acid may be explained also by use of these electronic mechanisms. Swern (16) has summarized the present knowledge of the per-acid oxidation of olefins, and electronically interpreted the effect of substituents on their rates of reactions. This interpretation may be applied equally well to linoleic acid oxidation with per-acids.

The stepwise method of preparation of the tetrahydroxystearic acids through the intermediate 12,13-dibromo-9-octadecenoic acid, has permitted the assignment of definite structures to the eight possible diastereoisomers. On the basis of these structures it is possible to predict the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acid that would be obtained on alkaline potassium permanganate or peracetic acid oxidations of the geometric isomers of linoleic acid. Thus, Kass and Burr (10) must have obtained cis-9-trans-12-octadecadienoic acid on the partial elaidinization of α-linoleic acid rather than the trans-9-cis-12-octadecadienoic acid suggested, because only alkaline oxidation of the former would give the two diastereoisomers of tetrahydroxystearic acid melting at 156–158° (164°) and 126°.

The tetrahydroxystearic acids described in this paper were obtained as well-formed crystals with the exception of the two lowest-melting (126°) members of the series. The possibility of the existence of eutectic mixtures is realized and we are continuing with the studies of these acids.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

Linoleic acid (XIII). α-Linoleic acid was prepared from corn oil through the tetrabromide by the method of McCutcheon (18). After debromination, the linoleic acid distilled in a vacuum (1 mm.) at 198–200°. The yield from the tetrabromostearic acid (m.p. 115°) was 88.9%, iodine value 180.8;[2] calc'd 181.0. Ultraviolet absorption analysis gave a specific α at 2340 Å of 87.2, while that reported by Mitchell and co-workers (19) for pure linoleic acid is 87.1.

12,13-Dibromo-9-octadecenoic acid (XIV). To a vigorously stirred solution of 31.2 g. (0.11 mole) of pure linoleic acid in 2700 cc. of petroleum ether cooled to 15°, a solution of 17.5 g. (0.11 mole) of bromine in 300 cc. of petroleum ether was added dropwise over a period of 2.5 hours. The reaction temperature was not allowed to go above −10°. At the end of the reaction, the solvent was removed *in vacuo* at *ca.* 35°. The last traces of solvent were removed by heating to 100° at a pressure of 1 mm. mercury. A viscous yellow oil (48.6 g.) remained.

Anal. Calc'd for $C_{18}H_{32}Br_2O_2$: Br, 36.32; Iodine Value, 57.60.
Found: Br, 37.92, 37.65; Iodine Value, 56.65.

Methyl ester of 12,13-dibromo-9-octadecenoic acid. The impure 12,13-dibromo-9-octa-

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[2] The iodine values reported here were determined by the Rosenmund-Kuhnhenn method (17).

decenoic acid (39.0 g.; 0.088 mole) was dissolved in 250 cc. of methanol and 10 cc. of 4 *N* methanolic HCl was added. This solution was refluxed for two hours with the addition of 5-cc. portions of the methanolic HCl at half-hour intervals. The solution was then poured into two volumes of saturated brine. The organic layer was extracted with ether (3 × 150 cc.), the ethereal solution was washed with saturated brine (4 × 200 cc.), dried over sodium sulfate, and evaporated to dryness. The residue, an amber colored oil, was obtained in quantitative yield. This oil was distilled at a pressure of 0.5 mm.; the main fraction (b.p. 225–227°) was redistilled, and the intermediate fraction (b.p. 225°) taken for analysis.

Anal. Calc'd for $C_{19}H_{34}Br_2O_2$: Br, 35.3; Iodine Value, 55.8.
Found: Br, 34.92; Iodine Value, 56.0.

Oxidation of the methyl ester of 12,13-dibromo-9-octadecenoic acid with potassium permanganate in acetone. The following modification of Hilditch's (20) method was used for establishing the position of the double bond in the dibrominated linoleic acid. A suspension of sodium carbonate (2 g.) in 150 cc. of acetone containing 9.3 g. (0.02 mole) of methyl 12,13-dibromo-9-octadecenoate (I.V., 56.0) was stirred at −5° to 0° during the gradual addition of finely powdered $KMnO_4$. Twenty-seven grams of $KMnO_4$ was added before a permanent pink color was obtained. The acetone was removed by distillation and the residue extracted with hot methanol (3 × 100 cc.). After addition of zinc dust (10 g.) to the methanol solution, it was refluxed for one hour. The unreacted zinc and zinc bromide were filtered off and the combined filtrate and washings evaporated. The oily residue was saponified in 100 cc. of 3 *N* aqueous KOH by heating on the steam-bath for two hours. The clear soap solution was then poured into excess dilute hydrochloric acid and extracted with ether (3 × 100 cc.). This ethereal solution, after washing with saturated brine (4 × 100 cc.). and drying over sodium sulfate, was evaporated. A residual oil was obtained, which on solution in 50 cc. of ether deposited 3.01 g. (78.0% yield) of impure azelaic acid. Two crystallizations from water gave 2.1 g. of crystals melting at 104.5–105.5° alone and on admixture with an authentic sample of azelaic acid.

Evaporation of the ether from the original filtrate gave an oil which was dissolved in glacial acetic acid (50 cc.). This solution was treated with hydrogen in the presence of Adams platinum oxide catalyst (15 mg.) until the uptake of hydrogen ceased. The catalyst was filtered off and the filtrate was diluted with 6 volumes of water. The oil (1.98 g., 61.0% yield) could not be crystallized. Part (1 g.) of this impure *n*-nonanoic acid was converted to 2-*n*-octylbenzimidazole (m.p. 138.5–139.5°) by refluxing with *o*-phenylenediamine, as outlined by Pool, Harwood, and Ralston (21). They report the melting point 139.5–140.5°.

trans-9,10-Dihydroxy-12-octadecenoic acid (XVIII). 12,13-Dibromo-9-octadecenoic acid (39.0 g.; 0.088 mole) was oxidized in dilute alkaline solution with potassium permanganate by the method of Riemenschneider *et al.* (7). The product was recovered by extracting the decolorized and acidified permanganate solution with ether (3 × 400 cc.). The clear ether solution was washed with saturated brine solution until the aqueous solutions were neutral to Congo Red paper and dried over sodium sulfate. Evaporation of the ether left 38.6 g. of a light yellow oil consisting of a mixture of oxidation products, along with trans-9,10-dihydroxy-12,13-dibromooctadecanoic acid.

The crude oil (38.6 g.) was dissolved in methanol (500 cc.) and the solution cooled to 0°. Zinc dust (30 g.) was added slowly because at first the reaction was vigorous and exothermic. After the reaction had become quiescent, the reaction mixture was refluxed on a steam-bath for two hours. On cooling, the solid (zinc and zinc bromide) was removed by filtration and the methanolic filtrate was diluted with water (500 cc.) and a white waxy, lighter-than-water solid separated. This was filtered off, washed with petroleum ether and triturated with dilute HCl solution. The remaining white solid was washed with water and petroleum ether and dried. This solid proved to be impure trans-9,10-dihydroxy-12-octadecenoic acid (m.p. 86–92°), yield 4.0 g. or 14.8%. After two recrystallizations from 50% aqueous ethanol 2.1 g. of 9,10-trans-dihydroxy-12-octadecenoic acid was obtained as shiny plates melting sharply at 97°.

Anal. Calc'd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.96; I. V., 80.6.
Found: C, 68.99; H, 11.25; I. V., 80.6.

trans-9,10-Dihydroxystearic acid from trans-9,10-dihydroxy-12-octadecenoic acid. The trans-9,10-dihydroxy-12-octadecenoic acid (100 mg., 0.0003 mole) was dissolved in glacial acetic acid (30 cc.) and hydrogenated in the presence of Adams platinum oxide catalyst (15 mg.). The product, recovered in the usual manner, melted at 125–128°, yield 98 mg. (97.4%). This was crystallized twice from 50% aqueous ethanol to yield 71 mg. of crystals melting at 132° alone and on admixture with a known sample of trans-9,10-dihydroxystearic acid (m. p. 132°).

Alkaline potassium permanganate oxidation of trans-9,10-dihydroxy-12-octadecenoic acid. Eighty-nine milligrams (0.00027 mole) of trans-9,10-dihydroxy-12-octadecenoic acid (m. p. 97°) was oxidized with aqueous alkaline permanganate solution using the method of Riemenschneider *et al.* (7). The crude product after filtration from the acidified and decolorized potassium permanganate solution melted at 138–149°, yield 55 mg., or 55.8%. This solid was extracted with acetone (3 × 1 cc.). The acetone-insoluble fraction, after one crystallization from 50% aqueous ethanol yielded 21 mg. of crystals melting at 173° (I). This melting point was not depressed by the diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 174°) obtained from the alkaline potassium permanganate oxidation of linoleic acid. The acetone extract, after removal of the acetone, was crystallized twice from 50% aqueous ethanol to give crystals melting sharply at 164° (II), yield 14 mg. The melting point of this compound was not depressed by the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 164°) obtained from the alkaline potassium permanganate oxidation of linoleic acid.

The acetylation and peracetic acid oxidation of trans-9,10-dihydroxy-12-octadecenoic acid. Trans-9,10-dihydroxy-12-octadecenoic acid (1.98 g. 0.006 mole) was dissolved in pyridine (5 cc.) and 1.08 g. (0.01 mole) of acetyl chloride was added dropwise to the pyridine solution cooled in an ice-water bath. After the exothermic reaction had subsided, the solution was allowed to stand at room temperature for twenty-four hours. It was poured into water (10 vols.) and extracted with ether (3 × 30 cc.). The ethereal extract was washed with dilute HCl to remove the pyridine, and with 10% brine until the aqueous washings were neutral to Congo Red. Evaporation of the ether left a light yellow oil.

This light yellow oil was further hydroxylated with peracetic acid solution using the conditions described by Swern *et al.* (22) for the hydroxylation of elaidic acid with peracetic acid; the only change was the use of three times the relative amount of H_2SO_4. This was found to hasten the reaction considerably, and less time was required for the theoretical uptake of oxygen. The uptake of peroxide was followed by titration (23). At the end of the reaction period, the acetic acid solution was poured into water (10 vols.), and the oil which separated was recovered. This oil was saponified by heating with 3 N aqueous KOH solution (50 cc.) for one hour on a steam-bath. On pouring the cooled soap solution into ice-cold dilute HCl solution, a yellow precipitate (m. p. 90–97°) formed, yield 870 mg. This solid was extracted with boiling ethyl acetate (100 cc.). The unextracted material (92 mg., yield 8.5%) melted at 158–163°. Crystallization from 50% aqueous ethanol yielded rod-shaped crystals (65 mg.) melting at 164–164.5°.

Anal. Calc'd for $C_{18}H_{36}O_6$: C, 62.07; H, 10.34.
Found: C, 61.80; H, 10.32.

A mixed melting point determination with the known diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 164°) from the alkaline potassium permanganate oxidation of linoleic acid was depressed to 151–157°.

The ethyl acetate extract was cooled to 0°, when white crystals separated. These crystals melted at 141–145°, yield 22 mg. The ethyl acetate filtrate was evaporated to dryness and the remaining oil was dissolved in ether (20 cc.) and stored at −35° for three days. The ether solution deposited white crystals (50 mg.) which were filtered off, washed with ether, and dried, m. p. 75–103°. Fractional crystallization from ethyl acetate gave a crop of crystals melting at 126° (3 mg.). This experiment was repeated to obtain more of these crystals melting at 126°.

Anal. Calc'd for $C_{18}H_{36}O_6$: C, 62.07; H, 10.34.
Found: C, 62.21; H, 10.40.

The melting point of this compound was depressed to 110–115° on admixture with the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m p. 126°) obtained by the peracetic acid oxidation of linoleic acid. The ether filtrate from the crystals melting at 75–103° was evaporated to dryness, and the remaining oil taken up in 3 N aqueous KOH (10 cc.) and poured into dilute HCl solution. To the milky suspension petroleum ether (10 cc.) was added and, the material left standing overnight in the refrigerator. The white crystals (22 mg.) which had formed at the interface were filtered off and dried. These crystals (m. p. 85–86°) are under investigation. A similar melting compound was found in the product from the peracetic acid oxidation of linoleic acid (12).

Peracetic acid oxidation of 12,13-dibromo-9-octadecenoic acid. Thirty-one grams (0.07 mole) of 12,13-dibromo-9-octadecenoic acid was hydroxylated with peracetic by the method already described. The oxidation was considered complete after two and a half hours. The reaction mixture was then poured into a saturated brine (8 vols.) to which 0.1 N sodium thiosulfate solution (3 cc.) had been added to remove the excess peroxide. The aqueous mixture was extracted with ether and the ether washed with saturated brine solution. Finally the ethereal extract was dried over anhydrous sodium sulfate and the ether evaporated. A light yellow oil remained, yield 31.4 g. This oil contained 9(10)-hydroxy-10(9)-acetoxy-12,13-dibromooctadecanoic acid, as well as other impurities. Several runs were made and 123.1 g. of yellow oil was collected. This oil was debrominated without further purification. The debromination was conducted as previously described and the product worked up in the same manner. The light yellow oil (81.6 g.) consisted of a mixture of 9(10)-hydroxy-10(9)-acetoxy-12-octadecenoic acid, linoleic acid, and lower oxidation products. This oil (I. V., 82.5, calc'd 80.6) was extracted with petroleum ether (6 × 100 cc.) to remove the linoleic acid, and the remaining clear oil (62.0 g.) was dissolved in acetone (350 cc.). The acetone was almost completely removed by distillation and the remaining solution was treated with petroleum ether when a white solid (0.3 g.) collected at the interface. It melted at 114–121° and after three crystallizations from 30% aqueous ethanol the melting point was raised to 124–126°. This melting point was not depressed when a sample was mixed with the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 126°) obtained from the peracetic acid oxidation of linoleic acid. The acid isolated here was formed by action of peracetic acid on the linoleic present as an impurity in the original 12,13-dibromo-9-octadecenoic acid. The petroleum ether was separated from the oily layer by decantation and the oil was extracted again with petroleum ether (12 × 50 cc.). The remaining oil had the iodine value 51.55, whereas the calculated iodine value for 9,10-dihydroxy-12-octadecenoic acid is 80.6. This oil was purified by converting it to the methyl ester as previously described and distillation. The methyl ester (37.8 g.; I. V., 48.2) was distilled at a pressure of *ca.* 0.5 mm. and a colorless fraction was collected at a vapor temperature of 186–188°. This fraction had the iodine value 73.2, calc'd 77.3. One more distillation, in which large first and last fractions were discarded, gave 8.8 g. of colorless oil, I. V., 76.5. This methyl ester of cis-9,10-dihydroxy-12-octadecenoic acid was then saponified in the usual manner to give a quantitative yield of cis-9,10-dihydroxy-12-octadecenoic acid, I. V., 80.2, calc'd 80.6.

cis-9,10-Dihydroxystearic acid from cis-9,10-dihydroxy-12-octadecenoic acid. The cis-9,10-dihydroxy-12-octadecenoic acid (0.276 g.; 0.0008 mole; I. V., 80.2) was dissolved in glacial acetic acid (30 cc.) and hydrogenated in the presence of Adams platinum oxide catalyst (15 mg.). After the uptake of hydrogen had ceased, the catalyst was removed by filtration and the acetic acid solution diluted with water (7 vols.). A white, flocculent precipitate (0.25 g., 93% yield) formed. This was filtered off, washed with water, and dried. The melting point 78–86° was raised to 94° by three crystallizations from ethanol, yield 184 mg. A sample of this compound on admixture with an authentic sample of cis-9,10-dihydroxystearic acid (m. p. 95°) gave no depression in melting point.

Acetylation of the cis-9,10-dihydroxy-12-octadecenoic acid and peracetic acid oxidation of the 9,10-diacetoxy-12-octadecenoic acid. Cis-9,10-dihydroxy-12-octadecenoic acid (1.95 g.; 0.0062 mole; I. V., 80.2) was acetylated by the method described for trans-9,10-dihydroxy-12-octadecenoic acid. The resulting oil was oxidized with peracetic acid in the usual manner. The oxidation product was a yellow oil which was saponified by heating on the steam-bath with 3 *N* aqueous KOH solution (100 cc.) for two hours. The soap was cooled, poured into ice-cold dilute HCl, and the waxy, yellow solid (1.47 g., 68.1% yield) filtered off. Trituration with ether (50 cc.) left white crystals (346 mg.), which were extracted with boiling acetone (6 × 10 cc.). The residual solid (91 mg.) after two crystallizations from 50% aqueous ethanol melted at 147–148° (III). A mixed melting point determination with a known sample of high-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 148°) obtained from the peracetic acid oxidation of linoleic acid was not depressed.

The combined acetone extracts on cooling gave 12 mg. of crystals which melted at 130–139°. The acetone filtrate was evaporated to dryness and again extracted with acetone (10 cc.). The acetone was evaporated off and the residue was crystallized twice from 50% aqueous ethanol to give 9 mg. of white amorphous solid (m. p. 125–126°) (IV). A mixed melting point determination with an authentic sample of the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid from the peracetic acid oxidation of linoleic acid was not depressed.

Alkaline potassium permanganate oxidation of cis-9,10-dihydroxy-12-octadecenoic acid. Three grams (0.009 mole) of cis-9,10-dihydroxy-12-octadecenoic acid (I. V. 80.2) was dissolved in 1.5% aqueous potassium hydroxide (300 cc.) and to the well-stirred solution 1% aqueous potassium permanganate (300 cc.) solution was added rapidly. After two minutes the reaction mixture was decolorized with sulfur dioxide, concentrated HCl (20 cc.) was added and the white waxy precipitate (2.10 g., 63.2% yield) was recovered by filtration. This solid was extracted with ether (180 cc.) which left white crystals (1.136 g.) melting at 131–142°. Extraction of the solid with boiling acetone (130 cc.) gave white crystals (276 mg.) which after two crystallizations from 50% aqueous ethanol melted sharply at 164°. This is the cis, trans, trans-9,10,12,13-tetrahydroxystearic acid (VII) and it depresses the mixed melting point to 150–158° on admixture with the trans, cis, trans-9,10,12,13-tetrahydroxystearic acid (II) from the alkaline potassium permanganate oxidation of linoleic acid. A mixed melting point determination between the cis, trans, trans-9,10,12,13-tetrahydroxystearic acid (m. p. 164°) (VII) and the trans,trans-cis-diastereoisomer (m. p. 165°) (V) gave on depression. However crystallographic studies show these two diastereoisomers to have different crystalline properties. The crystallographic data and infrared data will be published at a later date.

A sample of this new cis,trans,trans-9,10,12,13-tetrahydroxystearic acid (m. p. 164°) (VII) was submitted for analysis.

Anal. Calc'd for $C_{18}H_{36}O_6$: C, 62.07; H, 10.34.
Found: C, 61.93, 61.89; H, 10.64, 10.69.

The hot acetone extract from above was cooled to 0° and the crystals (25 mg.) which formed were filtered off and dried, m. p. 151–157°. Evaporation of the acetone left an oil which after trituration with ether deposited crystals (393 mg.) melting at 136–141°. Two crystallizations from 50% aqueous ethanol yielded 248 mg. of crystals melting at 144–148°. This material was extracted with boiling acetone (30 cc.), the acetone evaporated to dryness, and the remaining white amphorous solid crystallized twice from 50% aqueous ethanol. The resulting white shiny crystals (52 mg.) melted sharply at 141.5°. This compound (VIII) on admixture with the high-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 148°) (III) from the peracetic acid oxidation of linoleic acid melted at 135–138°.

Anal. Calc'd for $C_{18}H_{36}O_6$: C, 62.07; H, 10.34.
Found: C, 61.65; H, 10.54.

The authors are grateful to the National Research Council of Canada for full support of this investigation and a grant-in-aid to one of us (A. R. B.).

SUMMARY

1. A method is described for the preparation of the eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid from α-linoleic acid. The special arrangements of the hydroxyl groups in each diastereoisomer are deduced from this method of preparation.

2. Two new fatty acids cis- and trans-9,10-dihydroxy-12-octadecenoic acid are also described.

3. The present system of nomenclature applied to the tetrahydroxystearic acids is discussed.

KINGSTON, CANADA

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THE PREPARATION AND PROPERTIES OF THE EIGHT DIASTEREOISOMERS OF 9,10,12,13-TETRAHYDROXYSTEARIC ACID

A. F. McKAY AND A. R. BADER

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The eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid were prepared from α-linoleic acid (cis-9-cis-12-octadecadienoic acid). A new method of preparation was developed which establishes the spacial relationships of the hydroxyl groups in each diastereoisomer.

Hazura (1) was the first to isolate a 9,10,12,13-tetrahydroxystearic acid (sativic acid) from the alkaline potassium permanganate oxidation of linoleic acid. Further study (2–6) of this oxidation reaction resulted in methods for improving the yield and it is now established that two diastereoisomers of the tetrahydroxystearic acid are formed in this reaction. The melting points of these acids are 173° (I) and 164° (II). The more soluble one has also been reported to melt at 157–159°, but according to Riemenschneider *et al.* (7) this is an eutectic mixture of the α- and β-sativic[1] acids melting at 173° and 164°. Nicolet and Cox (8) obtained two different diastereoisomers of 9,10,12,13-tetrahydroxystearic acid by treating linoleic acid with hypochlorous and hypobromous acids to form the dichloro- and dibromo-dihydroxystearic acids. Replacement of the halogen atoms by hydroxyl groups gave two tetrahydroxystearic acids melting at 145° and 135°. Later work suggests that these acids are the same as the two diastereoisomers obtained in the peracetic acid oxidation of linoleic acid (9), or the alkaline potassium permanganate oxidation of linolelaidic acid (10) which are now described as melting at 146° (III) and 126° or 122° (IV). Kass and Burr (10) prepared a third set of diastereoisomers of 9,10,12,13-tetrahydroxystearic acid by the alkaline potassium permanganate oxidation of the trans-cis or cis-trans geometric isomer of linoleic acid. The melting points of these acids are given as 156–158° (V) and 126° (VI). The melting point of the former has now been raised to 164°. A seventh diastereoisomer of tetrahydroxystearic acid was re-

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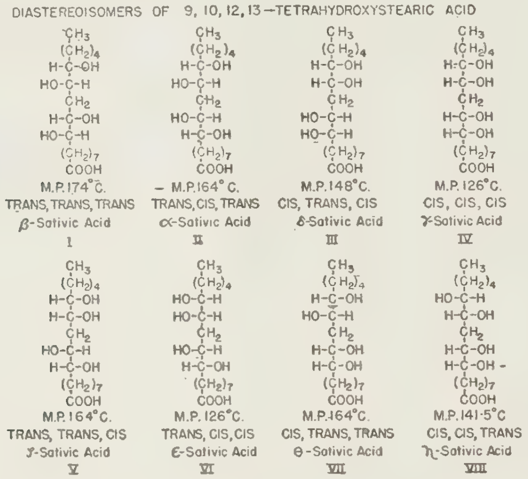
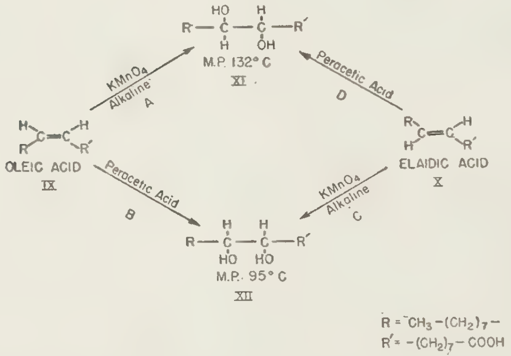
[1] The use of the name sativic acid for tetrahydroxystearic acid has led to a great deal of confusion in the study of the diastereoisomers of this acid. The main difficulty is that the terms α, β, γ etc., sativic acids give no indication of the structure of these compounds. Moreover the same Greek letters have been assigned to different diastereoisomers. Thus we propose that the system of nomenclature based on the use of the terms cis and trans be used to name these diastereoisomers. This system allows no misinterpretation of data and is more convenient for the correlation of experimental studies of these acids. In this method of naming the diastereoisomers of 9,10,12,13-tetrahydroxystearic acid three combinations of cis and trans are used *e.g.*, α-sativic acid becomes trans, cis, trans-9,10,12,13-tetrahydroxystearic acid. The first trans refers to the spacial relationship of the C_9 and C_{10} hydroxyl groups, the cis refers to the relative configuration of the C_{10} and C_{12} hydroxyl groups and the final trans to the spacial interrelationship of the C_{12} and C_{13} hydroxyl groups. The eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid are given in formulas I–VIII, with this proposed system of nomenclature together with the sativic acid system.

ported by McKay, Jones, and Sinclair (11), which also melts at 164° (VII). In this report the eighth diastereoisomer (m.p. 141.5°) (VIII) is described.

If one considers the simpler case of 9,10-dihydroxystearic acid, then only two diastereoisomers are theoretically possible. 9-Octadecenoic acid exists in two geometric isomers, the cis form commonly known as oleic acid (IX) and the trans form as elaidic acid (X). The two 9,10-dihydroxystearic acids melting at 132° (XI) and 95° (XII) are formed respectively by the alkaline potassium permanganate oxidation (A) and the peracetic acid oxidation (B) of oleic acid. In antithesis to this, the alkaline potassium permanganate (C) and peracetic acid (D) oxidations of elaidic acid (X) give the dihydroxystearic acids melting at 95° and 132° respectively. Infrared studies (12), and titration with lead tetraacetate (13) show the two hydroxyl groups in the higher-melting 9,10-dihydroxystearic



Scheme A



Scheme B

acid, to be trans to each other, and in the lower-melting diastereoisomer to be cis. Thus, alkaline potassium permanganate oxidation of a double bond supporting a cis configuration gives a trans α-glycol and vice versa. The opposite is true when peracetic acid is the oxidizing reagent. With these established facts in mind the eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid were prepared.

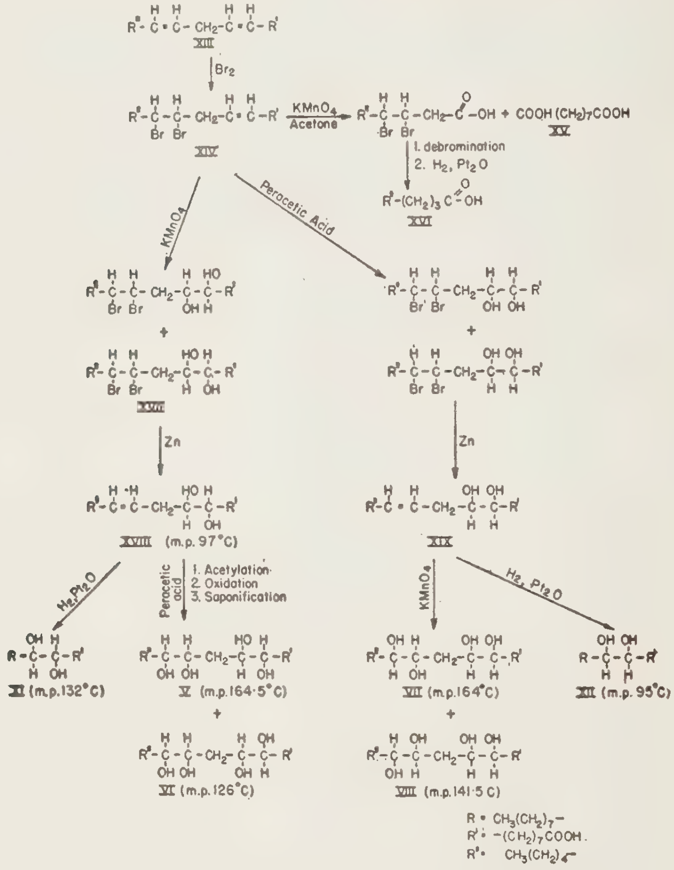
α-Linoleic acid (XIII) was brominated with slightly more than one molar equivalent of bromine at low temperatures ($-15°$). The desired dibromo derivative, 12,13-dibromo-9-octadecenoic acid (XIV) contained impurities of unchanged linoleic acid and 9,10,12,13-tetrabromostearic acid. The dibromination of linoleic acid and the oxidative degradation of the dibromo derivative have been reported by Toyama and Tutiya (14) without experimental details. In order to confirm the structure of 12,13-dibromo-9-octadecenoic acid, it was converted into its methyl ester (Iodine Value, 56.0), and then oxidized with potassium permanganate in acetone. The product, after debromination and hydrogenation gave azelaic acid (XV) in 78% yield and impure *n*-nonanoic acid (XVI) in 61% yield. These results prove that the double bond farther removed from the carboxyl group is preferentially brominated in the low temperature dibromination of α-linoleic acid.

Oxidation of 12,13-dibromo-9-octadecenoic acid with aqueous alkaline potassium permanganate solution gave a mixture of 9,10-dihydroxy-12,13-dibromostearic acids (XVII). Trans-9,10-dihydroxy-12-octadecenoic acid (m.p. 97°; I.V., 80.6) (XVIII) was obtained from this product on debromination. Another set of reactions, in which 12,13-dibromo-9-octadecenoic acid was oxidized with peracetic acid and the product debrominated, saponified, and then distilled, gave an oil identified as cis-9,10-dihydroxy-12-octadecenoic acid (I.V., 80.2) (XIX). The structures of both the trans and cis-9,10-dihydroxy-12-octadecenoic acids were substantiated by reduction of these compounds to the corresponding 9,10-dihydroxystearic acids melting at 132° (XI) and 95° (XII) respectively. Nearly theoretical yields were obtained in each case.

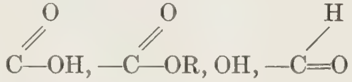
The trans-9,10-dihydroxy-12-octadecenoic acid (XVIII) was acetylated and then oxidized with peracetic acid solution. After saponification of the product and acidification of the resulting alkaline solution, the free acids were obtained. These acids, on partition by solvents, gave two racemates of 9,10,12,13-tetrahydroxystearic acid in which the C_9 and C_{10} hydroxyl groups were trans and the C_{12} and C_{13} hydroxyl groups were cis. These diastereoisomers melted at 164° (V) and 126° (VI). The isomer having the C_{10} and C_{12} hydroxyl groups cis to each other was assigned the lower melting point. It is well known that in a set of cis, trans isomers the lower-melting, more soluble member has the cis configuration.

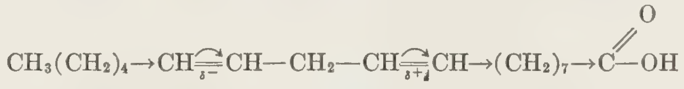
The fact that the spacial arrangement about the double bond was still cis in the trans-9,10-dihydroxy-12-octadecenoic acid was established on alkaline permanganate oxidation, when the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acids melting at 174° (I) and 164° (II) were obtained. These are the acids obtained from linoleic acid on oxidation with this reagent.

Still another set of diastereoisomers of tetrahydroxystearic acid was prepared by the alkaline permanganate oxidation of cis-9,10-dihydroxy-12-octadecenoic acid (XIX). These acids melted at 164° (VII) and 141.5° (VIII). In these acids, the C_9 and C_{10} hydroxyl groups are known to be cis to each other, and the C_{12} and C_{13} hydroxyl groups are known to be trans because of the method of preparation. If cis-9,10-dihydroxy-12-octadecenoic acid is acetylated and then oxidized with peracetic acid solution, the product on saponification gives the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acid melting at 148° (III) and 126° (IV). These are identical with the two diastereoisomers prepared from linoleic acid by peracetic acid oxidation. Therefore the previous treatment of cis-9,10-dihydroxy-12-octadecenoic acid did not alter the configuration about the remaining double bond.



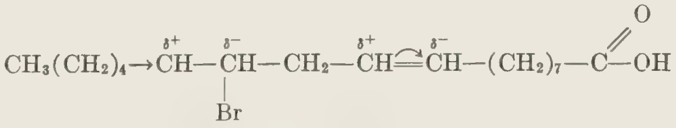
Scheme C

Riemenschneider *et al.* (7) concluded that bromination of cis-9-cis-12-octadecadienoic acid would give two racemates of 9,10,12,13-tetrabromostearic acid. This conclusion was supported by previous observations that bromine adds to a double bond exclusively by cis-addition or by trans-addition. Applying the same arguments to the oxidation of α-linoleic acid, they concluded that alkaline potassium permanganate oxidation or peracetic acid oxidation would give only two racemates of 9,10,12,13-tetrahydroxystearic acid. The present work and the earlier studies of Toyama and Tutiya (14) clearly establish that bromine adds first to the C_{12}-double bond of linoleic acid, by the isolation and identification of 12,13-dibromo-9-octadecenoic acid from the products of its partial bromination. The stepwise addition of bromine to cis-9-cis-12-octadecadienoic acid becomes clear when considered in the light of the fundamental postulates of the English school regarding rates of reactions of olefins (15). Olefins are nucleophilic in character, and any substituent which increases the electron density of the ethylenic group increases its rate of reaction with electrophilic reagents. An electron attractive group *e.g.*,  $\overset{O}{\overset{/\!/}{C}}\text{—OH}$, $\text{—}\overset{O}{\overset{/\!/}{C}}\text{—OR}$, OH, $\text{—}\overset{H}{\overset{/}{C}}\text{=O}$ etc., will have the reverse effect. Thus, in α-linoleic acid there are present two opposing forces, the electron repulsive alkyl group attached to C_{13} and the electron attractive carboxyl group. The inductive effect of these groups may be represented as follows:



$$CH_3(CH_2)_4\rightarrow CH\underset{\delta-}{\overset{\frown}{=}}CH—CH_2—CH\underset{\delta+}{\overset{\frown}{=}}CH\rightarrow(CH_2)_7\rightarrow\overset{O}{\overset{/\!/}{C}}—OH$$

The electron attractive carboxyl group will have a greater effect on reducing the electron density of the 9-double bond than of the 12-double bond while the electron repulsive alkyl group will have a greater effect in increasing the electron density of the 12-double bond than of the 9-double bond. Both of these effects operate to increase the difference of the electron densities of the two double bonds giving the 12-double bond the stronger nucleophilic character. The —CH_2— group between the two double bonds would aid in maintaining a potential difference. We have represented this by assigning the fractional charges δ^- and δ^+ to the ethylenic linkages as a whole rather than representing each ethylenic linkage as a polar entity as is general procedure, *e.g.*, $CH_3 \rightarrow \overset{\delta^+}{CH}\overset{\frown}{=}\overset{\delta^-}{CH_2}$. Thus the attack of the electrophilic reagent $:\underset{\cdot\cdot}{Br}:^+$ will be preferentially directed towards the 12-double bond. Once addition of this electrophilic reagent has occurred then the intermediate may be represented as:



$$CH_3(CH_2)_4\rightarrow\overset{\delta+}{C}H—\underset{\displaystyle Br}{\overset{\delta-}{C}H}—CH_2—\overset{\delta+}{C}H\overset{\frown}{=}\overset{\delta-}{C}H—(CH_2)_7—\overset{O}{\overset{/\!/}{C}}—OH$$

and the polarity between the C_{12} and C_{13} positions must be greater than the polarity between the C_9 and C_{10} positions. This would then favor the addition of the nucleophilic $:\ddot{\underset{\cdot\cdot}{\mathrm{Br}}}:^{-}$ ion to C_{13}. The over-all effect of these electron shifts causing an increased reaction rate for the C_{12}-double bond over that of the C_9-double bond. Besides the inductive effect of the carboxyl group one would expect a field effect to be operative. However, it is not possible to distinguish between the field and inductive effects.

The oxidation of linoleic acid may be explained also by use of these electronic mechanisms. Swern (16) has summarized the present knowledge of the per-acid oxidation of olefins, and electronically interpreted the effect of substituents on their rates of reactions. This interpretation may be applied equally well to linoleic acid oxidation with per-acids.

The stepwise method of preparation of the tetrahydroxystearic acids through the intermediate 12,13-dibromo-9-octadecenoic acid, has permitted the assignment of definite structures to the eight possible diastereoisomers. On the basis of these structures it is possible to predict the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acid that would be obtained on alkaline potassium permanganate or peracetic acid oxidations of the geometric isomers of linoleic acid. Thus, Kass and Burr (10) must have obtained cis-9-trans-12-octadecadienoic acid on the partial elaidinization of α-linoleic acid rather than the trans-9-cis-12-octadecadienoic acid suggested, because only alkaline oxidation of the former would give the two diastereoisomers of tetrahydroxystearic acid melting at 156–158° (164°) and 126°.

The tetrahydroxystearic acids described in this paper were obtained as well-formed crystals with the exception of the two lowest-melting (126°) members of the series. The possibility of the existence of eutectic mixtures is realized and we are continuing with the studies of these acids.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

Linoleic acid (XIII). α-Linoleic acid was prepared from corn oil through the tetrabromide by the method of McCutcheon (18). After debromination, the linoleic acid distilled in a vacuum (1 mm.) at 198–200°. The yield from the tetrabromostearic acid (m.p. 115°) was 88.9%, iodine value 180.8;[2] calc'd 181.0. Ultraviolet absorption analysis gave a specific α at 2340 Å of 87.2, while that reported by Mitchell and co-workers (19) for pure linoleic acid is 87.1.

12,13-Dibromo-9-octadecenoic acid (XIV). To a vigorously stirred solution of 31.2 g. (0.11 mole) of pure linoleic acid in 2700 cc. of petroleum ether cooled to 15°, a solution of 17.5 g. (0.11 mole) of bromine in 300 cc. of petroleum ether was added dropwise over a period of 2.5 hours. The reaction temperature was not allowed to go above $-10°$. At the end of the reaction, the solvent was removed *in vacuo* at *ca.* 35°. The last traces of solvent were removed by heating to 100° at a pressure of 1 mm. mercury. A viscous yellow oil (48.6 g.) remained.

Anal. Calc'd for $C_{18}H_{32}Br_2O_2$: Br, 36.32; Iodine Value, 57.60.
Found: Br, 37.92, 37.65; Iodine Value, 56.65.

Methyl ester of 12,13-dibromo-9-octadecenoic acid. The impure 12,13-dibromo-9-octa-

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[2] The iodine values reported here were determined by the Rosenmund-Kuhnhenn method (17).

decenoic acid (39.0 g.; 0.088 mole) was dissolved in 250 cc. of methanol and 10 cc. of 4 N methanolic HCl was added. This solution was refluxed for two hours with the addition of 5-cc. portions of the methanolic HCl at half-hour intervals. The solution was then poured into two volumes of saturated brine. The organic layer was extracted with ether (3 × 150 cc.), the ethereal solution was washed with saturated brine (4 × 200 cc.), dried over sodium sulfate, and evaporated to dryness. The residue, an amber colored oil, was obtained in quantitative yield. This oil was distilled at a pressure of 0.5 mm.; the main fraction (b.p. 225–227°) was redistilled, and the intermediate fraction (b.p. 225°) taken for analysis.

Anal. Calc'd for $C_{19}H_{34}Br_2O_2$: Br, 35.3; Iodine Value, 55.8.
Found: Br, 34.92; Iodine Value, 56.0.

Oxidation of the methyl ester of 12,13-dibromo-9-octadecenoic acid with potassium permanganate in acetone. The following modification of Hilditch's (20) method was used for establishing the position of the double bond in the dibrominated linoleic acid. A suspension of sodium carbonate (2 g.) in 150 cc. of acetone containing 9.3 g. (0.02 mole) of methyl 12,13-dibromo-9-octadecenoate (I.V., 56.0) was stirred at −5° to 0° during the gradual addition of finely powdered $KMnO_4$. Twenty-seven grams of $KMnO_4$ was added before a permanent pink color was obtained. The acetone was removed by distillation and the residue extracted with hot methanol (3 × 100 cc.). After addition of zinc dust (10 g.) to the methanol solution, it was refluxed for one hour. The unreacted zinc and zinc bromide were filtered off and the combined filtrate and washings evaporated. The oily residue was saponified in 100 cc. of 3 N aqueous KOH by heating on the steam-bath for two hours. The clear soap solution was then poured into excess dilute hydrochloric acid and extracted with ether (3 × 100 cc.). This ethereal solution, after washing with saturated brine (4 × 100 cc.). and drying over sodium sulfate, was evaporated. A residual oil was obtained, which on solution in 50 cc. of ether deposited 3.01 g. (78.0% yield) of impure azelaic acid. Two crystallizations from water gave 2.1 g. of crystals melting at 104.5–105.5° alone and on admixture with an authentic sample of azelaic acid.

Evaporation of the ether from the original filtrate gave an oil which was dissolved in glacial acetic acid (50 cc.). This solution was treated with hydrogen in the presence of Adams platinum oxide catalyst (15 mg.) until the uptake of hydrogen ceased. The catalyst was filtered off and the filtrate was diluted with 6 volumes of water. The oil (1.98 g., 61.0% yield) could not be crystallized. Part (1 g.) of this impure *n*-nonanoic acid was converted to 2-*n*-octylbenzimidazole (m.p. 138.5–139.5°) by refluxing with *o*-phenylenediamine, as outlined by Pool, Harwood, and Ralston (21). They report the melting point 139.5–140.5°.

trans-9,10-Dihydroxy-12-octadecenoic acid (XVIII). 12,13-Dibromo-9-octadecenoic acid (39.0 g.; 0.088 mole) was oxidized in dilute alkaline solution with potassium permanganate by the method of Riemenschneider *et al.* (7). The product was recovered by extracting the decolorized and acidified permanganate solution with ether (3 × 400 cc.). The clear ether solution was washed with saturated brine solution until the aqueous solutions were neutral to Congo Red paper and dried over sodium sulfate. Evaporation of the ether left 38.6 g. of a light yellow oil consisting of a mixture of oxidation products, along with trans-9,10-dihydroxy-12,13-dibromooctadecanoic acid.

The crude oil (38.6 g.) was dissolved in methanol (500 cc.) and the solution cooled to 0°. Zinc dust (30 g.) was added slowly because at first the reaction was vigorous and exothermic. After the reaction had become quiescent, the reaction mixture was refluxed on a steam-bath for two hours. On cooling, the solid (zinc and zinc bromide) was removed by filtration and the methanolic filtrate was diluted with water (500 cc.) and a white waxy, lighter-than-water solid separated. This was filtered off, washed with petroleum ether and triturated with dilute HCl solution. The remaining white solid was washed with water and petroleum ether and dried. This solid proved to be impure trans-9,10-dihydroxy-12-octadecenoic acid (m.p. 86–92°), yield 4.0 g. or 14.8%. After two recrystallizations from 50% aqueous ethanol 2.1 g. of 9,10-trans-dihydroxy-12-octadecenoic acid was obtained as shiny plates melting sharply at 97°.

Anal. Calc'd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.96; I. V., 80.6.
Found: C, 68.99; H, 11.25; I. V., 80.6.

trans-9,10-Dihydroxystearic acid from trans-9,10-dihydroxy-12-octadecenoic acid. The trans-9,10-dihydroxy-12-octadecenoic acid (100 mg., 0.0003 mole) was dissolved in glacial acetic acid (30 cc.) and hydrogenated in the presence of Adams platinum oxide catalyst (15 mg.). The product, recovered in the usual manner, melted at 125–128°, yield 98 mg. (97.4%). This was crystallized twice from 50% aqueous ethanol to yield 71 mg. of crystals melting at 132° alone and on admixture with a known sample of trans-9,10-dihydroxystearic acid (m. p. 132°).

Alkaline potassium permanganate oxidation of trans-9,10-dihydroxy-12-octadecenoic acid. Eighty-nine milligrams (0.00027 mole) of trans-9,10-dihydroxy-12-octadecenoic acid (m. p. 97°) was oxidized with aqueous alkaline permanganate solution using the method of Riemenschneider *et al.* (7). The crude product after filtration from the acidified and decolorized potassium permanganate solution melted at 138–149°, yield 55 mg., or 55.8%. This solid was extracted with acetone (3 × 1 cc.). The acetone-insoluble fraction, after one crystallization from 50% aqueous ethanol yielded 21 mg. of crystals melting at 173° (I). This melting point was not depressed by the diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 174°) obtained from the alkaline potassium permanganate oxidation of linoleic acid. The acetone extract, after removal of the acetone, was crystallized twice from 50% aqueous ethanol to give crystals melting sharply at 164° (II), yield 14 mg. The melting point of this compound was not depressed by the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 164°) obtained from the alkaline potassium permanganate oxidation of linoleic acid.

The acetylation and peracetic acid oxidation of trans-9,10-dihydroxy-12-octadecenoic acid. Trans-9,10-dihydroxy-12-octadecenoic acid (1.98 g. 0.006 mole) was dissolved in pyridine (5 cc.) and 1.08 g. (0.01 mole) of acetyl chloride was added dropwise to the pyridine solution cooled in an ice-water bath. After the exothermic reaction had subsided, the solution was allowed to stand at room temperature for twenty-four hours. It was poured into water (10 vols.) and extracted with ether (3 × 30 cc.). The ethereal extract was washed with dilute HCl to remove the pyridine, and with 10% brine until the aqueous washings were neutral to Congo Red. Evaporation of the ether left a light yellow oil.

This light yellow oil was further hydroxylated with peracetic acid solution using the conditions described by Swern *et al.* (22) for the hydroxylation of elaidic acid with peracetic acid; the only change was the use of three times the relative amount of H_2SO_4. This was found to hasten the reaction considerably, and less time was required for the theoretical uptake of oxygen. The uptake of peroxide was followed by titration (23). At the end of the reaction period, the acetic acid solution was poured into water (10 vols.), and the oil which separated was recovered. This oil was saponified by heating with 3 *N* aqueous KOH solution (50 cc.) for one hour on a steam-bath. On pouring the cooled soap solution into ice-cold dilute HCl solution, a yellow precipitate (m. p. 90–97°) formed, yield 870 mg. This solid was extracted with boiling ethyl acetate (100 cc.). The unextracted material (92 mg., yield 8.5%) melted at 158–163°. Crystallization from 50% aqueous ethanol yielded rod-shaped crystals (65 mg.) melting at 164–164.5°.

Anal. Calc'd for $C_{18}H_{36}O_6$: C, 62.07; H, 10.34.
Found: C, 61.80; H, 10.32.

A mixed melting point determination with the known diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 164°) from the alkaline potassium permanganate oxidation of linoleic acid was depressed to 151–157°.

The ethyl acetate extract was cooled to 0°, when white crystals separated. These crystals melted at 141–145°, yield 22 mg. The ethyl acetate filtrate was evaporated to dryness and the remaining oil was dissolved in ether (20 cc.) and stored at −35° for three days. The ether solution deposited white crystals (50 mg.) which were filtered off, washed with ether, and dried, m. p. 75–103°. Fractional crystallization from ethyl acetate gave a crop of crystals melting at 126° (3 mg.). This experiment was repeated to obtain more of these crystals melting at 126°.

Anal. Calc'd for $C_{18}H_{36}O_6$: C, 62.07; H, 10.34.
Found: C, 62.21; H, 10.40.

The melting point of this compound was depressed to 110–115° on admixture with the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m p. 126°) obtained by the peracetic acid oxidation of linoleic acid. The ether filtrate from the crystals melting at 75–103° was evaporated to dryness, and the remaining oil taken up in 3 *N* aqueous KOH (10 cc.) and poured into dilute HCl solution. To the milky suspension petroleum ether (10 cc.) was added and, the material left standing overnight in the refrigerator. The white crystals (22 mg.) which had formed at the interface were filtered off and dried. These crystals (m. p. 85–86°) are under investigation. A similar melting compound was found in the product from the peracetic acid oxidation of linoleic acid (12).

Peracetic acid oxidation of 12,13-dibromo-9-octadecenoic acid. Thirty-one grams (0.07 mole) of 12,13-dibromo-9-octadecenoic acid was hydroxylated with peracetic by the method already described. The oxidation was considered complete after two and a half hours. The reaction mixture was then poured into a saturated brine (8 vols.) to which 0.1 *N* sodium thiosulfate solution (3 cc.) had been added to remove the excess peroxide. The aqueous mixture was extracted with ether and the ether washed with saturated brine solution. Finally the ethereal extract was dried over anhydrous sodium sulfate and the ether evaporated. A light yellow oil remained, yield 31.4 g. This oil contained 9(10)-hydroxy-10(9)-acetoxy-12,13-dibromooctadecanoic acid, as well as other impurities. Several runs were made and 123.1 g. of yellow oil was collected. This oil was debrominated without further purification. The debromination was conducted as previously described and the product worked up in the same manner. The light yellow oil (81.6 g.) consisted of a mixture of 9(10)-hydroxy-10(9)-acetoxy-12-octadecenoic acid, linoleic acid, and lower oxidation products. This oil (I. V., 82.5, calc'd 80.6) was extracted with petroleum ether (6 × 100 cc.) to remove the linoleic acid, and the remaining clear oil (62.0 g.) was dissolved in acetone (350 cc.). The acetone was almost completely removed by distillation and the remaining solution was treated with petroleum ether when a white solid (0.3 g.) collected at the interface. It melted at 114–121° and after three crystallizations from 30% aqueous ethanol the melting point was raised to 124–126°. This melting point was not depressed when a sample was mixed with the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 126°) obtained from the peracetic acid oxidation of linoleic acid. The acid isolated here was formed by action of peracetic acid on the linoleic present as an impurity in the original 12,13-dibromo-9-octadecenoic acid. The petroleum ether was separated from the oily layer by decantation and the oil was extracted again with petroleum ether (12 × 50 cc.). The remaining oil had the iodine value 51.55, whereas the calculated iodine value for 9,10-dihydroxy-12-octadecenoic acid is 80.6. This oil was purified by converting it to the methyl ester as previously described and distillation. The methyl ester (37.8 g.; I. V., 48.2) was distilled at a pressure of *ca.* 0.5 mm. and a colorless fraction was collected at a vapor temperature of 186–188°. This fraction had the iodine value 73.2, calc'd 77.3. One more distillation, in which large first and last fractions were discarded, gave 8.8 g. of colorless oil, I. V., 76.5. This methyl ester of cis-9,10-dihydroxy-12-octadecenoic acid was then saponified in the usual manner to give a quantitative yield of cis-9,10-dihydroxy-12-octadecenoic acid, I. V., 80.2, calc'd 80.6.

cis-9,10-Dihydroxystearic acid from cis-9,10-dihydroxy-12-octadecenoic acid. The cis-9,10-dihydroxy-12-octadecenoic acid (0.276 g.; 0.0008 mole; I. V., 80.2) was dissolved in glacial acetic acid (30 cc.) and hydrogenated in the presence of Adams platinum oxide catalyst (15 mg.). After the uptake of hydrogen had ceased, the catalyst was removed by filtration and the acetic acid solution diluted with water (7 vols.). A white, flocculent precipitate (0.25 g., 93% yield) formed. This was filtered off, washed with water, and dried. The melting point 78–86° was raised to 94° by three crystallizations from ethanol, yield 184 mg. A sample of this compound on admixture with an authentic sample of cis-9,10-dihydroxystearic acid (m. p. 95°) gave no depression in melting point.

Acetylation of the cis-9,10-dihydroxy-12-octadecenoic acid and peracetic acid oxidation of the 9,10-diacetoxy-12-octadecenoic acid. Cis-9,10-dihydroxy-12-octadecenoic acid (1.95 g.; 0.0062 mole; I. V., 80.2) was acetylated by the method described for trans-9,10-dihydroxy-12-octadecenoic acid. The resulting oil was oxidized with peracetic acid in the usual manner. The oxidation product was a yellow oil which was saponified by heating on the steam-bath with 3 *N* aqueous KOH solution (100 cc.) for two hours. The soap was cooled, poured into ice-cold dilute HCl, and the waxy, yellow solid (1.47 g., 68.1% yield) filtered off. Trituration with ether (50 cc.) left white crystals (346 mg.), which were extracted with boiling acetone (6 × 10 cc.). The residual solid (91 mg.) after two crystallizations from 50% aqueous ethanol melted at 147–148° (III). A mixed melting point determination with a known sample of high-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 148°) obtained from the peracetic acid oxidation of linoleic acid was not depressed.

The combined acetone extracts on cooling gave 12 mg. of crystals which melted at 130–139°. The acetone filtrate was evaporated to dryness and again extracted with acetone (10 cc.). The acetone was evaporated off and the residue was crystallized twice from 50% aqueous ethanol to give 9 mg. of white amorphous solid (m. p. 125–126°) (IV). A mixed melting point determination with an authentic sample of the low-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid from the peracetic acid oxidation of linoleic acid was not depressed.

Alkaline potassium permanganate oxidation of cis-9,10-dihydroxy-12-octadecenoic acid. Three grams (0.009 mole) of cis-9,10-dihydroxy-12-octadecenoic acid (I. V. 80.2) was dissolved in 1.5% aqueous potassium hydroxide (300 cc.) and to the well-stirred solution 1% aqueous potassium permanganate (300 cc.) solution was added rapidly. After two minutes the reaction mixture was decolorized with sulfur dioxide, concentrated HCl (20 cc.) was added and the white waxy precipitate (2.10 g., 63.2% yield) was recovered by filtration. This solid was extracted with ether (180 cc.) which left white crystals (1.136 g.) melting at 131–142°. Extraction of the solid with boiling acetone (130 cc.) gave white crystals (276 mg.) which after two crystallizations from 50% aqueous ethanol melted sharply at 164°. This is the cis, trans, trans-9,10,12,13-tetrahydroxystearic acid (VII) and it depresses the mixed melting point to 150–158° on admixture with the trans, cis, trans-9,10,12,13-tetrahydroxystearic acid (II) from the alkaline potassium permanganate oxidation of linoleic acid. A mixed melting point determination between the cis, trans, trans-9,10,12,13-tetrahydroxystearic acid (m. p. 164°) (VII) and the trans,trans-cis-diastereoisomer (m. p. 165°) (V) gave on depression. However crystallographic studies show these two diastereoisomers to have different crystalline properties. The crystallographic data and infrared data will be published at a later date.

A sample of this new cis,trans,trans-9,10,12,13-tetrahydroxystearic acid (m. p. 164°) (VII) was submitted for analysis.

Anal. Calc'd for $C_{18}H_{36}O_6$: C, 62.07; H, 10.34.
Found: C, 61.93, 61.89; H, 10.64, 10.69.

The hot acetone extract from above was cooled to 0° and the crystals (25 mg.) which formed were filtered off and dried, m. p. 151–157°. Evaporation of the acetone left an oil which after trituration with ether deposited crystals (393 mg.) melting at 136–141°. Two crystallizations from 50% aqueous ethanol yielded 248 mg. of crystals melting at 144–148°. This material was extracted with boiling acetone (30 cc.), the acetone evaporated to dryness, and the remaining white amphorous solid crystallized twice from 50% aqueous ethanol. The resulting white shiny crystals (52 mg.) melted sharply at 141.5°. This compound (VIII) on admixture with the high-melting diastereoisomer of 9,10,12,13-tetrahydroxystearic acid (m. p. 148°) (III) from the peracetic acid oxidation of linoleic acid melted at 135–138°.

Anal. Calc'd for $C_{18}H_{36}O_6$: C, 62.07; H, 10.34.
Found: C, 61.65; H, 10.54.

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SUMMARY

1. A method is described for the preparation of the eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid from α-linoleic acid. The special arrangements of the hydroxyl groups in each diastereoisomer are deduced from this method of preparation.

2. Two new fatty acids cis- and trans-9,10-dihydroxy-12-octadecenoic acid are also described.

3. The present system of nomenclature applied to the tetrahydroxystearic acids is discussed.

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The Osmium Tetroxide Oxidation of Some Long-Chain Unsaturated Fatty Acids

By Alfred R. Bader

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The Osmium Tetroxide Oxidation of Some Long-Chain Unsaturated Fatty Acids

By Alfred R. Bader

As a means of extending the evidence of the configurations of the products of oxidation of oleic, elaidic, linoleic, erucic, and brassidic acid with permanganate and peracids, a study has been made of their oxidation by osmium tetroxide. Since this reacts through a cyclic ester intermediate,[1] a *cis*-ethylene must give an *erythro* diol and a *trans* ethylene a *threo* diol. In each case the oxidation products obtained were the ones obtained also in the alkaline permanganate oxidation of the same acids. Hence the 9,10-dihydroxystearic acid melting at 132° and the 13,14-dihydroxybehenic acid melting at 132° are the *erythro*-diols, the two isomers melting at 95° and 101°, respectively, are the *threo*-diols and the eight diastereoisomers of 9,10,12,13-tetrahydroxystearic acid have the configurations assigned them by McKay and Bader.[2]

This is in accord with the work of Wittcoff and co-workers[3,4] who pointed out that the criteria (*viz.*, formation of boric acid complexes, rate of oxidation with lead tetraacetate and periodate, and rate of formation of isopropylidene compounds) which characterize *cis*-glycols in cyclic structures also characterize *threo*- rather than *erythro*-diols in straight chain compounds.

Swern[5] has criticized McKay and Bader[2] for their supposed assumption that alkaline permanganate oxidation proceeds by "*trans* hydroxylation"; this criticism is due to the use[2] of the confusing designation "*trans*" glycol to describe a compound of the *erythro* series. "*trans*" was used[2] for *erythro* and "*cis*" for *threo*, because the vicinal hydroxyl groups in *threo* diols possess a closer spatial relationship than those in *erythro* diols.[4] The present work supports the actual conclusions reached[2,3,4,5] which are the opposite of those of Hilditch and co-workers[6,7,8] and of Dorée and Pepper.[9] They assumed that the alkalinity of the permanganate solutions causes inversion, but in the osmium tetroxide reaction the medium is acidic throughout and yet the same products are obtained.

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Experimental

Oleic,[10] elaidic,[11] linoleic,[12] erucic[9] and brassidic[9] acids were prepared by the standard procedures. One gram lots of each were oxidized with osmium tetroxide by the method of Butenandt.[13] In each case there were obtained in about 60% yield the *hydroxyacids obtained also in the alkaline potassium permanganate oxidation* of the same acids. Their identity was established by melting point and mixed melting point. The mixture of stereoisomers melting at 156° obtained in the oxidation of linoleic acid was separated into the two isomers melting at 173° and 164°, respectively, by the method of Riemenschneider and co-workers.[14] The experimental data are summarized in Table I.

TABLE I

	Crude product		Pure product		
Compound oxidized	Wt. g.	M. p., °C.	Wt., g.	M. p., °C.	Mixed m. p., °C.
Oleic acid	0.86	126–129	0.67	132	132
Elaidic acid	.82	88–91	.62	94–95	94–95
Erucic acid	.90	124–127	.70	132	131–132
Brassidic acid	.79	94–96	.59	101	101
Lineoleic acid	.80	156–157	.28	172–173	172–173
			.17	164	164

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Transesterification. I. Beta-Keto Esters

By Alfred R. Bader, Lowell O. Cummings and Henry A. Vogel

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Transesterification. I. β-Keto Esters

BY ALFRED R. BADER, LOWELL O. CUMMINGS AND HENRY A. VOGEL

A series of β-keto esters of higher alcohols has been prepared in essentially quantitative yields by transesterification with methyl and ethyl β-keto esters under mild conditions in the absence of catalysts. The generality of this reaction and its usefulness is discussed.

As part of a more extensive study of ester interchanges we have investigated the transesterification of methyl and ethyl acetoacetate with a series of alcohols. Such transesterifications of acetoacetic esters have been previously studied, mostly at high temperatures and with basic catalysts with the lower alcohols,[1] *l*-menthol,[2] allylic alcohols,[3] and glycerol,[4] but it has not been realized that these reactions differ from conventional transesterifications and can proceed without catalyst and at steam-bath temperatures. We have prepared the acetoacetates of a series of alcohols in essentially quantitative yields and believe that most primary and secondary alcohols can be esterified in this manner provided that they dissolve in methyl and ethyl acetoacetate and do not, as may some benzylic alcohols,[5] C-alkylate the β-keto ester. Tertiary alcohols react more sluggishly, and we have ob-

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TABLE I

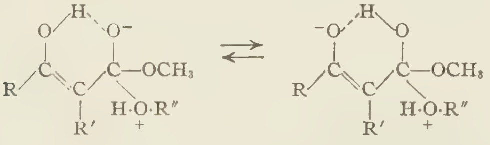
ACETOACETATES

Parent alcohol	Formula	M.p. or b.p., °C.	Solvent of recryst.	$n^{25}D$	$[\alpha]^{25}D$,[a] $CHCl_3$	Analyses,[b] %: Found, Carbon	Found, Hydrogen	Calcd., Carbon	Calcd., Hydrogen
Cholesterol	$C_{31}H_{50}O_3$	96	Ethanol–water		−33	78.61, 78.50	10.46, 10.51	79.09	10.71
Cholestanol	$C_{31}H_{52}O_3$	97	Methanol		+12	78.68, 78.72	11.13, 11.07	78.75	11.09
β-Sitosterol	$C_{33}H_{54}O_3$	99–100	IPE[c]–methanol		−24	79.20, 79.44	10.88, 10.94	79.46	10.91
Stigmasterol	$C_{33}H_{52}O_3$	113–114	IPE–methanol		−44	79.42, 79.60	10.60, 10.70	79.79	10.55
Dehydroepiandrosterone	$C_{23}H_{32}O_4$	163	Methanol		+ 1	74.13, 74.15	8.76, 8.66	74.16	8.66
1-Octanol	$C_{12}H_{22}O_3$	140–141 (16 mm.)		1.4372		66.85, 66.83	10.37, 10.32	67.25	10.35
1-Dodecanol	$C_{16}H_{30}O_3$	8–10	Methanol	1.4436		70.78, 70.80	11.32, 11.33	71.06	11.18
1-Octadecanol	$C_{22}H_{42}O_3$	40–41	Methanol			74.55, 74.45	11.96, 12.13	74.52	11.94
Cyclohexanol	$C_{10}H_{16}O_3$	130–131 (16 mm.)		1.4576		64.94, 64.96	8.92, 8.78	65.19	8.76
Menthol[3]	$C_{14}H_{24}O_3$	30–32	Ether						
Butyl carbitol	$C_{12}H_{22}O_5$	168–170 (10 mm.)		1.4415		58.04	8.90	58.51	9.01
Decamethylene glycol	$C_{18}H_{30}O_6$	33–34	Methanol			62.55	8.85	63.13	8.83

[a] Determined by Dr. C. J. W. Brooks. No mutarotation could be observed. [b] Determined by Micro-Tech Laboratories, Skokie, Illinois. [c] Isopropyl ether.

tained only a low yield of the acetoacetate of diacetone alcohol, the one tertiary alcohol studied. Other β-keto esters react similarly and the benzoylacetates and acetonedicarboxylates of cholesterol and 1-octadecanol have been prepared.

The shift in equilibrium is of course due to the removal of methyl or ethyl alcohol from the reaction mixture, yet esters such as ethyl *n*-butyrate, methyl caprylate, methyl crotonate, methyl benzoate and methyl levulinate do not react with alcohols under conditions more drastic than those required to complete the reactions with methyl or ethyl acetoacetate. We are now studying the transesterification of acids of strength similar or greater than that of acetoacetic acid to ascertain whether it is the inductive effect of the acetyl group which, by enhancing the electrophilic character of the ester carbonyl, facilitates the transesterification of acetoacetic esters or whether the ease of reaction is due to active hydrogen catalysis or to inherent structural features which stabilize such intermediates as Ia and Ib.


Ia Ib

No transesterification takes place when disubstituted β keto esters such as ethyl diethylacetoacetate[6] are employed, and we are not yet certain whether this is due solely to steric hindrance of esters of tertiary acids or whether an active hydrogen atom is a prerequisite for reaction.

This facile transesterification provides one of the few means to esterify an alcohol in neutral medium. Most acetoacetates of higher alcohols crystallize easily and all are more soluble in most organic solvents than the alcohols from which they are derived. Thus acetoacetates make good derivatives of alcohols, and may find use in the purification of natural products. The transesterification proceeds so easily that acetoacetates of higher alcohols may conceivably be formed under physiological conditions and be metabolic intermediates. In this connection it is of interest to note that cholesteryl acetoacetate differs from all other β-keto esters prepared by us in that it is difficult to crystallize from organic solvents as it forms quite stable gels.

Experimental

The β-keto esters used were Eastman Kodak Co. white label chemicals purified by vacuum distillation. The alcohols were crystallized to constant melting point or vacuum distilled just prior to use.

All solid acetoacetates were prepared by heating solutions of the parent alcohols in excess methyl or ethyl acetoacetate on the steam-bath for 3 to 15 hours and allowing the lower alcohols to distil off as formed. The excess methyl or ethyl acetoacetate was then removed by distillation *in vacuo* and the almost pure products were recrystallized as shown in Table I. The yields of analytically pure acetoacetates were always higher than 90%. Liquid acetoacetates were prepared similarly and were purified by fractional distillation.

The structures of two acetoacetates were proved by infrared spectroscopy, and the formation of a semicarbazone and a β-aminocrotonate.

Cholesteryl acetoacetate semicarbazone, prepared from cholesteryl acetoacetate, m.p. 96°, $\lambda_{max.}^{Chf.}$ 5.75, 5.83 μ,[7] $\lambda_{max.}^{isoöctane}$ 242.5 mμ (log ε 3.4)[8] melts at 189–190°, $[\alpha]^{25}D$ −25° (chloroform).

Anal. Calcd. for $C_{32}H_{53}O_3N_3$: C, 72.82; H, 10.12; N, 7.96. Found: C, 73.10; H, 10.32; N, 7.90.

Octadecyl β-aminocrotonate was prepared by passing gaseous ammonia through a methanolic solution of octadecyl acetoacetate, m.p. 40–41°, to which a crystal of ammonium acetate had been added. Recrystallized from methanol, it melts at 70–71°, $\lambda_{max.}^{ethanol}$ 274 mμ (log ε 4.3).

Anal. Calcd. for $C_{22}H_{43}O_2N$: C, 74.73; H, 12.26; N, 3.96. Found: C, 74.80, 74.95; H, 12.33, 12.31; N, 3.70.

Cholesteryl benzoylacetate obtained quantitatively from cholesterol (5 g.) and ethyl benzoylacetate (25 g.) and crystallized from a mixture of ethanol and butyl acetate melts at 151°.

Anal. Calcd. for $C_{36}H_{52}O_3$: C, 81.15; H, 9.84. Found: C, 81.11, 80.97; H, 9.88, 9.69.

Octadecyl benzoylacetate prepared similarly and crystallized from acetone melts at 55–57°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.92; H, 10.30.

Cholesteryl acetonedicarboxylate obtained from cholesterol and ethyl acetonedicarboxylate and crystallized from a mixture of methanol and isopropyl ether melts at 173°. It was accompanied by a more soluble oil, presumably the mixed ester, which could not be obtained crystalline.

Anal. Calcd. for $C_{59}H_{94}O_5$: C, 80.22; H, 10.73. Found: C, 80.57, 80.51; H, 10.71, 10.79.

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(6) A. McKenzie, *J. Chem. Soc.*, **89**, 381 (1906).

(7) We are indebted to Dr. Leon Mandell for the determination of this spectrum.

(8) We wish to thank Mrs. Ruth Ferguson for the determinations of ultraviolet spectra.

Octadecyl acetonedicarboxylate prepared similarly and crystallized from ethanol melts at 65.0–65.5°.

Anal. Calcd. for $C_{41}H_{80}O_5$: C, 75.40; H, 12.34. Found: C, 75.43, 75.37; H, 12.00, 11.94.

2-Acetoacetoxy-2-methyl-pentanone-4.—A solution of diacetone alcohol (300 g.) in methyl acetoacetate (1000 g.) was heated on the steam-bath for 24 hours. Fractionation through a short column yielded 1210 g. of unreacted starting materials and 54 g. of a fraction, b.p. 120–130° at 10 mm., from which 41 g. of pure acetoacetate was obtained on redistillation; b.p. 125–127° at 10 mm., n^{25}_D 1.4424, $\lambda_{max.}^{ethanol}$ 241.5 mμ (log ε 3.07), 306.5 mμ (log ε 2.34).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.22, 60.14; H, 8.19, 8.31.

Acknowledgment.—The authors wish to thank Drs. H. L. Gerhart and S. W. Gloyer for their interest in this work.

MILWAUKEE, WISCONSIN RECEIVED MARCH 31, 1951

[Reprinted from the Journal of the American Chemical Society, **80**, 437 (1958).]

Unsaturated Aromatic Amines; A Novel Synthesis of Indoles

By John E. Hyre and Alfred R. Bader

[Reprinted from the Journal of the American Chemical Society, **80**, 437 (1958).]

[CONTRIBUTION FROM THE LABORATORIES OF THE PITTSBURGH PLATE GLASS COMPANY, THE ALDRICH CHEMICAL COMPANY AND HARVARD UNIVERSITY]

Unsaturated Aromatic Amines; A Novel Synthesis of Indoles

BY JOHN E. HYRE[1a] AND ALFRED R. BADER[1b]

RECEIVED JUNE 14, 1957

Convenient preparations of N-allyl-, N-crotyl- and N-pentenylaniline are described. N-Crotylaniline reacts with polyphosphoric acid to yield 2,3-dimethylindole and a 2,3-dimethylindoline.

Our recent studies of unsaturated phenols[2] prompted a study of the preparations and reactions of simple unsaturated anilines.

N-Allylaniline,[3a-c,d] which had previously been

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[1] (a) Dept. of Chemistry, Harvard University; (b) Aldrich Chemical Company, Milwaukee, Wis.

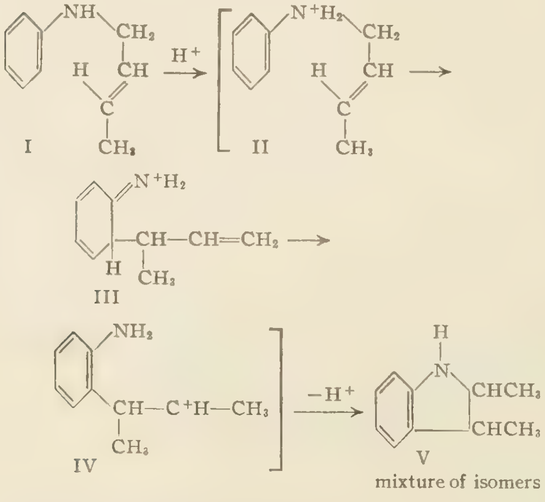
[2] A. R. Bader, THIS JOURNAL, **78**, 1709 (1956).

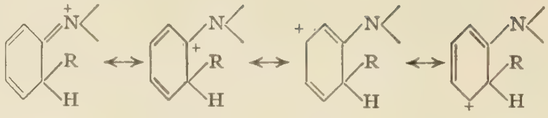
[3] (a) H. Schiff, *Ann. Suppl.*, **3**, 364 (1864); (b) F. B. Davis, R. Q Brewster, J. S. Blair and W. C. Thompson, THIS JOURNAL, **44**, 2638 (1922); (c) F. L. Carnahan and C. D. Hurd, *ibid.*, **52**, 4586 (1930); (d) *cf.* also the paper by C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, **22**, 1418 (1957), which appeared while our paper was in press.

prepared only in low yields, is obtained conveniently and in 75–80% yields by the alkenylation of aniline with allyl chloride in non-polar solvents, under the conditions which favor C-alkenylation in phenols.[4] Hickinbottom[5] obtained *p*-crotylaniline, N-crotylaniline and less than 1% of 2,3-dimethylindole in the reaction of aniline with butadiene in the presence of aniline hydrochloride at 230–260°. N-Crotylaniline was prepared also by Arbuzov[6] in the reaction of 2-phenyl-3,6-dihydro-1,2,2H-oxazine with sodium in ethanol, and by Danforth[7] in the reaction of aniline with butadiene and sodium at 120°. Infrared spectra and hydrogenation to N-*n*-butylaniline indicate that the N-butenylaniline prepared by a modification of Danforth's method is predominantly N-crotylaniline. The analogous reaction of aniline with isoprene yields N-pentenylaniline.

When N-crotylaniline, I, was refluxed with polyphosphoric acid, 2,3-dimethylindole and a liquid amine, $C_{10}H_{13}N$, were isolated in *ca.* 32% yield each. The liquid amine was characterized by a benzenesulfonamide melting at 101–103° which differs from the benzenesulfonamide, m.p. 70–71°, of the 2,3-dimethylindoline prepared by the action of zinc dust and acid on dimethylindole.[8] The liquid amine contains two C-methyl groups, and is readily converted to 2,3-dimethylindole by the action of chloranil.[9] Thus, the liquid product is a 2,3-dimethylindoline which differs from the product of the zinc and acid reduction of 2,3-dimethylindole.

The formation of 2,3-dimethylindole and just one of the 2,3-dimethylindolines is of interest for at least two reasons. One is that we may be dealing with a *proton-catalyzed Claisen-type* rearrangement of N-crotylaniline,[10] the driving force being the resonance stabilization of the rearranged ion III; in the anilinium ion II the charge cannot be distributed by resonance.





IIIa IIIb IIIc IIId

The second point of interest is the isolation of only one of the indolines, suggesting that the other isomer may have been selectively, stereospecifically dehydrogenated. If, as seems plausible, the *trans* isomer is the form obtained by metal–acid reduction,[8] and this is also the precursor of the 2,3-dimethylindole obtained here, then we are dealing with a *concerted, acid-catalyzed trans-elimination* of an α- and a β-hydrogen.[11]

This hypothesis explaining the isolation of only one 2,3-dimethylindoline postulates the dehydrogenation of the *trans*-2,3-dimethylindoline present in the reaction mixture. Because of electron availability, the salt would be more difficult to oxidize, and the conversion of the indoline cation to that of the indole would be thermodynamically more difficult because the indoline is a much stronger base than the indole.

Experimental

N-Allylaniline.—To a stirred and cooled mixture of 227 g. (10 moles) of sodium sand, 1000 cc. of toluene and 932 g. (10 moles) of aniline, a solution of 765 g. (10 moles) of allyl chloride in 500 cc. of toluene was added slowly. The reaction is somewhat exothermic and the reaction temperature was kept below 25°. The mixture was stirred at room temperature overnight and then refluxed for 7 hours. Methanol and water were then added, and the washed organic layer was fractionated through a 20″ Stedman column. The product (407 g., 77% based on unrecovered aniline) is a colorless oil, b.p. 68–70° (1.3 mm.), $n^{25}{}_{D}$ 1.5614, $d^{25}{}_{25}$ 0.9737.

Its toluenesulfonamide[3c] melts at 69°; the benzenesulfonamide forms needles from aqueous ethanol, m.p. 82–83°.

Anal. Calcd. for $C_{15}H_{15}NSO_2$: C, 65.94; H, 5.49. Found: C, 66.15; H, 5.42.

N-Allylacetanilide (acetic anhydride, sulfuric acid) forms needles from water, m.p. 46–47°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.43; H, 7.43. Found: C, 75.31; H, 7.53.

N-Crotylaniline.—A mixture of 448 g. (4.7 moles) of aniline, 334 g. (6.2 moles) of butadiene and 20 g. (0.87 moles) of sodium was heated in an autoclave at 120° for 18 hours. Methanol and water were added, and the washed organic layer was distilled *in vacuo* to yield 370 g. (79% based on unrecovered aniline) of N-crotylaniline, b.p. 81–82° at 1.7 mm.; $n^{25}{}_{D}$ 1.5553; $d^{25}{}_{25}$ 0.9607; λ^{EtOH}_{max} 249 mμ (log *e* 4.10); 295 mμ (log *e* 3.30); λ^{EtOH}_{min} 273 mμ (log *e* 3.0). The infrared spectrum in CS_2 shows a strong band at 10.4 μ indicative of a *trans* disubstituted double bond, RCH=CHR′.

N-Butylaniline.—Hydrogenation of N-crotylaniline (methanol, Adams platinum oxide catalyst, 60 p.s.i.) quantitatively yielded N-*n*-butylaniline, b.p. 235–237°, $n^{25}{}_{D}$ 1.5310, the infrared spectrum of which was identical with that of authentic N-*n*-butylaniline.

N-Pentenylaniline.—A mixture of 450 g. (4.7 moles) of aniline, 350 g. (5.1 moles) of isoprene and 20 g. of sodium similarly heated at 120° yielded N-pentenylaniline (216 g.), b.p. 94–95° at 1.7 mm., $n^{25}{}_{D}$ 1.5502, $d^{25}{}_{25}$ 0.9507. The product's infrared spectrum shows a pronounced band at 11.22 μ ($R_1R_2C{=}CH_2$) and weaker bands at 11.6 and 12.35 μ ($R_1CH{=}CR_2R_3$) suggesting that the product is largely VI perhaps accompanied by some VII.

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(4) L. Claisen and E. Tietze, *Ber.*, **59B**, 2344 (1926).

(5) W. J. Hickinbottom, *J. Chem. Soc.*, 1981 (1934).

(6) Y. A. Arbuzov, *Doklady Akad. Nauk, S.S.S.R.*, **63**, 531 (1948).

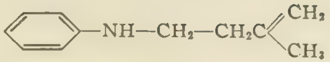
(7) J. Danforth, U. S. Patent 2,495,890 (Jan. 1950).

(8) A. Steche, *Ann.*, **242**, 371 (1887).

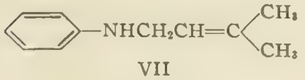
(9) P. L. Julian and H. C. Printy, THIS JOURNAL, **71**, 3206 (1949).

(10) For acid catalysis of the Claisen rearrangement, see W. Gerrard, M. F. Lappert and H. B. Silver, *Proc. Chem. Soc.*, 19 (1957).

(11) For a stereospecific amine dehydrogenation involving however nitrogen and an α-hydrogen, *cf.* F. L. Weisenborn and P. A. Diassi, THIS JOURNAL, **78**, 2022 (1956).



VI



VII

Anal. Calcd. for $C_{11}H_{15}N$: C, 81.93; H, 9.38. Found: C, 82.20, 82.10; H, 9.37, 9.50.

Reaction of Aniline with Butadiene at Higher Temperatures.—When aniline, butadiene and sodium are heated to a higher temperature, small quantities of N,N′-diphenylformamidine surprisingly are formed also. Thus, when a mixture of aniline (448 g., 4.7 moles), butadiene (358 g., 6.63 moles) and sodium (20 g., 0.87 moles) was heated at 170–190° for 18 hours, 4.2 g. of diphenylformamidine, m.p. 136–137° after crystallization from aqueous ethanol, was isolated by fractional distillation. The material (λ_{max}^{EtOH} 282 mμ, log *e* 4.34; λ_{min} 240.5 mμ, log *e* 371) was identified by analysis and mixed melting point with authentic diphenylformamidine.[12]

Under similar conditions, (a) 100 g. of N-crotylaniline and 5 g. of sodium, (b) 29 g. of N-crotylaniline, 19 g. of aniline and 3 g. of sodium, (c) 19 g. of aniline, 15 g. of butadiene and 8 g. of sodium hydroxide, (d) 29 g. of N-crotylaniline, 19 g. of aniline and 8 g. of sodium hydroxide, and (e) 28 g. of N-crotylaniline, 18 g. of aniline, 4 g. of sodium hydroxide and 2 g. of sodium yielded no detectable diphenylformamidine.

The reaction of equimolar quantities of N-crotylaniline and potassium hydroxide at 220° for six hours yielded largely aniline, characterized through its benzenesulfonamide, and an insoluble black solid.

2,3-Dimethylindole and *cis*-2,3-Dimethylindoline.—A mixture of N-crotylaniline (100 g. 0.67 mole) and polyphosphoric acid (50 g.) was refluxed with stirring under inert gas for seven hours. The two phase mixture was hydrolyzed with 20% aqueous potassium hydroxide, and the product was extracted with ether, washed and fractionally distilled *in vacuo* to yield three fractions: A, b.p. 50–70° at 2 mm., 8 g.; B, b.p. 72–76° at 2 mm., 32 g., and C, b.p. 150–165° at 12 mm., 32 g. Fraction A, n^{25}D 1.5802 consisted largely of aniline characterized by its benzenesulfonamide, m.p. 111–112°. Fraction B, n^{25}D 1.5513, boiled sharply at 74° at 2 mm. on redistillation.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.63; H, 8.84. Found: C, 81.62, 81.76; H, 8.94, 9.04. Kuhn-Roth C-methyl, calcd. for one C-methyl group: 10.2%. Found: 12.0%. λ_{max}^{EtOH} 242.5 mμ (log *e* 3.80); 294 mμ (log *e* 3.36); λ_{min} 272 mμ (log *e* 3.05).

Fraction B, *cis*-2,3-dimethylindoline, was characterized by its benzenesulfonamide which crystallized in needles from aqueous ethanol, m.p. 101–103°.

Anal. Calcd. for $C_{16}H_{17}NSO_2$: C, 66.87; H, 5.96. Found: C, 66.93, 67.00; H, 5.88, 5.72.

The infrared spectrum of *trans*-2,3-dimethylindoline,[8] b.p. 107–109° at 12 mm., differs from that of the *cis* isomer, and the *trans* isomer was characterized by a benzenesulfonamide melting at 70–71°.

Anal. Calcd. for $C_{16}H_{17}NSO_2$: N, 4.88. Found: N, 5.31, 5.28.

cis-2,3-Dimethylindoline was recovered unchanged after refluxing with polyphosphoric acid for 4 hours. Fraction C crystallized in the receiver, m.p. 103–104° after recrystallization from heptane.

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.71; H, 7.64; N, 9.65. Found: C, 82.76; H, 7.59; N, 9.65. λ_{max}^{EtOH} 228.5 mμ (log *e* 4.50); 284 mμ (log *e* 3.84); 292 mμ (inflection, log *e* 3.79); λ_{min} 248 mμ (log *e* 3.27).

Its picrate[13] forms red needles from ethanol, m.p. 156–157°; its addition compound with picryl chloride[14] crystallizes in brown needles from ethanol, m.p. 135–136°.

Reaction of *cis*-2,3-Dimethylindoline with Chloranil.[9]—A mixture of *cis*-2,3-dimethylindoline (1 g.), xylene (50 cc.) and chloranil (2 g.) was refluxed for 4 hours, filtered, freed of solvent and the residue dissolved in ether. The ethereal solution was dried after extraction with dilute aqueous hydrochloric acid to remove the more strongly basic indoline, and distilled to yield 0.37 g. (38%) of 2,3-dimethylindole.

Acknowledgment.—We wish to thank Professors M. G. Ettlinger and C. D. Hurd for valuable advice.

MILWAUKEE, WISCONSIN
CAMBRIDGE, MASSACHUSETTS

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[12] W. Weith, *Ber.*, **9**, 457 (1876).

[13] L. Wolff, *ibid.*, **21**, 125 (1888).

[14] M. Padoa and C. Chiaves, *Gazz. chim. ital.*, **38I**, 236 (1908).

[Reprinted from the Journal of the American Chemical Society, **79**, 6164 (1957).]

Unsaturated Phenols. IV. Crotylphenols

By Alfred R. Bader

[Reprinted from the Journal of the American Chemical Society, **79**, 6164 (1957).]

[Contribution from the Laboratories of the Pittsburgh Plate Glass Co. and the Aldrich Chemical Co.]

Unsaturated Phenols. IV.[1] Crotylphenols

By Alfred R. Bader[2]

Received June 20, 1957

Butadiene reacts with phenol in the presence of some Friedel-Crafts catalysts to yield largely a mixture of butenylphenols, with some higher phenols and ethers. *o*- and *p*-crotylphenol have been characterized. A correlation between the acidity functions of acid actalysts and their activity is discussed.

Although the synthesis of compounds related to the tocopherols has prompted studies of the reactions of phenols, specifically hydroquinones, with butadiene,[3] isoprene,[4] 2,3-dimethylbutadiene[4] and phytadiene,[5] the reaction of the simplest phenol with the simplest diene has been described only briefly. A patent[6] has alleged that *p*-crotylphenol is the major component of the monoalkenylphenolic fraction formed in 36% yield in the high temperature reaction of phenol with butadiene catalyzed by solid phosphoric acid.[7] Proell[8] has described the reaction of butadiene with phenol catalyzed by alkanesulfonic acid yielding a mixture of butenylphenols. Claisen[9] had previously described the preparation of chromans from phenol and dienes such as isoprene, and the preparation of pentenylphenols from these reactants under milder conditions has been studied by Pines and Vesely.[10]

The reaction of phenol with 1,3-butadiene at

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(1) For paper III, see This Journal, **78**, 1709 (1956).

(2) Aldrich Chemical Co., Milwaukee 12, Wisconsin.

(3) L. I. Smith and J. A. King, This Journal, **63**, 1887 (1941).

(4) L. F. Fieser, W. P. Campbell, E. M. Fry and M. D. Gates, *ibid.*, **61**, 3216 (1939).

(5) L. E. Smith, H. E. Ungnade, H. H. Hoehn and S. Wawzonek, *J. Org. Chem.*, **4**, 311 (1939).

(6) R. E. Schaad, U. S. Patent 2,283,465 (May, 1942).

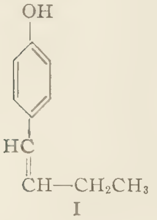
(7) V. N. Ipatieff, U. S. Patents 1,993,512 and 1,993,513 (March, 1935).

(8) W. Proell, *J. Org. Chem.*, **16**, 178 (1951).

(9) L. Claisen, *Ber.*, **54**, 200 (1921); German Patent 374,142 (April, 1923).

(10) H. Pines and J. A. Vesely, U. S. Patents 2,553,470 and 2,578,206 (May and December, 1951). Details of the reaction of phenol with isoprene will be described in paper V of this series.

room temperature in the presence of relatively mild Friedel–Crafts catalysts yields largely butenylphenols accompanied by only small amounts of ethers and higher phenols. Fractionation of the butylphenols obtained on hydrogenation showed the presence of *o*- and *p*-*n*-butylphenols, identified by physical constants and solid derivatives. Thus the possible structures for the original reaction products are *p*-1-butenylphenol (I), *p*-crotylphenol (II), *p*-3-butenylphenol (III) and the three corresponding *o*-substituted isomers. The absence of conjugated isomers such as I was shown by ultraviolet spectra and infrared spectra of the mixed butenylphenols and of cuts obtained by fractional distillation indicated the presence mainly of *o*- and *p*-crotylphenol.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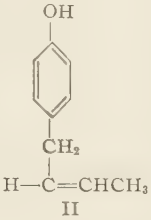
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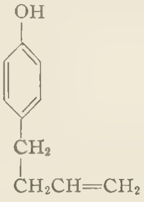
III

Low temperature crystallizations of the highest boiling butenylphenol fraction yielded a crystalline solid, m.p. 39°, the infrared spectrum of which shows a strong band at 10.35 μ, indicative of a symmetrically disubstituted *trans* double bond and no bands at 10.1–10.2 and 11.0 μ, characteristic of the vinyl group $RCH{=}CH_2$.[11] The spectrum of this crystalline isomer also shows an intense band at 12.1 and no absorption at 13.3 μ, and this evidence for *p*-substitution is in accord with this isomer's quantitative hydrogenation to the known[12] *p*-*n*-butylphenol. Assignment of structure II to this solid isomer was confirmed by its ultraviolet spectrum and by its isomerization by palladized charcoal to the conjugated isomer I, m.p. 85–86°.[1]

Fractionation of the non-crystallizable monobutenylphenols boiling over a 20° range and examination of the fractions' infrared spectra showed that the intensities of the band at 12.1 μ increased and those of the band at 13.3 μ decreased with increasing b.p., indicating increasing ratios of *p*-butenylphenols in the higher b.p. fractions. The presence of *o*-crotylphenol in an intermediate fraction was confirmed by the preparation of its phenylurethan melting at 65–66°, identical with the derivative of authentic *o*-crotylphenol.[13]

When titanium tetrachloride, alkanesulfonic acids or the aluminum chloride solvates were the catalysts, the non-crystallizable butenylphenol fractions showed no bands at 10.25 and 10.95 μ, whereas weak bands were present at those wave lengths in the spectra of the butenylphenols obtained with the other catalysts. Theoretically, *n*-butenylphenols with terminal unsaturation as in III are improbable as products of alkenylation,[14] and the weak bands at 10.25 and 10.95 μ may be caused by small amounts of methallyl- or *cis*-crotylphenols.[15]

Butadiene is less reactive than cyclopentadiene, and 85% phosphoric acid, the preferred[14] catalyst for the cycloalkenylation of phenol at 25°, is ineffective with butadiene at that temperature. As has been pointed out by Price,[16] only few direct comparisons of the relative activities of Friedel–Crafts catalysts are recorded in the literature. The composition of the products of the reaction of butadiene with phenol varies greatly with different catalysts, and it seemed of interest to compare the activities of a number of catalysts in this reaction. Comparison is complicated by the involvement of two reactions in the formation of 1:1 adducts, *i.e.*, the alkenylation and the acid-catalyzed ring closure of the *o*-isomer[17] and by further reactions of the alkenylphenols by oxidation and condensation.

Axe[18] has implied that the complex prepared by *saturating* phosphoric acid with boron fluoride, which is an effective catalyst in the butenylation of benzene, also can be used in the alkenylation of phenol. Actually, the use of this as of other strong Friedel–Crafts catalysts such as aluminum chloride and concentrated sulfuric acid leads almost exclusively to ethers and resinous products. The saturated BF_3–phosphoric acid catalyst diluted with an equal weight of 85% phosphoric acid is, however, one of the catalysts of choice; with it or with a mixture of phosphoric and sulfuric acids the mixed butenylphenols are accompanied by only small amounts of ethers and higher phenols. Aqueous sulfuric acid, titanium tetrachloride, alkanesulfonic acids,[8] arenesulfonic acids, aluminum chloride alcoholate and etherate and mixtures of polyphosphoric acid and phosphoric acid also catalyze the mono-butenylation at 15–25°.

The reaction temperature and the catalyst composition direct the orientation. With the complex of phosphoric acid and boron fluoride or with alkanesulfonic acids, *p*-substitution predominates at 15–25°, whereas II constitutes only 30% of the mono-butenylphenols when aqueous sulfuric acid is used at that temperature. This dependence of the product composition on the negative ion associated with the carbonium ion suggests that alkenylations do not involve simply the electrophilic attack on phenol of the diene's free, resonant carbonium ion.

The ranges of composition of the effective cat-

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[11] (a) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1412 (1948); (b) N. Sheppard and G. Sutherland, *Proc. Roy. Soc.* (*London*), **A196**, 195 (1949); (c) D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, 915 (1950).

[12] E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 265.

[13] L. Claisen and E. Tietze, *Ber.*, **59B**, 2351 (1926).

[14] A. R. Bader, THIS JOURNAL, **75**, 5967 (1953).

[15] H. Pines, B. Kvetinskas, J. A. Vesely and E. Baclawski, *ibid.*, **73**, 5173 (1951), have claimed on the basis of infrared spectra and hydrogenation to 2-*n*-butylthiophene that the products of the reaction of thiophene with butadiene are 2-(3-butenyl)-thiophene and 2-crotylthiophene. The evidence for the presence of the former was two bands at 910 and 970 cm.$^{-1}$, thought to be indicative of a vinyl group. However, the band at 970 cm.$^{-1}$ (10.3 μ) is at too long a wave length to be indicative of a vinyl group which never absorbs even in allylic substitution products[11c] and in 2-vinylthiophene with a conjugated, possibly perturbed group at more than 10.2 μ. Perhaps the lower boiling butenylthiophene is 2-*cis*-crotylthiophene.

[16] C. C. Price in R. Adams, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 2.

[17] See D. S. Tarbell, *ibid.*, Vol. II, pp. 18, 27.

[18] W. N. Axe, U. S. Patent 2,471,922 (May, 1949).

alyst mixtures are quite narrow, particularly with sulfuric acid (68–70% at 15–25°). Except for aqueous sulfuric acid, the acid catalysts effective for the mono-butenylation at room temperature have acidity functions[19] H_0 of *ca.* −6 to −7, corresponding to 77–83% aqueous sulfuric acid. It may be that but for its oxidizing action, say, 80% aqueous sulfuric acid would be the optimum concentration, and that 68–70% is the highest concentration not causing oxidation of the α-methylene group and the lowest catalyzing the alkenylation.[20] Once one effective catalyst is known in a given reaction, the determination of its acidity function appears helpful in suggesting the most convenient catalyst of similar H_0 to be tried.

Weaker catalysts such as 85% phosphoric acid become effective at higher temperatures; the resulting products contain largely *o*-substituted phenols. The reaction at 200° following the procedure of Schaad[6] yielded only a small amount of mixed mono-butenylphenols from which no *p*-crotylphenol could be isolated. The infrared spectrum of the mixture suggested that it consisted largely of *o*-substituted phenols.

Experimental

Butenylphenols.—To a stirred and cooled mixture of 940 g. (10 moles) of phenol, 1000 cc. of toluene, 100 g. of the complex prepared by saturating[21] 85% phosphoric acid with gaseous boron fluoride and 100 g. of 85% phosphoric acid, there was added slowly a cold solution of 270 g. (5 moles) of butadiene in 1000 cc. of toluene. The reaction was slightly exothermic, and the stirred mixture, which became faintly yellow, was kept at room temperature for 16 hr. It was then diluted with water, the toluene solution was washed and the solvent, unreacted phenol and a small amount of ethers removed by distillation *in vacuo*. The main fraction (659 g., 89%), b.p. 53–90° (0.1 mm.), $n^{25}D$ 1.539, $\lambda_{max}^{EtOH-0.1\%\ HOAc}$ 225 mμ ($\log \epsilon$ 3.9) and 279 mμ ($\log \epsilon$ 3.3), mixed butenylphenols, was a colorless oil, completely soluble in aqueous alkali. The yellow flask residue consisted of dibutenylphenols and higher phenols and ethers.

The mixed butenylphenols (180 g.) were fractionated through a 10″ column into 5 fractions: A, 5 g., b.p. 53–55° (0.1 mm.), $n^{25}D$ 1.5377; B, 25 g., b.p. 55–60° (0.1 mm.), $n^{25}D$ 1.5380; C, 28 g., b.p. 60–63° (0.1 mm.), $n^{25}D$ 1.5385; D, 8 g., b.p. 63–69° (0.1 mm.), $n^{25}D$ 1.5390; and E, 9 g., b.p. 69–72° (0.1 mm.), $n^{25}D$ 1.5385; their infrared spectra are in accord with those of two-component mixtures, progressing steadily from A (strong band at 13.3 μ, mostly *o*-crotylphenol) to E (strong band at 12.1 μ, mostly *p*-crotylphenol). The colorless flask residue (103 g.) crystallized in the ice-box; two low temperature crystallizations from ligroin yielded 75 g. of soft needles, m.p. 39°, of **p-crotylphenol (II)**; $\lambda_{max}^{EtOH-0.1\%\ HOAc}$ 225 mμ ($\log \epsilon$ 3.99), 279 mμ ($\log \epsilon$ 3.29); λ_{min} 215 mμ ($\log \epsilon$ 3.84), 247.5 mμ ($\log \epsilon$ 2.10).

Anal.[22] Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found, mixed mono-phenols: C, 81.06; H, 8.04. Found, fraction C: C, 80.82; H, 8.25. Found, II: C, 81.22, 81.07; H, 8.37, 8.19.

The solid isomer, II, was characterized by a ***p*-nitrophenylurethan** which formed white needles from aqueous methanol, m.p. 139–140°, and by a **phenoxyacetic acid** which after two crystallizations from water melted sharply at 80°.

Anal. Calcd. for $C_{17}H_{16}O_4N_2$: C, 65.37; H, 5.16. Found: C, 65.30; H, 5.50. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.85; H, 6.90.

The exothermic reaction of the mixed sodium butenylphenoxides with chloroacetic acid yields a mixture of aryloxyacetic acids, of which one is easily separated through its insolubility in ligroin. Ultraviolet and infrared spectra suggested this to be *o*-**crotylphenoxyacetic acid** which crystallized from water in soft, white needles, m.p. 137°; $\lambda_{max}^{EtOH-0.1\%\ HOAc}$ 215.0 mμ ($\log \epsilon$ 3.94), 271.5 mμ ($\log \epsilon$ 3.24), 277.5 mμ ($\log \epsilon$ 3.20); λ_{min} 242.5 mμ ($\log \epsilon$ 2.28), 275 mμ ($\log \epsilon$ 3.17). Its infrared spectrum in Nujol mull showed a strong band at 10.3 μ, probably indicative of a *trans* double bond, RCH=CHR′.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.45; H, 7.04.

Reaction of fraction B with phenyl isocyanate gave a good yield of a crystalline phenylurethan which crystallized in fine needles from methanol, m.p. 65–66°, identical with *o*-crotylphenyl phenylcarbamate.[18]

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.18; H, 6.19.

Hydrogenation of II (methanol, Adams platinum oxide catalyst, 100°) quantitatively yielded ***p*-*n*-butylphenol**,[12] m.p. 20–21°, $n^{25}D$ 1.5176, characterized by a phenoxyacetic acid, m.p. 80–81°.

Hydrogenation of the mixed butenylphenols (50 g.) yielded mixed *n*-butylphenols (50 g.), $n^{25}D$ 1.517, which fractional distillation separated into 15 g. of *o*-*n*-butylphenol, b.p. 94–97° (8 mm.), $n^{25}D$ 1.518, characterized by a crystalline phenoxyacetic acid[23] (crystallized from ligroin), m.p. 104–105°; and 24 g. of *p*-*n*-butylphenol, b.p. 113–116° (8 mm.), $n^{25}D$ 1.518, characterized as above.

A small quantity of ethers (3–6%) is formed in this room temperature reaction; these distil with unreacted phenol and can be separated by their insolubility in alkali. Their boiling range (205–225°) and the physical constants of the higher b.p. fraction (b.p. 220–225°, $n^{25}D$ 1.530, d^{25}_{25} 1.020) suggest that these ethers are a mixture of 2-ethylcoumaran and 2-methylchroman.[24]

The second catalyst of choice is a mixture of 85% phosphoric acid and concd. sulfuric acid. Adding a cooled solution of butadiene (60 g., 1.1 moles) in toluene (100 cc.) to a stirred mixture of phenol (94 g., 1 mole), toluene (100 cc.), 85% phosphoric acid (100 g.) and sulfuric acid (sp. gr. 1.84, 15 g.) and keeping the stirred mixture at 15–25° for 16 hr. yielded 115 g. (0.78 mole, 78%) of mixed butenylphenols a colorless oil, b.p. 80–120° (1.5 mm.), $n^{25}D$ 1.5385. The infrared spectrum of this mixture was similar to that of the mixed butenylphenols prepared with boron fluoride and phosphoric acid, and crystalline II was isolated from the higher b.p. fraction.

With 68% aqueous sulfuric acid and equimolar amounts of phenol and butadiene at 15°, the yield of mono-butenylphenols is 70%. Fractional distillation showed these to consist of *ca.* 60% *o*-crotylphenol and 30% of the crystalline isomer II.

The reactions catalyzed by boron fluoride, by the complex of phosphoric acid saturated with boron fluoride, by concd. sulfuric acid and by aluminum chloride are very exothermic and lead largely to higher phenols and ethers. Fair yields of butenylphenols are obtainable with polyphosphoric acid or, preferably, with mixtures of polyphosphoric acid and 85% phosphoric acid (2:1), titanium tetrachloride arenesulfonic acids and the aluminum chloride–alcohol and –ether complexes. Again, crystalline II was isolated by low temperature crystallizations from heptane from all mixed butenylphenols. Also, the higher b.p. liquid butenylphenol prepared by the procedure of Proell[8] crystallized at once on cooling and proved identical with II.

Zinc chloride and 85% phosphoric acid are inactive at 10–40°. Phosphoric acid (85%) becomes effective at 100–125°; at 140° the bulk of the product consists of ethers and higher phenols. Comparison of spectra showed that the maximum at 13.3 μ was more than that at 12.1 μ somewhat less intense than the corresponding maxima in the infrared spectra of mixed mono-butenylphenols prepared at lower temperatures, indicating somewhat more *p*-substitution in the latter.

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(19) L. P. Hammett and A. J. Deyrup, THIS JOURNAL, **54**, 2721 (1932); L. P. Hammett and M. A. Paul, *ibid.*, **56**, 827 (1934). I am much indebted to Mr. John E. Hyre for the determination of the acidity functions of the catalysts.

(20) I wish to thank Professor Paul D. Bartlett for this suggestion.

(21) 85% sirupy phosphoric acid exothermically absorbs approx its weight of boron fluoride.

(22) Analyses by the Micro-Tech Laboratories, Skokie, Ill.

(23) G. Sandulescu and A. Girard, *Bull. soc. chim.*, [4] **47**, 1300 (1930).

(24) C. D. Hurd and W. A. Hoffman, *J. Org. Chem.*, **5**, 212 (1940); W. Baker and J. Walker, *J. Chem. Soc.*, 646 (1935).

From the product of the reaction described by Schaad[9] (77 g. of phenol, 20 g. of butadiene, 25 g. of U.O.P. polymerization catalyst #2, 200°, 4 hr.), there was obtained besides much unreacted phenol, 11 g. of a phenolic fraction, A, b.p. 65–130° (1 mm.), $n^{25}\mathrm{D}$ 1.540; and 30 g. of dark, resinous material. The spectrum of A showed a strong band at 13.3 μ characteristic of *o*-substitution, only a weak band at 12.1 μ and no band at 10.35–10.40 μ, the position of one of the strongest bands of II, indicative of a symmetrically disubstituted *trans* double bond.

Acidity Functions.[10]—With anthraquinone as the Hammett indicator, the alkanesulfonic acid and polyphosphoric acid and the mixtures of 85% phosphoric acid and sulfuric acid and of polyphosphoric acid and phosphoric acid used as catalysts at 15–25° show acidity functions H_0 ranging from −6 to −7. The H_0 of 68–70% aqueous sulfuric acid is −5.0 to −5.2.

***p*-1-Butenylphenol (I).**—A mixture of 90 g. of II and 5 g. of 5% palladium-on-charcoal (Baker and Co., lot #785, activity 985) was refluxed under inert gas for 25 minutes when the reaction temperature had risen to 260°. The product was dissolved in ligroin and filtered, the solvent removed and the red, viscous oil (86 g.) distilled to yield a first fraction A (46 g.), b.p. 80–150° (0.5 mm.); a second fraction B (19 g.), b.p. 150–210° (0.5 mm.); and an orange resinous residue (18 g.). Crystallization of A from heptane yielded 5.5 g. of shiny, white platelets of the less soluble isomer I, identical with the compound prepared by alkali isomerization[1] of II. The infrared spectra of I and II in carbon disulfide are quite similar, except that I exhibits an intense band at 11.8 μ absent in the spectrum of II. The heptane mother liquor from I yielded 40 g. of unreacted II. Fraction B consisted largely of a colorless dimeric diphenol, b.p. 187–190° (0.4 mm.), which was accompanied by a fiery red impurity.

Anal. Calcd. $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.79; H, 8.13.

Butenylanisoles.—Anisole reacts much like phenol at 10–30°; mixed butenylanisoles were prepared in good yields with concd. sulfuric acid and with a 2:1 mixture of polyphosphoric acid and 85% phosphoric acid; b.p. 75–110° (10 mm.), $n^{25}\mathrm{D}$ 1.519, strong bands at 12.1 and 13.3 μ, indicating *o*- and *p*-substitution.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.87; H, 9.00.

Acknowledgment.—I wish to thank Professors M. G. Ettlinger and C. D. Hurd for valuable advice.

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Unsaturated Phenols. V. The Reaction of Isoprene with Phenol

By Alfred R. Bader and William C. Bean

[Reprinted from the Journal of the American Chemical Society, **80**, 3073 (1958).]

[Contribution from the Laboratories of the Aldrich Chemical Co. and the Pittsburgh Plate Glass Co.]

Unsaturated Phenols. V. The Reaction of Isoprene with Phenol[1]

By Alfred R. Bader and William C. Bean

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The reaction of isoprene with phenol, catalyzed by phosphoric acid, yields the *o*- and *p*-3-methylcrotylphenols IV and V, the γ-hydroxyisoamylphenols II and VIII, and the two chromans I and IX.

The reactions of isoprene with phenol have been studied briefly by Claisen[2] and by Pines and Vesely.[3] Claisen obtained 2,2-dimethylchroman (I) which proved identical with the ether synthesized by ring closure of the tertiary alcohol II prepared by the action of methylmagnesium iodide on ethyl dihydrocoumarate. Pines and Vesely, who used the alcohol and ether complexes of stannic chloride, and the ether complex of 85% phosphoric acid to prepare pentenylphenols, considered condensation to take place between phenol and the tertiary double bond of isoprene, but beyond that did not elaborate on the structures of the alkenylphenols formed. In the alkylation of phenol by the reso-

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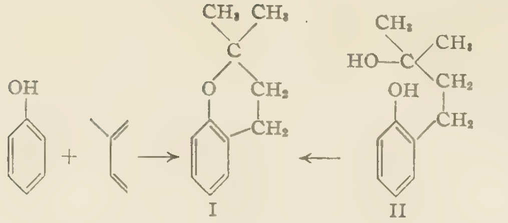
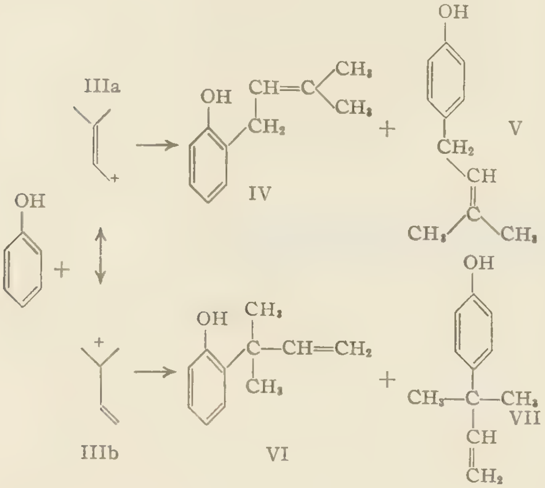
[1] For paper IV, see This Journal, **79**, 6164 (1957).

[2] L. Claisen, *Ber.*, **54B**, 200 (1921); German Patent 374,142 (Dec., 1920).

[3] H. Pines and J. A. Vesely, U. S. Patents 2,553,470 and 2,578,206 (May and Dec., 1951).

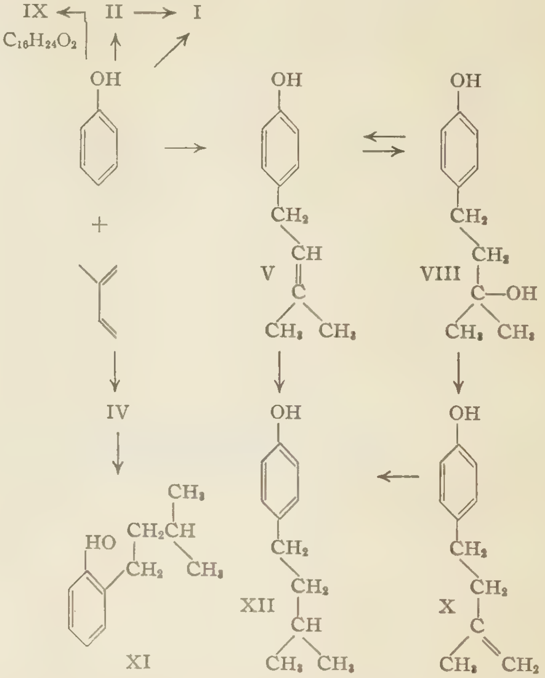


nant carbonium ion III one would *a priori* consider IV, V, VI and VII as possible products. However, alkenylations with butadiene,[1,4–6] isoprene[5,7,8] and 2,3-dimethylbutadiene[7] have shown that the products from the alkenylations with conjugated dienes are derived from that resonance hybrid of the carbonium ion which is *spatially most accessible;* compounds containing the crotyl, 3-methylcrotyl and 2,3-dimethylcrotyl groups are the predominant products in the alkenylations with butadiene, isoprene and 2,3-dimethylbutadiene respectively.



From the reaction of phenol with isoprene catalyzed by 71% phosphoric acid[9] at 20°, we obtained six products. The phenolic fraction yielded the 3-methylcrotylphenols IV and V and the crystalline tertiary alcohols II and VIII: the ethereal fraction consisted of 2,2-dimethylchroman I and an alcohol IX, $C_{16}H_{24}O_2$, melting at 51–52°.

That the pentenylphenols $C_{11}H_{14}O$ have structures IV and V rather than VI and VII was proved by (i) the hydrogenation of V to a *p*-amylphenol, m.p. 27–29°, different from the known *p-t*-amylphenol[10] melting at 94–95°; (ii) the infrared spectra of IV and V which did not contain bands at 910 and 990 cm.$^{-1}$ characteristic of —CH=CH_2[11]; and (iii) the alkali isomerizations[12] of IV and V to the corresponding conjugated phenols. Compounds such as VI and VII would not be expected to isomerize in alkali.



The 3-methylcrotylphenols IV and V prepared in these alkenylations could not be obtained crystalline. The *p*-isomer V, however, was easily characterized by its 2,6-bishydroxymethyl derivative, m.p. 110–111°, and the reaction of *p*-substituted phenols with formaldehyde appears to be one of the easiest means of characterization. Table I lists a number of similar dimethylol derivatives prepared. When V was treated with methanolic potassium hydroxide under the relatively mild conditions required to isomerize *o*-allyl- to *o*-propenylphenol, V remained non-conjugated, but the quite homogeneous phenol recovered crystallized easily, melted at 9–11°, and was characterized by the same bishydroxymethyl derivative melting at 110–111°. Apparently V is accompanied in the alkenylation by small amounts of an isomeric product, perhaps X, which prevents the crystallization of V, and which becomes isomerized to V in alkali.

The crystalline alcohol VIII, m.p. 134–135°, can be prepared also by the hydration of V, and is isolated particularly easily from the other products of the alkenylation because it is the only product sparingly soluble in toluene. The *o*-isomer II, m.p. 112°, had been prepared previously by Claisen[2]; its identity was proved by cyclization to I.

The dehydration of VIII yields one of two products, depending on conditions. In the presence of acid or iodine the predominant product is V characterized by its spectrum and bishydroxymethyl derivative. When, however, VIII is heated at atmospheric pressure without catalysts, dehy-

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(4) L. I. Smith and J. A. King, THIS JOURNAL, **63**, 1887 (1941).

(5) H. Pines, B. Kvetinskas, J. A. Vesely and E. Baclawski, *ibid.*, **73**, 5173 (1951).

(6) W. Proell, *J. Org. Chem.*, **16**, 178 (1951).

(7) L. F. Fieser, W. P. Campbell, E. M. Fry and M. D. Gates, THIS JOURNAL, **61**, 2559, 3216 (1939).

(8) L. I. Smith, H. W. Ungnade, H. H. Hoehn and S. Wawzonek, *J. Org. Chem.*, **4**, 311 (1939).

(9) For a method to determine the most convenient catalyst concentration by means of Hammett indicators, *cf.* paper IV.

(10) R. C. Huston and T. Y. Hsieh, THIS JOURNAL, **58**, 439 (1936).

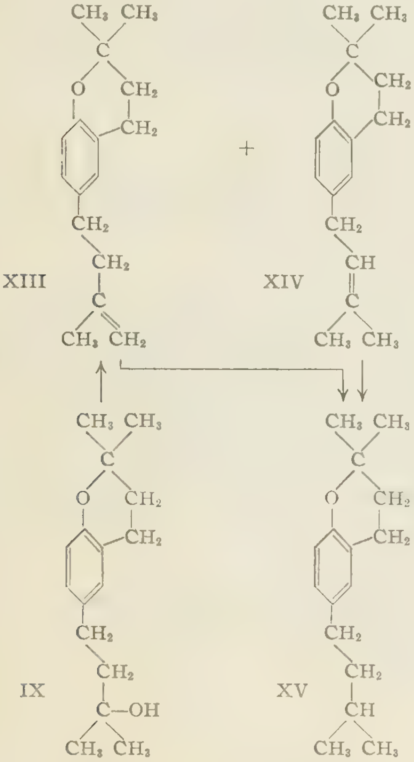
(11) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1412 (1948).

(12) A. R. Bader, THIS JOURNAL, **78**, 1709 (1956).

dration also occurs to a pentenylphenol melting at 9–12°. This product, however, depresses the m.p. of V, shows in the infrared a strong band at *ca.* 11.3 μ absent in the spectrum of V and characteristic of a double bond $RR'C{=}CH_2$,[11] cannot be characterized by a crystalline bishydroxymethyl derivative, and is assigned structure X.

The unsaturated phenols IV, V and X are easily hydrogenated to the isoamylphenols XI and XII melting at 12–14° and 27–29°, respectively. Such alkylphenols containing α-methylene groups are difficult to prepare by Friedel–Crafts reactions with alcohols, halides or alkenes, but are made conveniently by hydrogenation of the products of alkenylations with dienes.

The ether IX, $C_{16}H_{24}O_2$, is dehydrated easily either by heat or with 85% phosphoric acid at 25°, to yield the unsaturated ether XIII perhaps accompanied by some XIV. The infrared spectrum of IX in carbon disulfide shows a hydroxyl band at *ca.* 2.8 μ and a strong band at 12.2 μ characteristic of a substituted benzene ring bearing two adjacent hydrogen atoms. The spectrum of the dehydration product shows besides the band at 12.2 μ also a strong band at 11.25 μ characteristic of disubstituted terminal unsaturation. Hydrogenation of the unsaturated ether yields the chroman XV melting at 19–20°.



Experimental

Reaction of Isoprene with Phenol.—Preliminary experiments showed that 71% aqueous phosphoric acid corresponds in catalyst strength to the complexes used by Pines and Vesely,[8] and yields the same products. A cooled mixture of 125 g. (1.3 moles) of phenol, 90 g. (1.3 moles) of isoprene, 230 g. of toluene and 130 g. of 71% aqueous phosphoric acid was stirred at 20° for 16 hours. The reaction was somewhat exothermic. The reaction mixture was washed with water, and the toluene was distilled off *in vacuo*, leaving 212 g. of a faintly yellow oil. This mixture (200 g.) was stirred with aqueous potassium hydroxide solution to separate ethers from phenols. The ethers (24 g.) were fractionally distilled to yield 10 g. of **2,2-dimethylchroman** (I),[2] b.p. 224–226°, n^{25}_{D} 1.524, and 10 g. of IX, b.p. 150–152° (0.8 mm.), n^{25}_{D} 1.523; this crystallized slowly on standing and melts at 51–52°; λ_{max}^{EtOH} 220 mμ ($\log \epsilon$ 3.92), 225 mμ (infl., $\log \epsilon$ 3.89), 282 mμ ($\log \epsilon$ 3.40), 291 mμ ($\log \epsilon$ 3.34); λ_{min} 247.5 mμ ($\log \epsilon$ 2.32), 289 mμ ($\log \epsilon$ 3.32).

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.45; H, 9.82.

The phenolic fraction was distilled through a Stedman column to yield 28 g. of phenol; 23 g. of a fraction, b.p. 89–91° (1 mm.), n^{25}_{D} 1.538, largely ***o*-3-methylcrotylphenol** (IV); 3 g. of a mixture of IV and V; 40 g. of a fraction b.p. 104–105° at 1 mm., n^{25}_{D} 1.539, largely ***p*-3-methylcrotylphenol** (V)[13]; and 60 g. of yellow flask residue A; λ_{max}[14] of IV 275 mμ ($\log \epsilon$ 3.36), λ_{min} 242.5 mμ ($\log \epsilon$ 2.10); λ_{max} of V 225 mμ ($\log \epsilon$ 3.96), 279 mμ ($\log \epsilon$ 3.30); λ_{min} 219 mμ ($\log \epsilon$ 3.91), 247.5 mμ ($\log \epsilon$ 2.19).

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.69. Found: IV: C, 81.50; H, 8.97. Found V: C, 81.05; H, 8.36.

The infrared spectrum of IV in CS_2 shows a strong band at 13.3 μ characteristic of *o*-substitution and absent in the spectrum of V which shows a strong band at 12.2 μ characteristic of *p*-substitution and absent in the spectrum of IV. The spectrum of the fraction b.p. 104–105° at 1 mm. (largely V) showed a weak band at *ca.* 11.3 μ. When 30 g. of this fraction was refluxed with 30 g. of potassium hydroxide in methanol at 110° for six hours, no conjugation[12] had occurred, and the recovered phenol's b.p., refractive index and ultraviolet spectrum were identical with those of the starting material. Except for the disappearance of the weak band at *ca.* 11.3 μ, the infrared spectra were also identical. While the alkali-untreated *p*-substituted phenol could not be obtained crystalline, the product recovered from this alkali treatment crystallized in the ice-box and melted at 9–11°.

The *p*-3-methylcrotylphenol (V) (before and after the six-hour treatment with alkali) as well as other *p*-substituted phenols were characterized by their **2,6-bishydroxymethyl derivatives.** These are listed in Table I. A mixture of 4 g. of the phenol, 250 mg. of sodium hydroxide, 0.4 cc. of water and 4 g. of 37% formalin solution was let stand for 2 days. Toluene (10 cc.) and glacial acetic acid (3 cc.) were then added, the mixture was cooled thoroughly, and the crystalline product filtered and recrystallized.

A solution of flask residue A in toluene (200 ml.) was cooled, and the white solid, ***p*-(γ-hydroxyisoamyl)-phenol** (VIII) (12 g., m.p. 127–130°) was filtered and crystallized twice from xylene to yield 10 g. of flat needles, m.p. 134–135°; λ_{max} 224 mμ ($\log \epsilon$ 3.83), 279 mμ ($\log \epsilon$ 3.22); λ_{min} 245 mμ ($\log \epsilon$ 1.68).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.48; H, 9.11.

The infrared spectrum of VIII in Nujol showed it to be *p*-substituted. It was characterized by a phenoxyacetic acid which, crystallized from water, melts at 101–102°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.80; H, 7.71.

The alcohol VIII can be obtained simply by diluting the initial reaction mixture with toluene (1:10) and filtering the almost pure VIII which crystallizes on standing.

The mother liquor from VIII was distilled *in vacuo*. The fraction, 30 g., b.p. 145–175° (0.8 mm.), crystallized partially on standing and after four crystallizations from heptane and ethanol yielded 7 g. of ***o*-(γ-hydroxyisoamyl)-**

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(13) In one experiment, W. C. B. obtained a crystalline *p*-substituted pentenylphenol, $C_{11}H_{14}O$ (*Anal.* Found: C, 81.52; H, 8 77) melting after one crystallization from heptane at 86°. Despite many attempts, we were not able to obtain this product again. The infrared spectrum of the compound (2% soln. in CS_2) showed between 10 and 13μ strong bands at 11.05, 11.55, 11.8, 12.25 and 12.45 μ; λ_{max} 217.5 mμ ($\log \epsilon$ 3.75), 222.5 mμ (infl., $\log \epsilon$ 3.71), 282.5 mμ ($\log \epsilon$ 3.48); λ_{min} 245 mμ ($\log \epsilon$ 2.02).

(14) Unless noted otherwise, the solvent in all ultraviolet spectrum determinations was 0.1% acetic acid in ethanol.

TABLE I

2,6-BISHYDROXYMETHYL DERIVATIVES

p-Substituent	Solvent of crystn.	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2-Cyclopentenyl	Toluene	106	$C_{13}H_{16}O_3$	70.89	71.18	7.32	7.56
Crotyl	Aq. methanol	77–78	$C_{12}H_{16}O_3$	69.20	68.84	7.93	7.57
3-Methylcrotyl	Aq. methanol	110–111	$C_{13}H_{18}O_3$	70.24	70.44	8.16	8.27
Isoamyl	Aq. methanol	73–74	$C_{13}H_{20}O_3$	69.61	69.85	8.99	9.13
Crotyl allyl ether[a]	Toluene–heptane	80–81	$C_{15}H_{20}O_3$	72.55	72.59	8.12	8.27

[a] Made by the reaction of the sodium salt of 2,6-bishydroxymethyl-4-crotylphenol with allyl chloride.

phenol (II), m.p. 111–112°, which was characterized by cyclization to I;[2] λ_{max}[15] 274 mμ (log ϵ 3.35), 279 mμ (infl. log ϵ 3.32); λ_{min} 242.5 mμ (log ϵ 3.20).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.06; H, 9.09.

Hydrogenation of V (Adams platinum oxide catalyst, methanol, 80°) quantitatively yielded *p*-isoamylphenol (XII),[16] b.p. 103–105° (1 mm.), n^{25}D 1.514, which crystallized in the ice-box, m.p. 27–29°.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 79.99; H, 10.19.

Similar hydrogenation of IV yielded **o-isoamylphenol** (XI), b.p. 85–86° (0.5 mm.), n^{25}D 1.510, which crystallized in the ice-box, m.p. 12–14°.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.03; H, 10.10.

The phenol XI was characterized by a *p*-nitrophenylurethan which was crystallized from a mixture of heptane and toluene and melts at 90–92°.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: N, 8.53. Found: N, 8.83.

Hydration of V.—Stirring a heptane solution of V with 80% aqueous phosphoric acid at 25° for 4 hours gave a 90% yield of VIII.

Dehydration of VIII.—A mixture of 20 g. of VIII, 400 cc. of xylene and 1 cc. of 85% phosphoric acid was refluxed with water take-off under nitrogen for one hour. The mixture was washed with water and distilled *in vacuo* to yield 16 g. of a phenol, b.p. 101–103° (0.7 mm.), the infrared and ultraviolet spectra of which indicated it to be largely V with some X. This dehydration product was characterized by its 2,6-bishydroxymethyl derivative which melted at 109–110° after several crystallizations, and which did not depress the m.p. of the derivative of pure V.

The tertiary alcohol can also be dehydrated by refluxing its xylene solutions with iodine. A solution of 5 g. of VIII and 50 mg. of iodine in 100 cc. of xylene yielded, after refluxing with water take-off for 6 hours, 1.9 g. of unreacted VIII and 2.1 g. of unsaturated phenol, largely V. With 100 mg. of iodine, there was no unreacted VIII, 2.7 g. of crude V and 1.7 g. of higher boiling products. With larger quantities of iodine, more polymeric products and some conjugated phenols are obtained.

The dehydration of VIII also can be effected simply by refluxing or slow distillation in the absence of catalysts. The product X a colorless liquid, b.p. 107–110° (1.5 mm.), n^{25}D 1.537, crystallizes in the cold, melts at 9–12° and depresses the m.p. of pure V. Hydrogenation of X also yielded XII. It does not form a crystalline 2,6-bishydroxymethyl derivative, and its infrared spectrum in CS_2 shows a strong band at *ca.* 11.3 μ absent in the spectrum of V.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.69. Found: C, 81.04; H, 8.70.

The Dehydration of IX.—Twenty grams of IX was refluxed under nitrogen for 3 hours, and distilled to yield some water and 16 g. of a colorless liquid, XIII perhaps with some XIV, b.p. 112–115° (0.5 mm.), n^{25}D 1.525.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.60. Found: C, 83.07; H, 9.65.

Dehydration to the same product also can be effected by stirring a solution of IX in heptane with 85% phosphoric acid at 25°. Dehydration also takes place when a xylene solution of IX is refluxed with a small amount of 85% phosphoric acid. A molecular rearrangement must take place, however, as the product has a higher refractive index and a substantially different infrared spectrum. Also hydrogenation does not yield the crystalline chroman XV.

6-Isoamyl-2,2-dimethylchroman (XV).—Hydrogenation (Adams platinum oxide catalyst, methanol, 80°) of the unsaturated ether prepared by refluxing IX, or by treating it with phosphoric acid at 25°, yields a colorless liquid, b.p. 119–120° (1.7 mm.), n^{25}D 1.510, which crystallizes on cooling and melts at 19–20°.

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.50; H, 10.31.

Acknowledgment.—We wish to thank Professor Martin G. Ettlinger for helpful advice.

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[15] The maxima at 224–225 mμ present in the spectra of V and VIII are absent in the spectra of the *o*-substituted II and IV.

[16] Z. M. Nazarova, *J. Gen. Chem. U.S.S.R.*, **8**, 1336 (1938); *C. A.*, **33**, 4214 (1939) gives b.p. 245–250°, n^{27}D 1.505.

[Reprinted from the Journal of Medicinal Chemistry, 9, 981 (1966).]

6-Trimethylammoniopurinide

Rainer Klemm, Helmut Schulze, Martin G. Ettlinger, and Alfred R. Bader

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6-Trimethylammoniopurinide[1]

Rainer Klemm, Helmut Schulze, Martin G. Ettlinger,
and Alfred R. Bader

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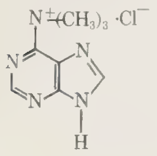
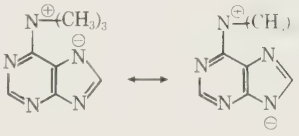
Milwaukee, Wisconsin*

Received August 18, 1966

Current clinical interest[2] in the carcinostatic activity of the antimetabolite 6-purinyltrimethylammonium chloride[3] (I) led us to investigate methods for the purification of this salt. Precipitation of its aqueous solution by organic solvents consistently yielded products low in chlorine.[4] During further study, an aqueous solution of I was passed through an anion-exchange column in its hydroxide form, yielding on evaporation a new substance, mp 190–192°, which was chlorine free and had structure II (see Experimental Section).



I



II etc.

Experimental Section

Purin-6-yltrimethylammonium chloride (**I**) was prepared by the method of Horwitz and Vaitkevicius.[3] Small quantities of crude I were purified by solution in cold water and quick precipitation with acetone; pure I melts at 191–192°.

6-Trimethylammoniopurinide (**II**).—A solution of 170 g of I in 1 l. of water was passed through an ion-exchange column with 1.5 l. of Dowex 1-X8 (hydroxyl form), and the column was then washed thoroughly with water. The combined eluates were then evaporated to dryness *in vacuo* at 50°, and the product crystallized from water and was dried *in vacuo* (P_2O_5) to yield 112 g of II, mp 190–192°.

Anal. Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.30, 54.30; H, 6.03, 6.20; N, 39.18, 39.49.

Structure II is supported by the nmr spectrum[5] in D_2O which shows, besides two equal peaks at 221 and 212 cycles below the signal from solvent protons, only one, much more intense, peak at 59 cycles above solvent reference. The dipolar salt II has the same melting point as 6-dimethylamino-1-methylpurine[6] (III), and the melting points of the respective picrates are also similar. However, the mixture melting point of II and III is depressed, the maximum of the ultraviolet spectrum of II is at much lower wavelength than that of III, and the nmr spectrum of III shows two well-separated methyl group signals. Electrometric titration shows that II is a weak base and the pK_a of the conjugate acid I is 6.8. This value appears reasonable, for purine has $pK_a = 8.9$,[7] and the trimethylammonium group would lower the pK.[8]

Similarly, the ultraviolet spectrum of II appears reasonable [$\lambda_{max}^{H_2O}$ (pH 10) 274 mμ (log ε 3.86)] when compared with that of purine anion[9] [λ_{max} (pH 11) 271 mμ (log ε 3.88)]; the trimethylammonium group, being nonconjugating, would be expected to have little effect. The spectrum of II at pH 1 (that is, of I), with λ_{max} 265 mμ (log ε 3.94), is also close to that of neutral purine [λ_{max} 263 mμ (log ε 3.90)].

Saline solutions of I and II are indistinguishable.

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[1] Alpurine (Trademark applied for).

[2] V. K. Vaitkevicius and M. L. Reed, *Proc. Am. Assoc. Cancer Res.*, **7**, 72 (1966).

[3] J. P. Horwitz and V. K. Vaitkevicius, *Experientia*, **17**, 552 (1961).

[4] Similar material, which can now be construed as a solvated equimolar mixture of I and II, was obtained by E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3274 (1962).

[5] We wish to thank Dr. George Slomp for determining the nmr spectrum of II.

[6] (a) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Am. Chem. Soc.*, **86**, 5320 (1964); (b) B. C. Pal and C. A. Horton, *J. Chem. Soc.*, 400 (1964); (c) we wish to thank Professor R. K. Robins for a sample of III.

[7] A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

[8] H. C. Brown, D. H. McDaniel, and O. Häfliger in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press Inc., New York, N. Y., 1955, p 592.

[9] S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

[Reprinted from the Journal of Organic Chemistry, **30**, 2051 (1965).]

The Oxidation of Dunnione with Alkaline Hydrogen Peroxide

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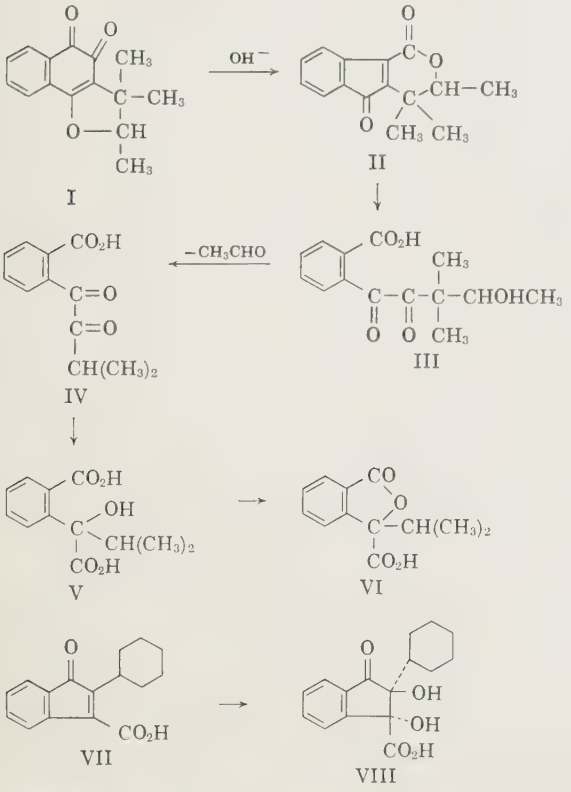
Research Laboratories, Aldrich Chemical Company, Milwaukee, Wisconsin 53210

Received November 5, 1964

Dunnione, the orange-red pigment of *Streptocarpus dunnii* Mast., has been shown by degradation[1,2] and synthesis[3,4] to be the *o*-naphthoquinone I. Treatment of I with alkali yields allodunnione (II) *via* a rearrangement common to all 2-hydroxy-3-alkyl-1,4-naphthoquinones.[5] The oxidation of dunnione and of allodunnione in alkali with hydrogen peroxide yields[1,2] acetaldehyde, phthalic acid, and a white, crystalline acid, $C_{12}H_{12}O_4$, m.p. 205–206°, formulated as the five-membered lactonic acid VI. This acid was presumed to be formed from allodunnione (II) by oxidation and loss of acetaldehyde from III by a reverse aldol condensation, followed by a benzilic acid rearrangement of IV and ring closure of V to VI. The alkaline hydrogen peroxide oxidation of indenonecarboxylic acids similar to allodunnione yields[6] diols such as VIII from VII, and as Price and Robinson[1,2] had not shown the $C_{12}H_{12}O_4$ oxidation product to be lactonic, we reinvestigated this substance.



I

II

III

IV

V

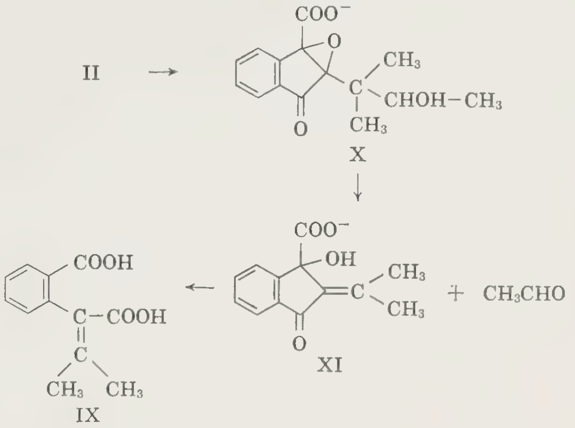
VI

VII

VIII

Following the published procedure[1] for the oxidation of natural dunnione, we obtained the crystalline acid, the infrared spectrum of which has its carbonyl absorptions between 5.9 and 6.0 μ, thus excluding VI for the structure of this oxidation product. This appeared to be a dicarboxylic acid and comparison with the known[7] α-isopropylidenehomophthalic acid (IX) by mixture melting point and by ultraviolet and infrared spectra established their identity. The structure of IX was confirmed by n.m.r. spectra of the acid and its dimethyl ester.

Presumably the oxidations of allodunnione and VII proceed *via* the epoxides, but while the epoxide of VII is simply hydrolyzed to the diol, the epoxide X more easily cleaves to acetaldehyde and XI. Such cleavages of derivatives of 1,3-diols are well known.[8] The formation[8d] of merolimonol from limonol appears particularly like the present example.



Paths for the oxidation of XI to IX can be written either by way of 2-isopropyl-1,3-indandione and V or through diverse rearrangements of known type,[9] some involving ring contraction to benzocyclobutenes. The degradation is certainly interesting, but since evidence is lacking, we refrain from further details of possible mechanisms.

Experimental

The oxidation of natural dunnione exactly as described[1] yields a crystalline, optically inactive solid, the melting point of which varies somewhat with the rate of heating from 205 to 215°; λ_{max}^{MeOH} 204 mμ (log ε 4.40) and 278 mμ (log ε 3.18).

α-Isopropylidenehomophthalic acid[7] made *via* its monomethyl ester, m.p. 141°, has infrared and ultraviolet spectra superimposable on those of the oxidation product. The melting point of a mixture is not depressed.

Proton magnetic resonance spectra for the isopropylidenehomophthalic acid were kindly obtained by Mr. H. E. Miller at Rice University with a Varian A-60 spectrometer (60 Mc.). The acid dissolved with sodium carbonate in deuterium oxide showed only a multiplet from aryl hydrogen atoms centered

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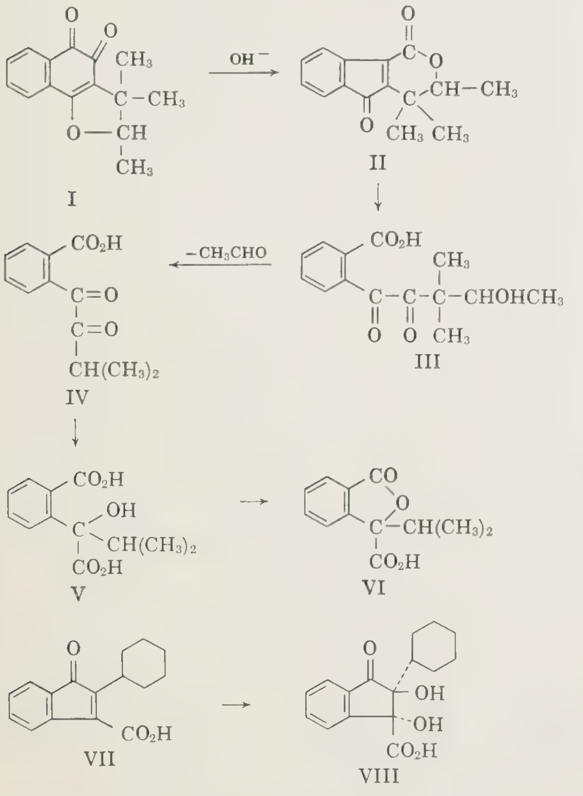

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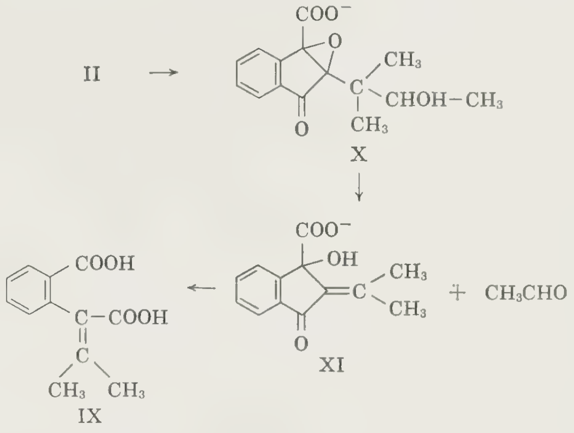

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[Reprinted from the Journal of Organic Chemistry, **28**, 2057 (1963).]

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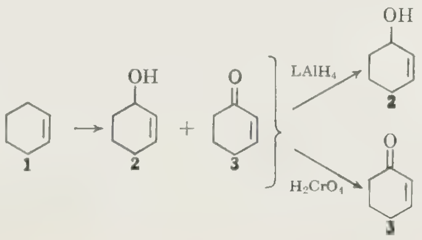
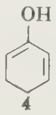
A re-examination of the oxidation of cyclohexene (**1**) with hydrogen peroxide–vanadium pentoxide (HP–VP, peroxyvanadic acid) revealed 2-cyclohexen-1-ol (**2**) to be a major reaction product. This contradicts an earlier report[2] claiming exclusive formation of 2-cyclohexen-1-one (**3**) as the volatile product. Similar oxidative experiments with the isomeric methylcyclohexenes (**7**, **13**, and **17**) demonstrate the reaction to be essentially nonselective as to site of oxidation and that both alcohols and ketones appear in the volatile products, these being a mixture of direct oxidation products and products derived from allylic shifts.

Treibs[2] and co-workers claimed 2-cyclohexen-1-ol (**2**) to be absent from the products of the oxidation of cyclohexene (**1**) with HP–VP and 2-cyclohexen-1-one (**3**) was reported to be the exclusive low boiling product (40% yield). *trans*-1,2-Cyclohexanediol (**6**) and adipic acid were reported as higher boiling products (9% yield for both). These authors considered 2-cyclohexen-1-one (**3**) to be present in part as the enol **4** to account for the formation of a borate ester.

We have demonstrated that 2-cyclohexen-1-ol (2)





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[1] (a) Presented before the Organic Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.; (b) Department of Chemistry, Oklahoma State University, Stillwater, Okla.; (c) Heidenheimer Chemisches Laboratorium, Heidenheim an der Brenz, Germany.

[2] W. Treibs, G. Franke, G. Leichsenring, and H. Roder, *Ber.*, **86**, 616 (1953).

is a major product of the oxidation of cyclohexene with HP–VP, and that it actually exceeds 2-cyclohexen-1-one (**3**) in the product mixture by a ratio of 2.3:1. The oxidation was repreated several times according to the published procedure,[2] and each experiment gave essentially the same product boiling at 61–63° (14 mm.) in reasonable agreement with the reported value. However, gas chromatographic studies show the presence of two sharply defined and completely separated peaks. The mixture of volatile products shows a maximum $\lambda_{\max}^{\text{EtOH}}$ 225 mμ (ε 3905) while the reported[3] maximum for **3** is 225 mμ (ε 11,270). Strong hydroxyl group absorption was noted in the infrared spectrum of the mixture. These data suggested the mixture to be **2** and **3**. Attempts to separate the mixture by fractional distillation through a spiral column and by preferential reaction with semicarbazide hydrochloride were ineffective. Accordingly, the products were directly interconverted and the identity of the components established through isolation of the individual pure compounds by oxidation to **3** and reduction to **2**.

A Jones' oxidation[4] with chromic acid in acetone solution readily converted the entire mixture to **3**. The course of the reaction was followed conveniently with gas chromatographic analyses at regular intervals. The peak of the gas chromatogram of the reaction product at termination of the oxidation coincides exactly with the smaller and second peak of the chromatogram of the original mixture. The oxidation product was identified as **3** through its ultraviolet spectrum, in agreement with Woodward's rules,[5] its ininfrared spectrum, and the melting point of its red 2,4-dinitrophenylhydrazone.[6] Other syntheses of **3**, each by a different procedure, have been reported.[7]

Reduction of the original volatile oxidation mixture with lithium aluminum hydride in ether solution gave a single product. This product shows no carbonyl band in its infrared spectrum but shows strong absorption in the hydroxyl and double bond regions. These data and the melting point of the phenylurethane derivative,[6] 107–109°, established the identity of the product as 2-cyclohexen-1-ol (**2**).

A reconstituted mixture (70% **2** and 30% **3**) prepared from pure **2** and **3** gives essentially identical spectra (ultraviolet and infrared) and gas chromatographic curve as those from the original mixture obtained by oxidizing cyclohexene with HP–VP.

Pure 2-cyclohexen-1-ol (**2**) was oxidized with HP–VP under the same conditions used for the oxidation of cyclohexene. The steam volatile products from this reaction were shown through gas chromatographic analyses to be a mixture of **2** and **3** in a ratio of 7.3:1. This experiment suggests **2** to be one of the precursors of **3**.

Several routes may exist for the formation of the various products obtained from the oxidation of cyclohexene with HP–VP. 2-Cyclohexen-1-ol (**2**) and 2-cyclohexen-1-one (**3**) may be rationalized as being formed from cyclohexene hydroperoxide by the indicated routes in Fig. 1. *trans*-1,2-Cyclohexanediol (**6**) may arise from cleavage of cyclohexene oxide which has been reported along with **2** as a product of the bimolecular epoxidation of cyclohexene by cyclohexene hydroperoxide.[8,9]

cis-1,2-Cyclohexanediol (**5**) and adipic acid are formed by direct oxidation of the double bond of cyclohexene. We suggest that peroxyvanadic acid, $H_3[V(O_2)O_3]$,[10] attacks the double bond of cyclohexene to form a cyclic ester of peroxyvanadic acid in a reaction reminiscent of the osmic ester formation of olefins.[11,12] The cyclic ester may then be hydrolyzed to *cis*-1,2-cyclohexanediol (**5**) or undergo cleavage to adipic aldehyde in the manner of periodate oxidation of 1,2-glycols.[13] The aldehyde is oxidized in turn to adipic acid. This rationalization suggested the possible presence of some *cis*-1,2-cyclohexanediol (**5**) in the reaction products. The diol **5** is not formed as a major product but we were able to establish its presence through gas chromatographic studies by enrichment of the crude reaction product with authentic *cis*-diol **5**. The diols **5** and **6** are present in the crude reaction product in the ratio of 1:15. The presence of the *trans*-diol **6** was established readily through gas chromatographic studies and direct isolation from the reaction products. Distillation and recrystallization afforded a pure sample of the diol **6** which shows no depression in melting point on admixture with authentic *trans*-1,2-cyclohexanediol (**6**). The proposed routes permit accumulation of *trans*-diol **6** with simultaneous formation of adipic acid.

Milas[14] reported that the HP–VP oxidation of cyclohexene in *t*-butyl alcohol gives a small amount of *cis*-1,2-cyclohexanediol (**5**), an unidentified aldehyde, and considerable quantities of adipic acid. This suggests that it may be possible to control selectively direct attack on the double bond over allylic attack by altering the reaction conditions.

An interesting parallel to the HP–VP oxidation of cyclohexene is provided by the work of Farmer and Moore.[15] These investigators demonstrated that both 2-cyclohexen-1-ol (**2**) and 2-cyclohexen-1-one (**3**) are formed (ratio 6:1) when cyclohexene (**1**) is oxidized with *t*-butyl hydroperoxide at 140°. These authors also demonstrated that oxidation of 1-methyl-1-cyclohexene (**7**) with *t*-butyl hydroperoxide yielded both ketones and alcohols among the products and that all possible allylic positions except on the methyl group were attacked. This is to be expected for a nonselective oxidation process and was rationalized through a free radical mechanism with a hydroperoxide and an olefin radical as intermediates.

The effect of change in concentration of hydrogen peroxide on the composition of the products from the oxidation of cyclohexene was studied with gas chromatography. We found an increase of hydrogen peroxide

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[3] H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953).

[4] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

[5] R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).

[6] F. C. Whitmore and G. W. Pedlow, Jr., *ibid.*, **63**, 758 (1941).

[7] For a reference list of other preparations of 2-cyclohexen-1-one, see K. I. Williamson, R. T. Keller, G. S. Fonken, J. Szmuszkovicz, and W. S Johnson, *J. Org. Chem.*, **27**, 1612 (1962).

[8] R. Criegee, H. Pilz, and H. Flygare, *Ber.*, **72**, 1799 (1939).

[9] E. H. Farmer and A. Sundralingam, *J. Chem. Soc.*, 121 (1942).

[10] N. V. Sidgwick, "Chemical Elements and Their Compounds," Vol. 1, Oxford University Press, New York, N. Y., 1950, p. 810.

[11] R. Criegee, *Ann.*, **522**, 75 (1936).

[12] N. A. Milas and S. Sussmann, *J. Am. Chem. Soc.*, **58**, 1302 (1936).

[13] E. L. Jackson, "Organic Reactions," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 341.

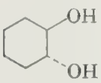
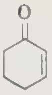
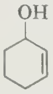
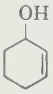
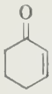
[14] N. A. Milas, *J. Am. Chem. Soc.*, **59**, 2342 (1937).

[15] E. H. Farmer and C. G. Moore, *J. Chem. Soc.*, 149 (1951).

concentration from 1/6 to 1/3 and 1/2 mole caused an increase in yield of **2** and **3**. However, additional increase of hydrogen peroxide failed to increase the yield, and not all the peroxide was consumed during the reaction. The results of these studies on 1/6, 1/3, and 1/2 mole of hydrogen peroxide per mole of cyclohexene are presented in Table I. Thus, the maximum yields of the mixture of **2** and **3** may be obtained with the 1/2 mole ratio.

TABLE I[a]

SUMMARY OF CYCLOHEXENE OXIDATIONS WITH HYDROGEN PEROXIDE

Moles of hydrogen peroxide per mole cyclohexene	Ratio of peak areas					Ratio		
		:		:			:	
1/6	1		1.9		3.2	1.7		
1/3	1		2.8		5.0	1.8		
1/2	1		3.0		4.1	1.3		

[a] These data are the average of two analyses.

To account for formation of a borate ester Treibs,[2] *et al.*, stated that 2-cyclohexen-1-one (**3**) exists in part as the enol **4**. In our hands, pure 2-cyclohexen-1-one (**3**) failed to give significant yields of borate ester since major portions of unchanged boric acid and 2-cyclohexen-1-one (**3**) were recovered (84 and 67%, respectively). We were, however, able to isolate a low yield (3.2%) of 2-cyclohexen-1-one (**3**) by steam distilling the pot residue after unchanged **3** had been distilled at 25–35° (0.05 mm.). To isolate **3** from the pot residue suggests that some **3** may have reacted with boric acid through the enol **4**. However, under identical conditions, 2-cyclohexene-1-ol reacted completely with boric acid, and a 78% yield of borate ester was isolated.

The HP–VP oxidations of each of the methylcyclohexenes (**7**, **13**, and **17**) in acetone were studied to determine whether the methyl substituent has any steric effect or directive influence on the site of the oxidation and, hence, the isomer composition. The gas chromatogram of the reaction products from 1-methyl-1-cyclohexene (**7**) showed seven *major* components of which five have been identified by successive enrichment with authentic products. The identified products from the oxidation of 1-methyl-1-cyclohexene (**7**) are **8**–**12** (see Table II).

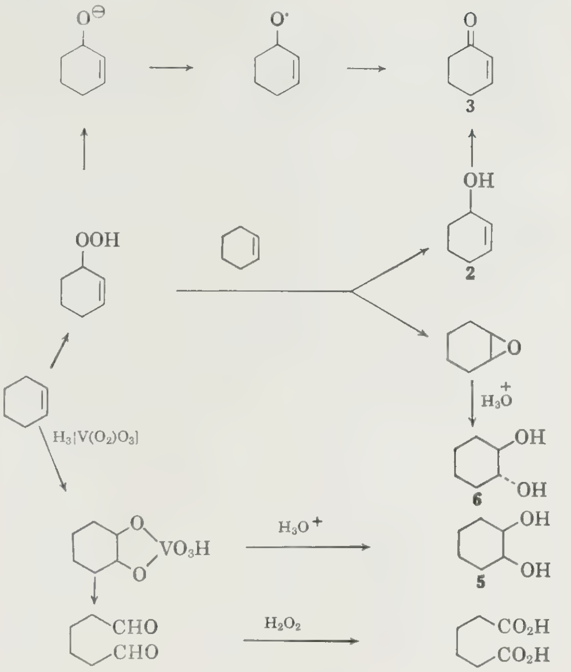
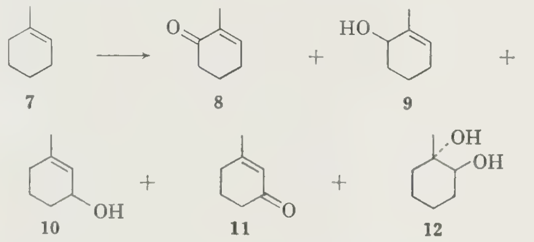


Figure 1



Reduction of the reaction mixture containing **8**, **9**, **10**, **11**, and **12** with lithium aluminum hydride caused

TABLE II

GAS CHROMATOGRAPHIC ANALYSES OF HP–VP–METHYLCYCLOHEXENE OXIDATION PRODUCTS

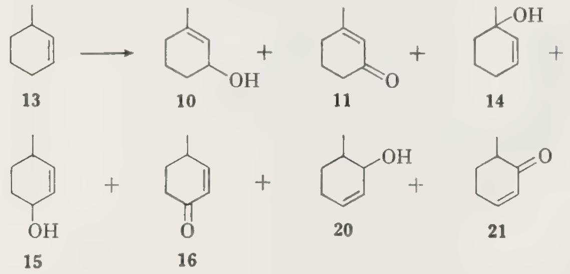
Starting material	Moles of hydrogen peroxide per mole of methylcyclohexene	Column	Oxidation products (time of emergence in min.; relative area)							
7	1/6	Carbowax[a]	Unknown alc.	Unknown ketone (2.8; 1.6)	**8** (5.9; 1)	**9** (8; 3.2)	**10** (8.8; shoulder)	**11** (12; 1.6)	**12** (22.2; 6.6)	
7	1/6	PDEAS[b]	Unknown (2.1; 1.2)	**10** (3.2; 1)	**9** (4.5; 3.3)	**8** (5.4; 1.2)	**11** (12.2; 1.4)	**12** (24.8; 10.7)		
13	1/6	PDEAS[c]	Unknown alc. (1.0; 1.3)	**14** (2.1; 3.3)	**20** (3.2; 5.7)	**15** (5.0; 3.2)	**10** (6.2; 6.3)	**21** (6.5; shoulder)	**16** (8.0; 1.0)	**11** (15; 2.1)
17	1/6	PDEAS[d]	Unknown (5.5; 1.4)	**20** (6.1; 5.3)	Unknown (6.7; shoulder)	**18** (7.0; 2.9)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 2.8)		
17	1/3	PDEAS[d]	Unknown (5.5; 0.7)	**20** (6.1; 2.8)	Unknown (6.7; shoulder)	**18** (7.0; 1.2)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 4.0)		
17	1/2	PDEAS[d]	Unknown (5.5; 0.5)	**20** (6.1; 3.6)	Unknown (6.7; shoulder)	**18** (7.0; 1.5)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 4.2)		

[a] 10% Carbowax 20M on alkaline firebrick; 1/4 in. × 5 ft.; temperature programmed from 130–200°; helium flow, 80 ml./min. [b] 15% PDEAS on acid-washed firebrick; 1/4 in. × 5 ft.; 140°; [c] Same as *b*, except 135°. [d] 15% PDEAS on acid-washed firebrick; 1/4 in. × 4 m.; 160°; helium flow, 65 ml./min. [e] From PDEAS the alcohol **10** emerges with the ketone **21**; these can, however, be separated on Carbowax at 115°. A quantitative estimation is, however, difficult because **21** polymerizes on the alkaline support.

disappearance of **8** and **11**, and an increase of **9** and **10**; this latter compound is present as a minor component in the crude oxidation product. Oxidation of the mixture containing **8**, **9**, **10**, and **11** with Jones' reagent in acetone solution[4] caused disappearance of **9** and **10** with simultaneous increase of **8** and **11**.

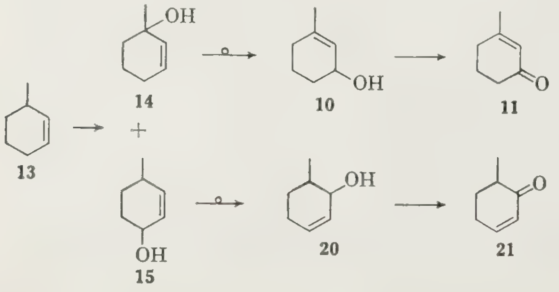
1-Methyl-1-cyclohexene (**7**) was oxidized with chromium trioxide in acetic acid, according to the method of Whitmore and Pedlow,[6] to determine whether this closely related reaction gives the reported mixture of 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexen-1-one (**11**) in the ratio of 1:9.6. We obtained a ratio of 1:7.8. Gas chromatographic analyses also showed the presence of five additional, minor products.

3-Methyl-1-cyclohexene (**13**) was oxidized with the HP–VP oxidant, and the crude product steam distilled to minimize high boiling products (presumed to be diols). These were observed as six minor peaks appearing late in the gas chromatogram. The gas chromatogram of the steam-distilled mixture showed eight peaks, of which seven have been identified (see Table II). The presence of the expected oxidation products **14**, **15**, and **16** from **13** was established by gas chromatographic studies of samples successively enriched with authentic materials.

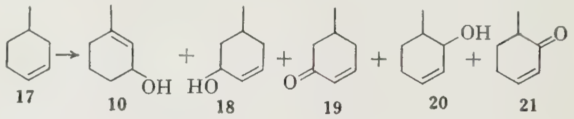


The identities of the remaining peaks were established in a circuitous manner. The total mixture was oxidized with Jones' reagent to a mixture of three ketones with gas chromatography peaks in the ratio 1.0:1.7:3.0. These peaks were shown to be due to ketones **21**, **16**, and **11** in this order, by collecting the ketones in a 2,4-dinitrophenylhydrazine solution as they emerged from the column. The 2,4-dinitrophenylhydrazones were recrystallized and melted at 147–151°, 164–165°, and 176–178°, respectively. An admixture with authentic 2,4-dinitrophenylhydrazones showed no depression in melting point. The presence of the alcohols **10** and **20** was then shown in the HP–VP oxidation mixture by enrichment with authentic materials.

The presence of the abnormal oxidation products **10**, **11**, **20**, and **21** among the expected allylic oxidation products suggested that allylic rearrangement takes place during the HP–VP oxidation of 3-methyl-1-cyclohexene (**13**). The products **10**, **11**, **20**, and **21** are presumed to form as shown (bottom, col. 1).



4-Methyl-1-cyclohexene (**17**) was oxidized similarly and five of the seven major steam-volatile products were identified by enrichment of the product mixture with authentic materials (see Table II). The presence of the unexpected alcohol **10** was confirmed by oxidizing the mixture with Jones' reagent, and showing the presence of **11** in the product by enrichment with authentic **11** in gas chromatographic studies, and by isolating the 2,4-dinitrophenylhydrazone of **11** as it emerged from the column.



While **13** yields both the normal oxidation products, **15** and **16**, and the products of the allylic shift, **20** and **21**, we were unable to detect **15** and **16**, the corresponding products produced by allylic shift accompanying **18** and **19** in the oxidation of **17**.

Experimental

Starting Materials.—The cyclohexene (**1**) used for the HP–VP oxidation was homogenous by gas chromatography (Ucon Polar column at 40°). 1-Methyl-1-cyclohexene (**7**), b.p. 110.3°, showed a single gas chromatographic peak (Ucon Polar column at 50°). 3-Methyl-1-cyclohexene (**13**), b.p. 102.5°, was obtained by fractional distillation from a mixture of 1-methyl-1-cyclohexene (**7**) and 3-methyl-1-cyclohexene (**13**). The gas chromatographic curve (200-ft. squalane capillary column at 26°, hydrogen flame detector) of the fractionated 3-methyl-1-cyclohexene showed 3-methyl-1-cyclohexene (**13**) to be 99% pure. Under these conditions 3-methyl-1-cyclohexene (**13**) and 4-methyl-1-cyclohexene (**17**) showed separation. 4-Methyl-1-cyclohexene (**17**), b.p. 102.7°, was shown to be 99% pure through the same gas chromatographic procedure as described for 3-methyl-1-cyclohexene.

Oxidations with HP–VP.[2] **(a) Cyclohexene, $^1/_6$ Mole Hydrogen Peroxide.**—To an 8-l. vessel equipped with stirrer, condenser, and dropping funnel were added 500 g. (6.1 moles) of cyclohexene (**1**) and 5.0 l. of acetone. To the well stirred mixture was added the catalyst prepared by mixing 20 ml. of 30% hydrogen peroxide and 2.0 g. of vanadium pentoxide at 5–10° and diluting with 200 ml. of precooled (−10°) acetone. The catalyst mixture was filtered as rapidly as possible so that the temperature did not rise above −2° during preparation. The flask was cooled in a water bath and 100 ml. (*ca.* 1 mole total) of 30% hydrogen peroxide was added to the agitated mixture over about 30 min. The reaction was maintained at 30°. After about 10 ml. of hydrogen peroxide was added, the color changed from orange to green. If the color change did not take place, an additional 5.0 ml. of hydrogen peroxide was added. The mixture was stirred an additional hour and then allowed to stand overnight. The reaction mixture was then held at reflux for 1 hr. with stirring and checked for hydrogen peroxide with titanium sulfate solution (if hydrogen peroxide was present, more cyclohexene was added and the reaction held at reflux for an additional hour). If peroxide was absent, acetone and excess cyclohexene were distilled (4 to 4.5 l.), the distillate diluted with water, and about 100 g. of cyclohexene was recovered from the water-insoluble layer. The residue was dried over anhydrous sodium sulfate, filtered, and distilled at 61–63° (14 mm.) to give 42–45 g. of a mixture of 2-cyclohexen-ol (**2**) and 2-cyclohexen-1-one (**3**). Gas chromatographic studies on 15% phenyldiethanolamine succinate (PDEAS) substrate supported on a column of 60–80-mesh acid-washed firebrick ($^1/_4$ in. × 5 ft.) showed the presence of two sharply defined, completely separated peaks (2 min. at 140°; 80 ml. helium/min.; Wilkens Model A-90P, thermal conductivity detector). A cleaner product containing less impurities in the gas chromatogram was obtained if the crude product was steam distilled before final distillation. The distilled product gave $\lambda_{\max}^{\mathrm{EtOH}}$ 225 mμ (ϵ 3905)[16]; $\lambda_{\max}^{\mathrm{CS_2}}$ 3.0 and 5.95 μ.

(b) **Cyclohexene, $^{1}/_{3}$ Mole Hydrogen Peroxide and** (c) **Cyclohexene, $^{1}/_{2}$ Mole Hydrogen Peroxide.**—These oxidations were carried out essentially as described for part a. The yield of product boiling at 61–64° (14 mm.) was 63–65 g. for $^{1}/_{3}$ mole and 78–80 g. for $^{1}/_{2}$ mole. Gas chromatographic data on parts a, b, and c are summarized in Table I and described as part of the Jones' oxidation procedure.

(d) **1-Methyl-1-cyclohexene** (**7**).—The oxidation of **7** was similar to part a and was carried out in a 2-l., three-necked flask containing 1 l. of acetone and 96 g. (1 mole) of **7**. The catalyst was prepared from 0.4 g. of vanadium pentoxide and 2 ml. of cold 30% hydrogen peroxide and diluted with 30 ml. of acetone after 2–3 min.; see Table II for gas chromatographic data of the steam-distilled product mixture. 1-Methyl-*trans*-1,2-cyclohexanediol (**12**) crystallized directly from the reaction mixture and was also isolated as a high boiling fraction, b.p. 100° (12 mm.), m.p. 84–86°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.53; H, 10.83. Found: C, 64.51; H, 10.59.

(e) **3-Methyl-1-cyclohexene** (**13**) **and** (f) **4-Methyl-1-cyclohexene** (**17**).—These olefins were oxidized in the same manner as described in part d, and the results are tabulated in Table II.

Oxidation of 1-Methyl-1-cyclohexene (**7**) **with Chromic Acid.**—1-Methyl-1-cyclohexene (**7**) (96 g. 1.0 mole), was oxidized according to the precedure of Whitmore and Pedlow[6] except that the reaction mixture was steam distilled rather than extracted. The steam distillate was saturated with salt, extracted with ether, the ether dried over anhydrous magnesium sulfate, filtered, and distilled. The distillation residue was directly injected onto a $^{1}/_{4}$ in. × 5 ft. gas chromatographic column containing 15% PDEAS on 60–80-mesh acid-washed firebrick. Flow rate was 80 ml. helium/min. and column temperature was 140°. Two major peaks in the ratio of 1:7.8 were observed. These were established as 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexene-1-one (**11**) by successively enriching the reaction product with authentic ketones **8** and **11** and analyzing by gas chromatography.

Jones' Oxidations[4] of the Reaction Products from HP–VP Oxidations. (a) **Crude Mixture of 2-Cyclohexen-1-ol** (**2**) **and 3-Cyclohexen-1-one** (**3**).—The crude reaction product from the oxidation of cyclohexene with HP–VP[2] was steam distilled, the steam distillate saturated with salt, extracted with ether, the ether layer dried over anhydrous magnesium sulfate, filtered, and the ether distilled slowly under water aspirator vacuum. The concentrate (424 g.) was dissolved in 5 l. of redistilled acetone and oxidized by dropwise addition of Jones' reagent[4] to the well stirred solution. The reagent is a mixture of 267 g. of chromium trioxide and 230 ml. of sulfuric acid (Spectro Grade 1.84) made up to 1.0 l. with distilled water.[4] The temperature of the reaction was maintained at 20–30° by cooling in a water bath. Progress of the oxidation (2 hr.) was followed by occasionally withdrawing a 1-ml. sample to which was added about 25 mg. of sodium bicarbonate and the pH checked to ensure neutrality. The sample was shaken; the solution decanted and dried over anhydrous magnesium sulfate. The supernatent liquid was directly injected onto the PDEAS column at 140°. Two peaks were observed before oxidation was begun. As the oxidation proceeded, the second peak grew at the expense of the first peak until at termination only the second peak remained. The orange-yellow end point was maintained for about 10 min. This end point is demonstrated easily with a drop of Jones' reagent in a few mililiters of acetone. A few drops of isopropyl alcohol will consume the excess reagent. The reaction product was decanted and the suspension of green salts rinsed with a few mililiters of acetone. Sodium bicarbonate (50 g.) was added to reaction mixture, suspension filtered, anhydrous magnesium sulfate (500 g.) added, the suspension filtered once more, and the acetone distilled through a Vigreux column. On occasion it was necessary once more to dry the product with anhydrous magnesium sulfate before final distillation. Distillation at 61° (14 mm.) gave 371 g. of 2-cyclohexen-1-one (**3**); $\lambda_{\max}^{\mathrm{EtOH}}$ 224 mμ (ϵ 11,716) and $\lambda_{\max}^{\mathrm{CS_2}}$ 5.95 μ.[16] The red 2,4-dinitrophenylhydrazone was recrystallized from isopropyl alcohol and melts at 166–167°.[3,6]

(b) **Products from 1-Methyl-1-cyclohexene** (**7**).—The crude reaction product obtained from the HP–VP oxidation of 1-methyl-1-cyclohexene (**7**) was steam distilled, the steam distillate saturated with salt, extracted with ether, the ether separated and concentrated by distillation. The concentrate was oxidized with Jones' reagent in a manner similar to part a but on a smaller scale. The oxidation product was isolated by steam distillation, extracted with ether, and the dried ether concentrate injected onto an alkaline Carbowax 20M gas chromatographic column, temperature programmed from 30–200°.

The peaks represented by 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexen-1-one (**11**) were identified by enriching the reaction product sample with authentic materials. The peaks due to the alcohols **9** and **10** were not present in the gas chromatogram.

(c) **Products from 3-Methyl-1-cyclohexene** (**13**).—The Jones' oxidation of the products from HP–VP oxidation of **13** was conducted in the same manner as for part b. The gas chromatogram (PDEAS column at 135°) showed three peaks in the ratio of 1.0: 1.7:3.0. The ketones were collected from the PDEAS column in a 2,4-dinitrophenylhydrazine solution. The resulting red 2,4-dinitrophenylhydrazone derivatives were collected, recrystallized, and found to melt at 147–151°, 164–165°, and 176–178°. Admixtures of these red 2,4-dinitrophenylhydrazones with 2,4-dinitrophenylhydrazones derivatives of authentic 6-methyl-2-cyclohexen-1-one (**21**), 4-methyl-2-cyclohexen-1-one (**16**), and 3-methyl-2-cyclohexene-1-one (**11**), respectively, show no depression in melting point. The ketones from the individual peaks were collected in ether as they emerged from the column and used to identify peaks in the chromatogram of the crude reaction product and as a source for lithium aluminum hydride reduction to obtain the respective alcohols.

(d) **Products from 4-Methyl-1-cyclohexene** (**17**).—The Jones' oxidation of **17** was carried out as in part b. The presence of **11**, which emerged last on the PDEAS column, was shown by enrichment with authentic **11** and by the isolation of its red 2,4-dinitrophenylhydrazone derivative, m.p. 176–178°, which does not depress the melting point of the 2,4-dinitrophenylhydrazone of authentic 3-methyl-2-cyclohexen-1-one (**11**).

Lithium Aluminum Hydride Reductions. (a) **Mixture of 2-Cyclohexen-1-ol** (**2**) **and 2-Cyclohexen-1-one** (**3**).—To a 5-l., three-necked flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel with pressure equalizing side arm, containing 42 g. lithium aluminum hydride dissolved in 3 l. of anhydrous ether, was added a 300-g. sample of a mixture comprised of 37% 2-cyclohexen-1-one (**3**) and 63% 2-cyclohexen-1-ol (**2**) at a rate to maintain gentle reflux. Two hours were required for addition. The reaction mixture was stirred an additional 4 hr. at reflux temperature and water was added dropwise until evolution of gases ceased. The suspension was allowed to settle; the ether solution was decanted and tested with water to ensure complete destruction of lithium aluminum hydride. The suspended salts were rinsed twice with 200-ml. portions of ether and the combined ether solution dried over anhydrous magnesium sulfate, filtered, and ether distilled. The concentrate was distilled at 64–65° (10.5 mm.) to give 240 g. of 2-cyclohexen-1-ol (**2**) whose infrared spectrum showed $\lambda_{\max}^{\mathrm{CS_2}}$ 3.0 and 6.08 μ. The gas chromatogram (PDEAS at 115°) showed a single major peak and no peak corresponding to 2-cyclohexen-1-one (**3**). The phenyl urethane melts at 107–109°.[6]

(b) **Crude Products from 1-Methyl-1-cyclohexene** (**7**).—The crude HP–VP products of 1-methyl-1-cyclohexene (**7**) were reduced with lithium aluminum hydride as described under part a. The products were isolated by steam distillation. The steam distillate was saturated with salt and extracted with ether; the ether layer was separated and washed with small portions of water, dried over anhydrous magnesium sulfate, filtered, and distilled. The concentrate was analyzed with gas chromatography (PDEAS column at 130°). The peaks corresponding to the ketones **8** and **11** were completely absent. The peaks corresponding to the alcohols **9** and **10** were found to have increased.

Borate Ester Preparation. (a) **From 2-Cyclohexen-1-ol** (**2**).—A mixture of 49.0 g. (0.5 mole) of 2-cyclohexene-1-ol (**2**), 8.4 g. (0.136 mole) boric acid, and 100 ml. of dry benzene was heated at reflux temperature for approximately 2 hr. until water–benzene azeotrope (7.0 ml. total) no longer collected in the Dean–Stark separator. The boric acid completely dissolved within a few minutes after reflux was attained. Most of the benzene (75 ml.) was distilled at atmospheric pressure and the product distilled through a short-path Vigreux column at 30–115° (0.04 mm.). The benzene forerun was discarded and the product fractionated

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[16] D. Dusterhoft of Lakeside Laboratories kindly carried out these determinations.

through a spiral column to give 15.8 g. recovered **2** and 32.0 g. (0.133 mole, 78% yield based on boric acid) of colorless boric acid ester, b.p. 133–145° (0.2 mm.). A center cut, b.p. 142–145° (0.2 mm.), was used for analyses and infrared spectrum; $\lambda_{\max}^{\text{neat}}$ 2.95, 6.08, 7.05, 7.24, 7.60, 8.00, 9.60, 9.40, 9.56, 10.42, 10.76, 11.11, and 13.80 μ.

Anal. Calcd. for $C_{18}H_{27}BO_3$: B, 3.57. Found: B, 3.73.

A 14.9-g. (0.049 mole) sample of the borate ester of **2** was steam distilled, the distillate extracted with ether, the ether extract dried over anhydrous magnesium sulfate, filtered, and the ether distilled to give 12.3 g. (85% recovery) of regenerated 2-cyclohexen-1-ol (**2**). The infrared spectrum and gas chromatogram (PDEAS at 140°) were identical with those of original **2**. The contents of the steam distillation reaction flask were colorless.

(b) **From 2-Cyclohexen-1-one (3).**—Under conditions similar to part a, 2-cyclohexen-1-one (**3**) (0.5 mole) and boric acid (0.136 mole) in 100 ml. of benzene gave 2 ml. of water–benzene azeotrope. The dark-colored reaction product was filtered to yield 7.1 g. (84% recovery) of unchanged boric acid. The filtrate was distilled at 25–35° (0.05 mm.) to give 32.1 g. (66% recovery) of 2-cyclohexene-1-one whose gas chromatogram (PDEAS at 125°) and infrared spectrum were identical with those of original ketone **3**.

The dark-colored, viscous pot residue was steam distilled to give 1.6 g. (0.016 mole, 3.2%) of regenerated 2-cyclohexen-1-one (**3**) whose infrared spectrum, gas chromatogram (PDEAS at 125°) and gas chromatogram of an admixture with **3** were identical with 2-cyclohexene-1-one (**3**). A dark-colored tar remained in the steam distillation flask.

Preparation of Comparison Compounds. (a) ***cis*-1,2-Cyclohexanediol (5).**—A sample of a mixture of *cis*-1,2-cyclohexanediol (**5**) and *trans*-1,2-cyclohexanediol (**6**) was separated by gas chromatography on PDEAS at 162° and collected in ethyl acetate. The retention times were 11.5 and 12.4 min., respectively.

(b) **2-Methyl-2-cyclohexen-1-one (8).**—2-Methyl-2-cyclohexen-1-one (**8**) was obtained by dehydrohalogenation[17] of 2-chloro-2-methylcyclohexanone[18] with lithium bromide and lithium carbonate in dimethylformamide. The ketone **8**, $n^{23}\text{D}$ 1.4852, $\lambda_{\max}^{\text{neat}}$ 6.05 μ, gives a single peak on the PDEAS gas chromatographic column at 145°. Its red 2,4-dinitrophenylhydrazone crystallized from isopropyl alcohol melts at 207–209°.[19]

(c) **2-Methyl-2-cyclohexen-1-ol (9).**—The alcohol **9** was obtained from the ketone **8** *via* lithium aluminum hydride reduction in ether solution followed by steam distillation. The product shows a single gas chromatographic peak on the PDEAS column at 145°.

(d) **3-Methyl-2-cyclohexen-1-ol (10).**—A sample of 3-methyl-2-cyclohexen-1-one (**11**) was reduced with lithium aluminum hydride in ether to give 3-methyl-2-cyclohexen-1-ol (**10**), $n^{23}\text{D}$ 1.4835, b.p. 82–84° (15 mm.,) and $\lambda_{\max}^{\text{neat}}$ 3.07 and 6.08 μ. Gas chromatographic analysis on PDEAS at 140° shows a single peak.

(e) **3-Methyl-2-cyclohexen-1-one (11).**—A 182-g. (1.0 mole) sample of 4-carbethoxy-3-methyl-2-cyclohexen-1-one,[20] $n^{23}\text{D}$ 1.4842, was hydrolyzed by steam distilling from 1 l. of 15% sulfuric acid. The steam distillate was saturated with salt and extracted with ether; the ether layer was washed with water, dried over anhydrous magnesium sulfate, filtered, and distilled to give 87 g. (0.79 mole, 79% yield) of 3-methyl-2-cyclohexene-1-one (**11**), b.p. 80–95° (9 mm.,) $n^{25}\text{D}$ 1.4910, and $\lambda_{\max}^{\text{neat}}$ 6.05 and 6.2 μ. The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate melts at 176–178°.

(f) **1-Methyl-2-cyclohexen-1-ol (14).**—A 24-g. sample (0.25 mole) of 2-cyclohexen-1-one was added to 2 equivalents of methylmagnesium iodide contained in a 1-l., three-necked flask equipped with stirrer, condenser protected with a calcium chloride tube, and dropping funnel. The 2-cyclohexene-1-one was added to the chilled (−5°) reaction flask over a 2-hr. period. The reaction mixture was allowed to come to room temperature and then heated at reflux temperature for 0.5 hr. The reaction mixture was then poured onto 500 g. of ice, and the product was directly steam distilled without addition of ammonium chloride or acid. [It was intentional that acid was avoided to minimize isomerization of 1-methyl-2-cyclohexen-1-ol (**14**) to 3-methyl-2-cyclohexen-1-ol (**10**).] The steam distillate (1 l.) was saturated with salt, extracted with 200 cc. of ether, and washed with two small portions of water; the ether layer separated, dried over anhydrous magnesium sulfate, filtered, and the ether distilled. The concentrate was analyzed with gas chromatography (PDEAS column at 100°) and found to be a mixture of 36% 1-methyl-2-cyclohexen-1-ol (**14**),[6] 58% 3-methylcyclohexanone,[6] and 6% 3-methyl-2-cyclohexen-1-ol (**10**).[6] The 3-methylcyclohexanone and the alcohol **10** were identified by enriching the total reaction product with authentic materials and analyzing by gas chromatography. A pure sample of the alcohol **14** was obtained by collection from the PDEAS column at 125°.

(g) **4-Methyl-2-cyclohexen-1-ol (15).**—The ketone **16** was reduced with lithium aluminum hydride in ether to give 4-methyl-2-cyclohexen-1-ol (**15**) which shows essentially a single gas chromatographic peak; the yield of **15** was 71%.

(h) **4-Methyl-2-cyclohexen-1-one (16).**—A procedure similar to j was employed in the preparation of 4-methyl-2-cyclohexen-1-one (**16**) from 4-methylcyclohexanone. The ketone **16** gave a red 2,4-dinitrophenylhydrazone which melts at 168–169° on recrystallization from isopropyl alcohol.

(i) **5-Methyl-2-cyclohexen-1-ol (18).**—A sample of 5-methyl-2-cyclohexen-1-one (**19**) was purified by gas chromatography on PDEAS, reduced by lithium aluminum hydride, and the product isolated by steam distillation. The product, 5-methyl-2-cyclohexen-1-ol (**18**), shows a single peak on the PDEAS gas chromatographic column.

(j) **5-Methyl-2-cyclohexen-1-one (19).**—A 112-g. sample of *dl*-3-methylcyclohexanone was chlorinated with sulfuryl chloride in carbon tetrachloride solution.[19] The chlorocyclohexanone was distilled at 35–87° (0.1 mm.) and shown by gas chromatography on PDEAS at 170° to contain 3-methylcyclohexanone in the initial cut. Center cuts, b.p. 50–80° (0.1 mm.), were free of 3-methylcyclohexanone but appeared to be a mixture of 2-chloro-3-methylcyclohexanone and 2-chloro-5-methylcyclohexanone since double peaks were observed in the gas chromatogram on PDEAS at 170° column temperature.

Dehydrohalogenation[17] in the presence of lithium bromide and lithium carbonate in dimethylformamide solvent was carried out on a 50-g. sample of the mixture of chloro ketones. The product was isolated by steam distillation and extraction of the steam distillate with ether. Dimethylformamide was removed from the ether extract by washing with water. The product, b.p. 34–54° (0.1 mm.), was shown by gas chromatography on PDEAS at 170° to be a mixture containing the desired product, 5-methyl-2-cyclohexen-1-one (**19**) (3.5 min. retention time), as well as 3-methyl-2-cyclohexen-1-one (**11**) and 3-methylphenol (6.2 and 14 min., respectively). The latter compounds were identified by enriching the mixture with authentic materials. A pure sample of 5-methyl-2-cyclohexen-1-one (**19**) was obtained by collecting the ketone as it emerged from the column. An orange 2,4-dinitrophenylhydrazone was prepared from the collected sample and found to melt at 148–149°[21] after recrystallization from methanol.

(k) **6-Methyl-2-cyclohexen-1-ol (20).**—A sample of 6-methyl-2-cyclohexen-1-one (**21**) was purified through gas chromatography (PDEAS column at 150°) by collecting in ether solution. The ether solution was added dropwise to a stirred solution of lithium aluminum hydride in ether. The reaction was heated at reflux temperature for approximately 0.5 hr., cooled, and the excess lithium aluminum hydride cautiously destroyed by the dropwise addition of water. Additional water was added and the reaction product steam distilled. The alcohol **20** was isolated from the steam distillate by extraction with ether, the ether solution dried, concentrated, and analyzed by gas chromatography (PDEAS column at 120°) which showed essentially a single peak with a slight trailing shoulder. This shoulder was assumed to be due to the presence of *cis* isomer. The yield of **20** was 72%. The alcohol **20** was added to a sample of the HP–VP oxidation product of 4-methyl-1-cyclohexene (**17**) and this enrichment established the presence of **20** in the reaction mixture.

(l) **6-Methyl-2-cyclohexen-1-one (21)** was generously donated by D. R. Coulson and E. J. Warawa of Columbia University. Reduction with lithium aluminum hydride gave 6-methyl-2-cyclohexen-1-ol (**20**).

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The Molybdate-catalyzed Hydrogen Peroxide Oxidation of beta-Naphthol

By Alfred R. Bader

[Reprinted from the Journal of the American Chemical Society, **73**, 3731 (1951).]

[Contribution from the Research Laboratories of the Paint Division of the Pittsburgh Plate Glass Company]

The Molybdate-catalyzed Hydrogen Peroxide Oxidation of β-Naphthol

By Alfred R. Bader

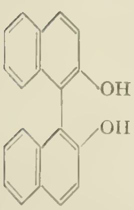
The red compound, m.p. 148°, isolated by Raacke-Fels, *et al.*,[1] in the molybdate-catalyzed hydrogen peroxide oxidation of β-naphthol has been shown to be 4-(2′-hydroxy-1′-naphthyl)-1,2-naphthoquinone.

During studies on the influence of molybdates on hydrogen peroxide oxidations, Raacke-Fels, *et al.*, discovered[1] that β-naphthol was oxidized in the presence of a catalytic amount of ammonium molybdate in a mixture of ethanol, acetic acid and water to a red compound, m.p. 148°, soluble in aqueous carbonate but insoluble in bicarbonate. Raacke-Fels, *et al.*, showed the molecular weight of this compound to be about twice that of β-naphthol, but examined it no further and assigned no structural formula to it.

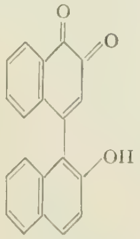
In the present investigation, it was found that solutions of this red oxidation product of β-naphthol, of empirical formula $C_{20}H_{12}O_3$, were decolorized by alkaline hydrosulfite in the cold, and that it reacted easily with *o*-phenylenediamine in acetic acid to form a yellow monophenazine, $C_{26}H_{16}ON_2$, m.p. 293–294°, which acetic anhydride and sodium acetate converted to a phenazine monoacetate, $C_{28}H_{18}O_2N_2$, m.p. 181–182°. Thus is appeared that β-naphthol had dimerized in the molybdate-catalyzed oxidation, and that one of the β-naphthol moieties had become oxidized to a 1,2-quinone system. That this is correct was confirmed by the ultraviolet spectrum of the red oxidation product (Fig. 1) which is perfectly explained by summation of the spectra of non-coplanar[2] β-naphthol[3] and 1,2-naphthoquinone.[4]

Fig. 1.—Absorption spectra in absolute ethanol of 4-(2′-hydroxy-1′-naphthyl)-1,2-naphthoquinone (II), ——; β-naphthol, - - - - -; and 1,2-naphthoquinone, — —.

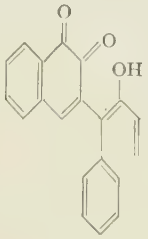
Dimerization of β-naphthol yields β-dinaphthol (I) which oxidation could not convert into a hydroxy-1,2-naphthoquinone, and so oxygenation of β-naphthol must precede dimerization. 1,2-Naphthoquinone and its hydroquinone couple at positions 3 and 4,[5,6] and thus II and III are the possible formulations of the monoquinonoid dimer of β-naphthol. Peracetic acid oxidation distinguished between these unambiguously, as it yielded 4-(2′-carboxyphenyl)-5,6-benzcoumarin(IV) which has been synthesized[7] by the condensation of β-naphthol and phthalylacetic acid. This coumarin had been isolated previously in both the alkaline permanganate[7,8] and the molybdate-catalyzed peracetic acid[1] oxidations of β-naphthol, and II may be an intermediate in these oxidations. The identity of the peracetic acid oxidation product of the quinone II and the coumarin synthesized by the elegant method of Dischendorfer and Danziger was established by melting point, mixed melting point, iden-



I



II



III

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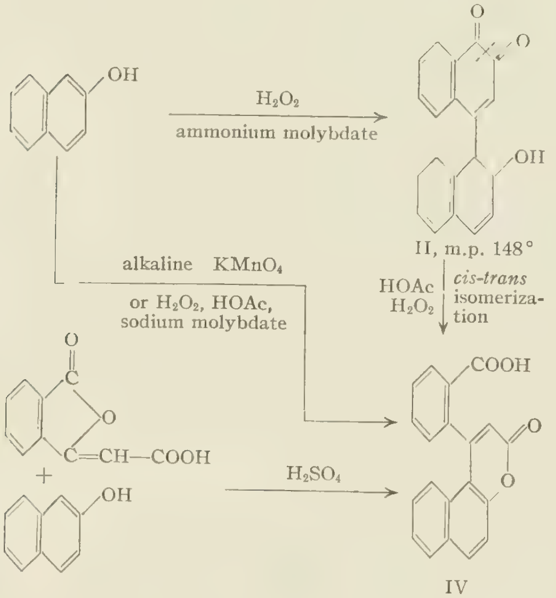
TABLE I

ULTRAVIOLET ABSORPTION SPECTRA IN ABSOLUTE ETHANOL[a]

Compound	Absorption maxima, wave lengths in mμ, log ε values					
β-Naphthol[3]	226 (4.83)		274 (3.63)	286 (3.30)	331 (3.30)	
1,2-Naphthoquinone[4]		250 (4.35)			340 (3.40)	405 (3.40)
4-(2′-Hydroxy-1′-naphthyl)-1,2-naphthoquinone	230 (4.86)	252.5 (4.42)	274.5 (3.92)	288 (3.78)	332.5 (3.70)	405 (3.37)
4-(2′-Carboxyphenyl)-5,6-benzcoumarin	229 (4.70)				320 (3.95)	351 (4.03)
4-(2′-Carbomethoxyphenyl)-5,6-benzcoumarin	230 (4.74)				320 (3.93)	352 (4.02)
3-Bromo-4-(2′-carboxyphenyl)-5,6-benzcoumarin	228 (4.69)				325 (4.01)	357.5 (4.14)

[a] Thanks are due to Miss Merle Manchester for conducting the spectrographic determinations.

tical ultraviolet spectra and the preparation of identical methyl esters and monobromo derivatives from both.



Experimental

4-(2′-Hydroxy-1′-naphthyl)-1,2-naphthoquinone (II) prepared by the method of Raacke-Fels, *et al.*,[1] was dissolved in a minimum of glacial acetic acid; the solution was filtered to remove a small quantity of an orange impurity, and the quinone was precipitated by the addition of a concentrated sodium chloride solution and recrystallized several times from aqueous acetone, m.p. 148–149°. The yield from 1 g. of β-naphthol was 0.7 g. (67%).

Anal. Calcd. for $C_{20}H_{12}O_3$: C, 79.98; H, 4.03. Found: C, 79.69, 79.58; H, 4.28, 4.30.

The phenazine, prepared by condensation of the 1,2-quinone (II) with *o*-phenylenediamine in acetic acid, formed yellow needles from ethanol, m.p. 293–294°.

Anal. Calcd. for $C_{26}H_{16}ON_2$: C, 83.85; H, 4.33; N, 7.52. Found: C, 84.17, 84.03; H, 4.66, 4.71; N, 7.57, 7.47.

The yellow **phenazine acetate**, prepared by refluxing the phenazine with acetic anhydride, glacial acetic acid and sodium acetate and crystallized from aqueous ethanol, melted at 181–182°.

Anal. Calcd. for $C_{28}H_{18}O_2N_2$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.33; H, 4.80; N, 6.72.

4-(2′-Carboxyphenyl)-5,6-benzcoumarin (IV).—A solution of 3.2 g. of the quinone II in 120 cc. of glacial acetic acid and 20 cc. of 20% aqueous hydrogen peroxide was allowed to stand at room temperature for 40 hours. The resulting yellow solution was poured into water, and the light cream precipitate (2.3 g.) was filtered, dried and crystallized with charcoal from ethanol to yield 1.8 g. (53%) of almost white, shiny platelets, m.p. 278–279°, which did not depress the m.p. of the coumarin prepared by the sulfuric acid condensation of β-naphthol and phthalylacetic acid.[7]

The monobromides,[7] m.p. 250–252°, prepared from the oxidation product and the synthetic coumarin were identical.

4-(2′-Carbomethoxyphenyl)-5,6-benzcoumarin, prepared by the action of diazomethane[9] on a solution of the acid in a mixture of ether and methanol, formed faintly yellow, stout needles, m.p. 153–154°, identical with the ester prepared by the method of Dischendorfer, *et al.*[7]

Anal. Calcd. for $C_{21}H_{14}O_4$: C, 76.35; H, 4.27. Found: C, 76.23; H, 4.40.

Acknowledgment.—The author wishes to thank Drs. H. L. Gerhart, S. W. Gloyer and H. A. Vogel for their interest in this work, and Dr. M. G. Ettlinger, whose many valuable suggestions speeded the solution of this problem.

MILWAUKEE, WISCONSIN RECEIVED MARCH 15, 1951

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[9] Prepared by the convenient method of A. F. McKay, THIS JOURNAL, **70**, 1974 (1948).

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Transesterification. I. Beta-Keto Esters

By Alfred R. Bader, Lowell O. Cummings and Henry A. Vogel

[Reprinted from the Journal of the American Chemical Society, **73**, 4195 (1951).]

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION OF THE PITTSBURGH PLATE GLASS COMPANY]

Transesterification. I. β-Keto Esters

BY ALFRED R. BADER, LOWELL O. CUMMINGS AND HENRY A. VOGEL

A series of β-keto esters of higher alcohols has been prepared in essentially quantitative yields by transesterification with methyl and ethyl β-keto esters under mild conditions in the absence of catalysts. The generality of this reaction and its usefulness is discussed.

As part of a more extensive study of ester interchanges we have investigated the transesterification of methyl and ethyl acetoacetate with a series of alcohols. Such transesterifications of acetoacetic esters have been previously studied, mostly at high temperatures and with basic catalysts with the lower alcohols,[1] *l*-menthol,[2] allylic alcohols,[3] and glycerol,[4] but it has not been realized that these reactions differ from conventional transesterifications and can proceed without catalyst and at steam-bath temperatures. We have prepared the acetoacetates of a series of alcohols in essentially quantitative yields and believe that most primary and secondary alcohols can be esterified in this manner provided that they dissolve in methyl and ethyl acetoacetate and do not, as may some benzylic alcohols,[5] C-alkylate the β-keto ester. Tertiary alcohols react more sluggishly, and we have ob-

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TABLE I

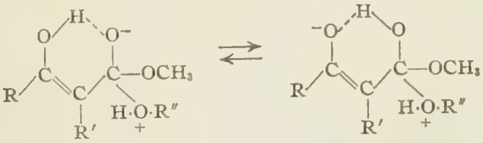
ACETOACETATES

Parent alcohol	Formula	M.p. or b.p., °C.	Solvent of recryst.	n^{25}_D	$[\alpha]^{25}_D$,[a] CHCl$_3$	Analyses,[b] %: Found Carbon	Found Hydrogen	Calcd. Carbon	Calcd. Hydrogen
Cholesterol	$C_{31}H_{50}O_3$	96	Ethanol–water		−33	78.61, 78.50	10.46, 10.51	79.09	10.71
Cholestanol	$C_{31}H_{52}O_3$	97	Methanol		+12	78.68, 78.72	11.13, 11.07	78.75	11.09
β-Sitosterol	$C_{33}H_{54}O_3$	99–100	IPE[c]–methanol		−24	79.20, 79.44	10.88, 10.94	79.46	10.91
Stigmasterol	$C_{33}H_{52}O_3$	113–114	IPE–methanol		−44	79.42, 79.60	10.60, 10.70	79.79	10.55
Dehydroepiandrosterone	$C_{23}H_{32}O_4$	163	Methanol		+ 1	74.13, 74.15	8.76, 8.66	74.16	8.66
1-Octanol	$C_{12}H_{22}O_3$	140–141 (16 mm.)		1.4372		66.85, 66.83	10.37, 10.32	67.25	10.35
1-Dodecanol	$C_{16}H_{30}O_3$	8–10	Methanol	1.4436		70.78, 70.80	11.32, 11.33	71.06	11.18
1-Octadecanol	$C_{22}H_{42}O_3$	40–41	Methanol			74.55, 74.45	11.96, 12.13	74.52	11.94
Cyclohexanol	$C_{10}H_{16}O_3$	130–131 (16 mm.)		1.4576		64.94, 64.96	8.92, 8.78	65.19	8.76
Menthol[3]	$C_{14}H_{24}O_3$	30–32	Ether						
Butyl carbitol	$C_{12}H_{22}O_5$	168–170 (10 mm.)		1.4415		58.04	8.90	58.51	9.01
Decamethylene glycol	$C_{18}H_{30}O_6$	33–34	Methanol			62.55	8.85	63.13	8.83

[a] Determined by Dr. C. J. W. Brooks. No mutarotation could be observed. [b] Determined by Micro-Tech Laboratories, Skokie, Illinois. [c] Isopropyl ether.

tained only a low yield of the acetoacetate of diacetone alcohol, the one tertiary alcohol studied. Other β-keto esters react similarly and the benzoylacetates and acetonedicarboxylates of cholesterol and 1-octadecanol have been prepared.

The shift in equilibrium is of course due to the removal of methyl or ethyl alcohol from the reaction mixture, yet esters such as ethyl *n*-butyrate, methyl caprylate, methyl crotonate, methyl benzoate and methyl levulinate do not react with alcohols under conditions more drastic than those required to complete the reactions with methyl or ethyl acetoacetate. We are now studying the transesterification of acids of strength similar or greater than that of acetoacetic acid to ascertain whether it is the inductive effect of the acetyl group which, by enhancing the electrophilic character of the ester carbonyl, facilitates the transesterification of acetoacetic esters or whether the ease of reaction is due to active hydrogen catalysis or to inherent structural features which stabilize such intermediates as Ia and Ib.



Ia Ib

No transesterification takes place when disubstituted β keto esters such as ethyl diethylacetoacetate[6] are employed, and we are not yet certain whether this is due solely to steric hindrance of esters of tertiary acids or whether an active hydrogen atom is a prerequisite for reaction.

This facile transesterification provides one of the few means to esterify an alcohol in neutral medium. Most acetoacetates of higher alcohols crystallize easily and all are more soluble in most organic solvents than the alcohols from which they are derived. Thus acetoacetates make good derivatives of alcohols, and may find use in the purification of natural products. The transesterification proceeds so easily that acetoacetates of higher alcohols may conceivably be formed under physiological conditions and be metabolic intermediates. In this connection it is of interest to note that cholesteryl acetoacetate differs from all other β-keto esters prepared by us in that it is difficult to crystallize from organic solvents as it forms quite stable gels.

Experimental

The β-keto esters used were Eastman Kodak Co. white label chemicals purified by vacuum distillation. The alcohols were crystallized to constant melting point or vacuum distilled just prior to use.

All solid acetoacetates were prepared by heating solutions of the parent alcohols in excess methyl or ethyl acetoacetate on the steam-bath for 3 to 15 hours and allowing the lower alcohols to distil off as formed. The excess methyl or ethyl acetoacetate was then removed by distillation *in vacuo* and the almost pure products were recrystallized as shown in Table I. The yields of analytically pure acetoacetates were always higher than 90%. Liquid acetoacetates were prepared similarly and were purified by fractional distillation.

The structures of two acetoacetates were proved by infrared spectroscopy, and the formation of a semicarbazone and a β-aminocrotonate.

Cholesteryl acetoacetate semicarbazone, prepared from cholesteryl acetoacetate, m.p. 96°, $\lambda^{\text{Chf.}}_{\text{max.}}$ 5.75, 5.83 μ,[7] $\lambda^{\text{isoöctane}}_{\text{max.}}$ 242.5 mμ (log ε 3.4)[8] melts at 189–190°, $[\alpha]^{25}_D$ −25° (chloroform).

Anal. Calcd. for $C_{32}H_{53}O_3N_3$: C, 72.82; H, 10.12; N, 7.96. Found: C, 73.10; H, 10.32; N, 7.90.

Octadecyl β-aminocrotonate was prepared by passing gaseous ammonia through a methanolic solution of octadecyl acetoacetate, m.p. 40–41°, to which a crystal of ammonium acetate had been added. Recrystallized from methanol, it melts at 70–71°, $\lambda^{\text{ethanol}}_{\text{max.}}$ 274 mμ (log ε 4.3).

Anal. Calcd. for $C_{22}H_{43}O_2N$: C, 74.73; H, 12.26; N, 3.96. Found: C, 74.80, 74.95; H, 12.33, 12.31; N, 3.70.

Cholesteryl benzoylacetate obtained quantitatively from cholesterol (5 g.) and ethyl benzoylacetate (25 g.) and crystallized from a mixture of ethanol and butyl acetate melts at 151°.

Anal. Calcd. for $C_{36}H_{52}O_3$: C, 81.15; H, 9.84. Found: C, 81.11, 80.97; H, 9.88, 9.69.

Octadecyl benzoylacetate prepared similarly and crystallized from acetone melts at 55–57°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.92; H, 10.30.

Cholesteryl acetonedicarboxylate obtained from cholesterol and ethyl acetonedicarboxylate and crystallized from a mixture of methanol and isopropyl ether melts at 173°. It was accompanied by a more soluble oil, presumably the mixed ester, which could not be obtained crystalline.

Anal. Calcd. for $C_{59}H_{94}O_5$: C, 80.22; H, 10.73. Found: C, 80.57, 80.51; H, 10.71, 10.79.

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[6] A. McKenzie, *J. Chem. Soc.*, **89**, 381 (1906).

[7] We are indebted to Dr. Leon Mandell for the determination of this spectrum.

[8] We wish to thank Mrs. Ruth Ferguson for the determinations of ultraviolet spectra.

Octadecyl acetonedicarboxylate prepared similarly and crystallized from ethanol melts at 65.0–65.5°.

Anal. Calcd. for $C_{41}H_{80}O_5$: C, 75.40; H, 12.34. Found: C, 75.43, 75.37; H, 12.00, 11.94.

2-Acetoacetoxy-2-methyl-pentanone-4.—A solution of diacetone alcohol (300 g.) in methyl acetoacetate (1000 g.) was heated on the steam-bath for 24 hours. Fractionation through a short column yielded 1210 g. of unreacted starting materials and 54 g. of a fraction, b.p. 120–130° at 10 mm., from which 41 g. of pure acetoacetate was obtained on redistillation; b.p. 125–127° at 10 mm., n^{25}_D 1.4424, $\lambda^{\text{ethanol}}_{\text{max.}}$ 241.5 mμ (log ε 3.07), 306.5 mμ (log ε 2.34).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.22, 60.14; H, 8.19, 8.31.

Acknowledgment.—The authors wish to thank Drs. H. L. Gerhart and S. W. Gloyer for their interest in this work.

MILWAUKEE, WISCONSIN

RECEIVED MARCH 31, 1951

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Transesterification. II. Esters of Strong Organic Acids

By Alfred R. Bader and Henry A. Vogel

[Reprinted from the Journal of the American Chemical Society, **74**, 3992 (1952).]

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION OF THE PITTSBURGH PLATE GLASS COMPANY]

Transesterification. II. Esters of Strong Organic Acids

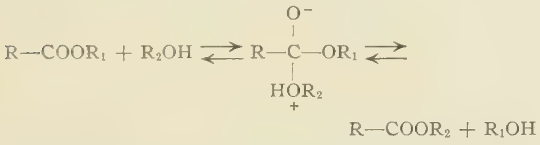
BY ALFRED R. BADER AND HENRY A. VOGEL

RECEIVED FEBRUARY 22, 1952

The transesterification of β-keto esters has been compared with that of esters of other strong organic acids. Malonates and oxalates, like acetoacetates, are transesterified under mild conditions, and it is suggested that the ease of transesterification of β-keto esters is due mainly to special structural features inherent in these esters, while that of oxalates is due to the inductive effect of the neighboring group.

In our first communication[1] we reported on the transesterification of β-keto esters which proceeds at steam-bath temperatures in the absence of catalysts. We have now completed a qualitative study of transesterifications of acids of strength similar and greater than that of acetoacetic acid to determine whether this facile transesterification is due to the inductive effect of the acetyl group, to intermolecular catalysis by active hydrogen or to structural features unique in β-keto esters. Table I lists the acids investigated, their ionization constants and the products obtained after heating representative primary and secondary alcohols with excess ester on the steam-bath without catalysts for 16 hours.

In any ester interchange one has the equilibria



$$R{-}COOR_1 + R_2OH \rightleftarrows R{-}\overset{O^-}{\underset{\underset{+}{HOR_2}}{C}}{-}OR_1 \rightleftarrows R{-}COOR_2 + R_1OH$$

the equilibrium constants of which are probably not greatly different from 1[2] and the reason for the ease of transesterification of acetoacetates at first considered most likely was the inductive effect of the acetyl group which removes electrons from the ester carbonyl, increases its electrophilic reactivity and thus the speed with which the equilibria are set up. A correlation is that acetoacetic acid is over ten times as strong an acid as acetic. Our qualitative data indicate, however, that the inductive effect can only be a mildly contributory factor in the ease of transesterification of β-keto esters because esters of some stronger acids do not react under our experimental conditions. Nor does it seem likely that the ease of transesterification of β-keto esters is due to an active hydrogen catalysis because we have found that when alcohols are heated in unreactive esters such as ethyl butyrate containing ethyl acetoacetate in a molar ratio of 10:1, the higher acetoacetate is the sole reaction product. Such experiments are, however, not entirely conclusive because one would expect the acetoacetate to be the more basic ester and its reaction might be the only one catalyzed.

TABLE I

Acid	$10^5 K_1$ at 25°	Products
Caprylic	1.44[a]	None
Butyric	1.50[b]	None
Crotonic	2.03[b]	None
Levulinic	......	None
Benzoic	6.27[b]	None
Lactic	13.9[c]	None
Acetoacetic	26[d]	Acetoacetates
Benzoylacetic	......	Benzoylacetates
Furoic	68[e]	None
Fumaric	95.7[f]	Small amt. fumarates
Tartaric	104[g]	None
Phthalic	112[h]	None
Malonic	177[f]	Mixed and symm. malonates
Ethyl-*n*-butylmalonic	......	None
Maleic	1200[f]	None
Oxalic	5900[i]	Mixed and symm. oxalates

[a] C. G. Derrick, THIS JOURNAL, **33**, 1152 (1911). [b] J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939). [c] A. W. Martin and H. V. Tartar, THIS JOURNAL, **59**, 2672 (1937). [d] K. J. Pedersen, *J. Phys. Chem.*, **38**, 993 (1934). [e] W. L. German, G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1604 (1937). [f] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 201. [g] I. Jones and F. G. Soper, *J. Chem. Soc.*, 1836 (1934). [h] W. J. Hamer, G. D. Pinching and S. F. Acree, *J. Research Natl. Bur. Standards*, **35**, 539 (1945); *C.A.*, **40**, 3044 (1946). [i] R. Gane and C. K. Ingold, *J. Chem. Soc.*, 2153 (1931).

After the completion of this work, our attention was drawn to a paper by Carroll[3] which independently describes the facile alcoholysis of acetoacetic and related esters. Carroll attempted to determine the rates of transesterification of acetoacetates by measuring the rates of distillation of lower alcohols evolved, and on the basis of these possibly inaccurate data concluded that the rate determining step is first order with respect to the ester when pri-

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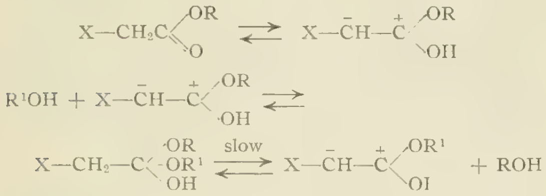
(1) A. R. Bader, L. O. Cummings and H. A. Vogel, THIS JOURNAL, **73**, 4195 (1951).

(2) P. R. Fehlandt and H. Adkins, *ibid.*, **57**, 193 (1935).

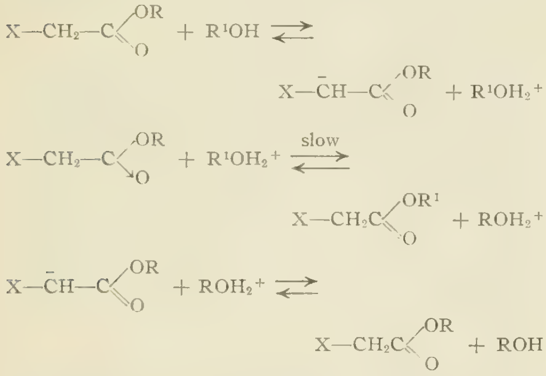
(3) M. F. Carroll, *Proc. XIth. Intern. Congr. Pure and Applied Chem.*, **2**, 39 (1947); *C. A.*, **45**, 7015 (1951).

mary and secondary alcohols are used, and second order when tertiary alcohols are used. For the unimolecular reaction, Carroll was undecided between two mechanisms:

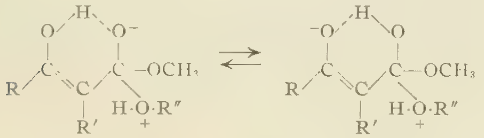
Mechanism A



Mechanism B



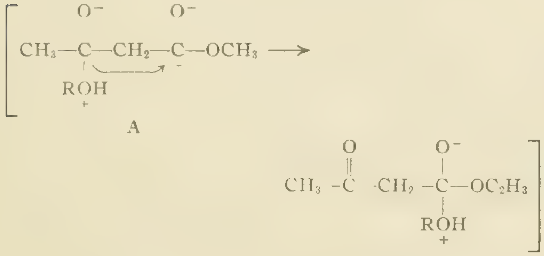
We do not believe that either mechanism could be operative and prefer a mechanism involving the cyclic intermediates Ia ⇄ Ib previously suggested.[1]



Ia Ib

Although these intermediates suffer from the loss of conjugate carbonyl resonance of the acetoacetate enol, they offer the distinct advantage of possessing stronger than normal hydrogen bonds because these involve the electrostatic attraction of the proton to a *real* negative charge.

An alternate mechanism considered was A → B. The presumed rate determining step (*viz.*, the addition of the alcohol to the ester) should be facilitated by participation of the more electrophilic keto carbonyl, and is followed by a rapid intramolecular shift of the alcohol to the ester carbonyl. Shifts such as A → B are familiar from rearrangements of the pinacol–pinacolone type, and this mechanism is analogous to one proposed to account for the increased S_N2 reactivity of positive halogens.[4]



A B

The unambiguous way of distinguishing between this pinacolic and the enolic mechanism was to compare the complete non-reactivity of ethyl diethylacetoacetate[5] with that of a monoalkyl ester offering the same degree of steric hindrance. The dialkyl ester does not react with *l*-menthol even at 190°, while ethyl *s*-butylacetoacetate interchanges quite readily at 150°. Thus an active hydrogen appears to be a prerequisite for reaction, suggesting that the cyclic enol mechanism is operative.

Because their enolization is so slight, we are undecided whether malonates exchange by a mechanism involving a similarly chelated enol, or whether their reactions are largely inductively facilitated as are those of fumarates and oxalates.

These facile transesterifications provide convenient methods for the esterification of alcohols under mild, neutral conditions in the absence of catalysts, and in addition to the β-keto esters reported,[1] we have prepared the acetoacetates of ergosterol and cortisone. With esters of the monobasic acids the yields are usually quantitative, while with malonates and oxalates the mixed esters formed predominantly are easily separated from the much more insoluble symmetrical products.

Experimental

Materials.—Cholesterol was recrystallized from a mixture of isopropyl ether and methanol, m.p. 148.9–149.4° (cor.), $\alpha^{25}D$ −35° (hexane), saponification number 0.0.

Octadecyl alcohol (Eastman Kodak Co. white label) was recrystallized from methanol, m.p. 58.4–58.8° (cor.), saponification value 0.0.

All esters except methyl furoate were products of the Eastman Kodak Co. or the Matheson Co. and were redistilled before use. Methyl furoate prepared from furoic acid (Fischer method) boiled at 181–182°.

Method.—Except where stated otherwise, 5.0 g. of cholesterol and 5.0 g. of octadecyl alcohol were each heated under an air condenser on the steam-bath with 25 g. of the esters for 16 hours. The unreacted lower esters were then removed by distillation *in vacuo*, and the residues were triturated with methanol, filtered and dried. When no transesterification had taken place, the identity of the residues with cholesterol and octadecyl alcohol, respectively, was ascertained by m.p., mixed m.p. and determination of the saponification number.

Results.—Cholesterol and octadecyl alcohol, each of saponification number less than 10, were recovered from methyl caprylate, ethyl butyrate, methyl crotonate, methyl levulinate, methyl benzoate, ethyl lactate, methyl furoate, ethyl tartrate, methyl phthalate, ethyl ethyl-*n*-butylmalonate and ethyl maleate.

The reaction product of cholesterol with ethyl fumarate had a saponification number of 12 after 18 hours and of 40 after 56 hours; the reaction product of octadecyl alcohol had a saponification number of 60 after 18 hours.

17-Hydroxy-11-dehydrocorticosterone-21-acetoacetate hydrate prepared from cortisone[6] by the standard procedure[1] and crystallized from aqueous ethanol and chloroform melts at 107–109°.

Anal. Calcd. for $C_{25}H_{32}O_7 \cdot H_2O$: C, 64.92; H, 7.41. Found: C, 64.93, 64.94; H, 7.42, 7.50.

Ergosteryl acetoacetate[7] prepared similarly forms shiny platelets from aqueous ethanol, m.p. 124–125°; λ^{EtOH}_{max}

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[4] J. W. Baker, *Trans. Faraday Soc.*, **37**, 643 (1941).

[5] A. McKenzie, *J. Chem. Soc.*, **89**, 381 (1906).

[6] We wish to thank Dr. M. Tishler of Merck and Co. for a generous sample of cortisone.

[7] Thanks are due to Dr. H. Bolker for a generous sample of ergosterol.

271.5 mμ (log ε 4.09), 281.5 mμ (log ε 4.10), 292.0 mμ (log ε 3.86); $\alpha^{25}\text{D}$ −79.3° (chloroform).

Anal. Calcd. for $C_{32}H_{48}O_3$: C, 79.95; H, 10.06. Found: C, 79.80, 79.60; H, 10.12, 10.10.

Twenty-five g. of *l*-menthol and 10 g. of ethyl *s*-butylacetoacetate[8] were heated at 145–150° for five hours; the unreacted starting materials were removed by distillation *in vacuo* and the almost water white flask residue (9.0 g.) was distilled to yield 7.5 g. of water-white **l-menthyl s-butylacetoacetate**, b.p. 108–111° (0.3 mm.), $n^{25}\text{D}$ 1.4582.

Anal. Calcd. for $C_{18}H_{32}O_3$: C, 72.92; H, 10.88. Found: C, 73.01, 72.96; H, 11.08, 11.02.

Malonates.—Ten grams of cholesterol and 100 cc. of ethyl malonate were heated on the steam-bath for 15 hours, the excess ethyl malonate was removed by distillation *in vacuo*, and the product chromatographed on Fisher adsorption alumina, 80–200 mesh. There were isolated from the hexane eluate 7.8 g. of white flakes, m.p. 60–63° which after crystallization from ethanol yielded 6.5 g. of pure **ethyl cholesteryl malonate** melting at 63.5–64.0°, $\alpha^{25}\text{D}$ −31° (chloroform), and 0.7 g. of the much less soluble **dicholesteryl malonate** which after crystallization from isopropyl ether melts at 178°, $\alpha^{25}\text{D}$ −33° (chloroform).

Anal. Calcd. for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 76.76; H, 10.71. Calcd. for $C_{57}H_{92}O_4$: C, 81.37; H, 11.02. Found: C, 81.30, 81.37; H, 10.90, 11.13.

Five grams of octadecyl alcohol and 50 cc. of ethyl malonate were heated on the steam-bath for 18 hours, the unreacted ethyl malonate was removed as above, and the residue dissolved in hot acetone. On cooling, white shiny platelets of **dioctadecyl malonate** (250 mg.) deposited which after recrystallization from acetone melt sharply at 64°. The combined mother liquors were evaporated to dryness, dissolved in hexane and chromatographed. The first eluates yielded 4.3 g. of a waxy solid, **ethyl octadecyl malonate**, m.p. 30–32°.

Anal. Calcd. for $C_{23}H_{44}O_4$: C, 71.82; H, 11.53. Found: C, 71.54; H, 11.76. Calcd. for $C_{39}H_{76}O_4$: C, 76.91; H, 12.58. Found: C, 77.28, 77.10; H, 12.74, 12.81.

Oxalates.—Ten grams of β-sitosterol, 75 cc. of ethyl oxalate and 25 cc. of toluene were heated on a steam-bath for 16 hours, the solvent and unreacted ethyl oxalate were removed by distillation *in vacuo*, and the residue was separated by solubility in a mixture of ethanol and acetone into the sparingly soluble **di-β-sitosteryl oxalate** (0.7 g.) and the more soluble **ethyl β-sitosteryl oxalate** (9.2 g.). The symmetrical ester crystallized from a mixture of toluene and ethanol in flat, shiny needles, m.p. 195–196°, while the mixed ester, crystallized from a mixture of ethanol and acetone, melts at 65–66°.

Anal. Calcd. for $C_{33}H_{54}O_4$: C, 77.00; H, 10.57. Found: C, 77.03; H, 10.70. Calcd. for $C_{60}H_{98}O_4$: C, 81.57; H, 11.18. Found: C, 81.87; H, 11.20.

Cholesterol treated similarly yielded corresponding amounts of **dicholesteryl oxalate**[9] which forms fine needles from a mixture of ethanol and toluene, m.p. 220–222°, and **ethyl cholesteryl oxalate** which after crystallization from a mixture of ethanol and acetone melts at 94.5–95.5°, $\alpha^{25}\text{D}$ −33° (chloroform).

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 77.00, 76.94; H, 10.70, 10.54.

Ethyl octadecyl oxalate prepared similarly and crystallized from ethanol melts at 36.5–37.0°.

Anal. Calcd. for $C_{22}H_{42}O_4$: C, 71.30; H, 11.43. Found: C, 71.18, 71.20; H, 11.51, 11.47.

Competitive Reactions.—Ergosterol (1.0 g.) dissolved in a mixture of 58 g. (0.5 mole) of redistilled ethyl butyrate and 6.5 g. (0.05 mole) of redistilled ethyl acetoacetate was heated on the steam-bath for three hours. The solvent mixture (42 g.) was then removed quickly by distillation *in vacuo*, and the residual water-white solution was diluted with 50 cc. of hot ethanol and 30 cc. of water. On cooling the solution deposited shiny white platelets (0.80 g., m.p. 122–124°) which after two crystallizations from aqueous ethanol yielded similar crystals (0.7 g.) which melted at 124–125° and did not depress the m.p. of authentic ergosteryl acetoacetate. Their infrared spectra in chloroform were identical.

Anal. Calcd. for $C_{32}H_{48}O_3$: C, 79.95; H, 10.06. Found: C, 79.79; H, 10.09.

Similar treatment of cholesterol and β-sitosterol with methyl acetoacetate in large molar excesses of methyl benzoate and methyl phthalate also yielded only the corresponding acetoacetates.

Acknowledgment.—The authors wish to thank Professor Martin G. Ettlinger and Dr. E. E. van Tamelen for many helpful suggestions and Drs. H. L. Gerhart and S. W. Gloyer for their kind interest.

MILWAUKEE, WISCONSIN

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[8] Prepared by the general procedure of "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 243.

[9] I. H. Page and H. Rudy, *Biochem. Z.*, **220**, 304 (1930).

[Reprinted from the Journal of the American Chemical Society, **74**, 6305 (1952).]

The Reaction of Diketene with Ketones

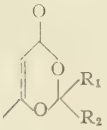
by Michael F. Carroll and Alfred R. Bader

[Reprinted from the Journal of the American Chemical Society, **74**, 6305 (1952).]

THE REACTION OF DIKETENE WITH KETONES

Sir:

Although the preparation of diketene in acetone is a commercial process, its reactions with ketones to form compounds formulated as 2,2-disubstituted-4-methyl-6-keto-1,3-dioxenes, I, have escaped observation.

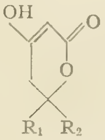


Ia, $R_1 = R_2 = CH_3$
Ib, $R_1 = CH_3$, $R_2 = C_6H_5$

The *p*-toluenesulfonic acid catalyzed reaction of diketene with acetone at 90° yields Ia (91%), b.p. 61–64° (5 mm.), $n^{20}{}_D$ 1.464, $d^{20}{}_4$ 1.079, $\lambda_{max.}^{EtOH}$ 247.5 mμ, log ϵ 3.9; *Anal.* Calcd. for $C_7H_{10}O_3$: C, 59.14; H, 7.09; Found: C, 59.20; H, 7.15. The product from acetophenone, Ib, is crystalline, m.p. 93–94°, $\lambda_{max.}^{EtOH}$ 247.5 mμ, log ϵ 3.86, $\lambda_{max.}^{isooctane}$ 240 mμ, log ϵ 3.85; *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57, H, 5.92; Found, C, 70.21; H, 5.81. These ketodioxenes are pleasant smelling liquids or crystalline solids easily handled in the absence of alkali. As many of their reactions parallel those of diketene they may conveniently be used in its place. Thus I reacts with alcohols, aniline and with mild alkali to yield acetoacetates, acetoacetanilide and dehydracetic acid, respectively. I does not react with carbonyl reagents and this and the ultraviolet spectra rule out structures II and III also considered.

$$CH_3COCH_2COOC\begin{matrix}\nearrow CH_2\\ \searrow R_1\end{matrix}$$

II



III

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Unsaturated Phenols. II. Attempted Syntheses of *o*-Vinylphenol

By Alfred R. Bader

[Reprinted from the Journal of the American Chemical Society, **77**, 4155 (1955).]

Unsaturated Phenols. II.[1] Attempted Syntheses of *o*-Vinylphenol

By Alfred R. Bader

Received March 25, 1955

As part of a more extensive study of unsaturated phenols, small quantities of *o*-vinylphenol were required. At least five apparently convenient syntheses are described in the literature: (i) the reaction of phenol with ethylene oxide,[2] (ii) the sulfuric acid-catalyzed rearrangement and dehydration of β-phenoxyethanol,[2] (iii) the reaction of vinyl acetate with phenol,[3] (iv) the decarboxylation of *o*-hydroxycinnamic acid,[4] and (v) the thermal decomposition of the benzodioxin obtained from phenol and acetaldehyde.[5]

Smith and Niederl claimed that phenol and ethylene oxide react in the presence of sulfuric acid to give a 65% yield of *o*-vinylphenol, characterized by its tetrabromide and phenoxyacetic acid reported previously.[4b] Many attempts to repeat the work of Smith and Niederl were unsuccessful. The ultraviolet spectrum of the crude reaction product, mainly unreacted phenol, showed no conjugated unsaturation. The crude reaction product was brominated, and the bromophenols were separated by chromatography; no tetrabromide, easily obtained from *o*-vinylphenol, could be isolated.

Smith and Niederl[2] postulated β-phenoxyethanol as the intermediate in the formation of *o*-vinylphenol from phenol and ethylene oxide. Support for this was found in the alleged reaction of β-phenoxyethanol with sulfuric acid at room temperature to yield *o*-vinylphenol. Actually, β-phenoxyethanol is recovered unchanged from the reaction conditions described (identical infrared spectra and physical constants).[6]

The reaction of vinyl acetate with phenol in the presence of sulfuric acid has been reported[3] to yield a polymer from which *o*-vinylphenol has been alleged to be easily obtainable by thermal depolymerization. The product of the very vigorous reaction is a polymer, but no *o*-vinylphenol could be obtained therefrom.

The decarboxylation of *o*-hydroxycinnamic acid[4] provides a convenient method for the preparation of *o*-vinylphenol.

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(1) For paper I see This Journal, **75**, 5967 (1953).

(2) R. A. Smith and J. B. Niederl, *ibid.*, **53**, 806 (1931).

(3) J. B. Niederl, R. A. Smith and M. E. McGreal, *ibid.*, **53**, 3390 (1931).

(4) (a) H. Kunz-Krause and P. Manicke, *Arch. Pharm.*, **566**, 555 (1929); (b) K. Fries and G. Fickewirth, *Ber.*, **41**, 367 (1908).

(5) E. Adler, H. v. Euler and G. Gie, *Arkiv Kemi, Mineral., Geol.*, **16A**, No. 12, 1 (1943); *C. A.*, **38**, 5839 (1944).

(6) Adler, *et al.*,[5] also were unable to obtain *o*-vinylphenol from β-phenoxyethanol.

Aldrich Chemical Company, Inc.
Milwaukee 12, Wisconsin

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Unsaturated Phenols. IV. Crotylphenols

By Alfred R. Bader

[Reprinted from the Journal of the American Chemical Society, **79**, 6164 (1957).]

[CONTRIBUTION FROM THE LABORATORIES OF THE PITTSBURGH PLATE GLASS CO. AND THE ALDRICH CHEMICAL CO.]

Unsaturated Phenols. IV.[1] Crotylphenols

BY ALFRED R. BADER[2]

RECEIVED JUNE 20, 1957

Butadiene reacts with phenol in the presence of some Friedel-Crafts catalysts to yield largely a mixture of butenylphenols, with some higher phenols and ethers. *o*- and *p*-crotylphenol have been characterized. A correlation between the acidity functions of acid actalysts and their activity is discussed.

Although the synthesis of compounds related to the tocopherols has prompted studies of the reactions of phenols, specifically hydroquinones, with butadiene,[3] isoprene,[4] 2,3-dimethylbutadiene[4] and phytadiene,[5] the reaction of the simplest phenol with the simplest diene has been described only briefly. A patent[6] has alleged that *p*-crotylphenol is the major component of the monoalkenylphenolic fraction formed in 36% yield in the high temperature reaction of phenol with butadiene catalyzed by solid phosphoric acid.[7] Proell[8] has described the reaction of butadiene with phenol catalyzed by alkanesulfonic acid yielding a mixture of butenylphenols. Claisen[9] had previously described the preparation of chromans from phenol and dienes such as isoprene, and the preparation of pentenylphenols from these reactants under milder conditions has been studied by Pines and Vesely.[10]

The reaction of phenol with 1,3-butadiene at

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[1] For paper III, see This Journal, **78**, 1709 (1956).

[2] Aldrich Chemical Co., Milwaukee 12, Wisconsin.

[3] L. I. Smith and J. A. King, This Journal, **63**, 1887 (1941).

[4] L. F. Fieser, W. P. Campbell, E. M. Fry and M. D. Gates, *ibid.*, **61**, 3216 (1939).

[5] L. E. Smith, H. E. Ungnade, H. H. Hoehn and S. Wawzonek, *J. Org. Chem.*, **4**, 311 (1939).

[6] R. E. Schaad, U. S. Patent 2,283,465 (May, 1942).

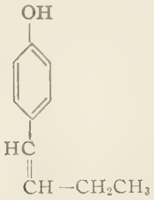
[7] V. N. Ipatieff, U. S. Patents 1,993,512 and 1,993,513 (March, 1935).

[8] W. Proell, *J. Org. Chem.*, **16**, 178 (1951).

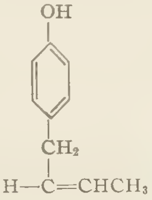
[9] L. Claisen, *Ber.*, **54**, 200 (1921); German Patent 374,142 (April, 1923).

[10] H. Pines and J. A. Vesely, U. S. Patents 2,553,470 and 2,578,206 (May and December, 1951). Details of the reaction of phenol with isoprene will be described in paper V of this series.

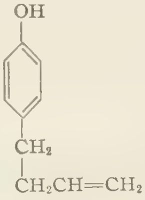
room temperature in the presence of relatively mild Friedel–Crafts catalysts yields largely butenylphenols accompanied by only small amounts of ethers and higher phenols. Fractionation of the butylphenols obtained on hydrogenation showed the presence of *o*- and *p*-*n*-butylphenols, identified by physical constants and solid derivatives. Thus the possible structures for the original reaction products are *p*-1-butenylphenol (I), *p*-crotylphenol (II), *p*-3-butenylphenol (III) and the three corresponding *o*-substituted isomers. The absence of conjugated isomers such as I was shown by ultraviolet spectra and infrared spectra of the mixed butenylphenols and of cuts obtained by fractional distillation indicated the presence mainly of *o*- and *p*-crotylphenol.



I



II



III

Low temperature crystallizations of the highest boiling butenylphenol fraction yielded a crystalline solid, m.p. 39°, the infrared spectrum of which shows a strong band at 10.35 μ, indicative of a symmetrically disubstituted *trans* double bond and no bands at 10.1–10.2 and 11.0 μ, characteristic of the vinyl group $RCH{=}CH_2$.[11] The spectrum of this crystalline isomer also shows an intense band at 12.1 and no absorption at 13.3 μ, and this evidence for *p*-substitution is in accord with this isomer's quantitative hydrogenation to the known[12] *p*-*n*-butylphenol. Assignment of structure II to this solid isomer was confirmed by its ultraviolet spectrum and by its isomerization by palladized charcoal to the conjugated isomer I, m.p. 85–86°.[1]

Fractionation of the non-crystallizable monobutenylphenols boiling over a 20° range and examination of the fractions' infrared spectra showed that the intensities of the band at 12.1 μ increased and those of the band at 13.3 μ decreased with increasing b.p., indicating increasing ratios of *p*-butenylphenols in the higher b.p. fractions. The presence of *o*-crotylphenol in an intermediate fraction was confirmed by the preparation of its phenylurethan melting at 65–66°, identical with the derivative of authentic *o*-crotylphenol.[13]

When titanium tetrachloride, alkanesulfonic acids or the aluminum chloride solvates were the catalysts, the non-crystallizable butenylphenol fractions showed no bands at 10.25 and 10.95 μ, whereas weak bands were present at those wave lengths in the spectra of the butenylphenols obtained with the other catalysts. Theoretically, *n*-butenylphenols with terminal unsaturation as in III are improbable as products of alkenylation,[14] and the weak bands at 10.25 and 10.95 μ may be caused by small amounts of methallyl- or *cis*-crotylphenols.[15]

Butadiene is less reactive than cyclopentadiene, and 85% phosphoric acid, the preferred[14] catalyst for the cycloalkenylation of phenol at 25°, is ineffective with butadiene at that temperature. As has been pointed out by Price,[16] only few direct comparisons of the relative activities of Friedel–Crafts catalysts are recorded in the literature. The composition of the products of the reaction of butadiene with phenol varies greatly with different catalysts, and it seemed of interest to compare the activities of a number of catalysts in this reaction. Comparison is complicated by the involvement of two reactions in the formation of 1:1 adducts, *i.e.*, the alkenylation and the acid-catalyzed ring closure of the *o*-isomer[17] and by further reactions of the alkenylphenols by oxidation and condensation.

Axe[18] has implied that the complex prepared by *saturating* phosphoric acid with boron fluoride, which is an effective catalyst in the butenylation of benzene, also can be used in the alkenylation of phenol. Actually, the use of this as of other strong Friedel–Crafts catalysts such as aluminum chloride and concentrated sulfuric acid leads almost exclusively to ethers and resinous products. The saturated BF_3–phosphoric acid catalyst diluted with an equal weight of 85% phosphoric acid is, however, one of the catalysts of choice; with it or with a mixture of phosphoric and sulfuric acids the mixed butenylphenols are accompanied by only small amounts of ethers and higher phenols. Aqueous sulfuric acid, titanium tetrachloride, alkanesulfonic acids,[8] arenesulfonic acids, aluminum chloride alcoholate and etherate and mixtures of polyphosphoric acid and phosphoric acid also catalyze the mono-butenylation at 15–25°.

The reaction temperature and the catalyst composition direct the orientation. With the complex of phosphoric acid and boron fluoride or with alkanesulfonic acids, *p*-substitution predominates at 15–25°, whereas II constitutes only 30% of the mono-butenylphenols when aqueous sulfuric acid is used at that temperature. This dependence of the product composition on the negative ion associated with the carbonium ion suggests that alkenylations do not involve simply the electrophilic attack on phenol of the diene's free, resonant carbonium ion.

The ranges of composition of the effective cat-

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(11) (a) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1412 (1948); (b) N. Sheppard and G. Sutherland, *Proc. Roy. Soc.* (*London*), ***A*196**, 195 (1949); (c) D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, 915 (1950).

(12) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 265.

(13) L. Claisen and E. Tietze, *Ber.*, **59B**, 2351 (1926).

(14) A. R. Bader, THIS JOURNAL, **75**, 5967 (1953).

(15) H. Pines, B. Kvetinskas, J. A. Vesely and E. Baclawski, *ibid.*, **73**, 5173 (1951), have claimed on the basis of infrared spectra and hydrogenation to 2-*n*-butylthiophene that the products of the reaction of thiophene with butadiene are 2-(3-butenyl)-thiophene and 2-crotylthiophene. The evidence for the presence of the former was two bands at 910 and 970 cm.$^{-1}$, thought to be indicative of a vinyl group. However, the band at 970 cm.$^{-1}$ (10.3 μ) is at too long a wave length to be indicative of a vinyl group which never absorbs even in allylic substitution products[11c] and in 2-vinylthiophene with a conjugated, possibly perturbed group at more than 10.2 μ. Perhaps the lower boiling butenylthiophene is 2-*cis*-crotylthiophene.

(16) C. C. Price in R. Adams, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 2.

(17) See D. S. Tarbell, *ibid.*, Vol. II, pp. 18, 27.

(18) W. N. Axe, U. S. Patent 2,471,922 (May, 1949).

alyst mixtures are quite narrow, particularly with sulfuric acid (68–70% at 15–25°). Except for aqueous sulfuric acid, the acid catalysts effective for the mono-butenylation at room temperature have acidity functions[19] H_0 of *ca.* −6 to −7, corresponding to 77–83% aqueous sulfuric acid. It may be that but for its oxidizing action, say, 80% aqueous sulfuric acid would be the optimum concentration, and that 68–70% is the highest concentration not causing oxidation of the α-methylene group and the lowest catalyzing the alkenylation.[20] Once one effective catalyst is known in a given reaction, the determination of its acidity function appears helpful in suggesting the most convenient catalyst of similar H_0 to be tried.

Weaker catalysts such as 85% phosphoric acid become effective at higher temperatures; the resulting products contain largely *o*-substituted phenols. The reaction at 200° following the procedure of Schaad[6] yielded only a small amount of mixed mono-butenylphenols from which no *p*-crotylphenol could be isolated. The infrared spectrum of the mixture suggested that it consisted largely of *o*-substituted phenols.

Experimental

Butenylphenols.—To a stirred and cooled mixture of 940 g. (10 moles) of phenol, 1000 cc. of toluene, 100 g. of the complex prepared by saturating[21] 85% phosphoric acid with gaseous boron fluoride and 100 g. of 85% phosphoric acid, there was added slowly a cold solution of 270 g. (5 moles) of butadiene in 1000 cc. of toluene. The reaction was slightly exothermic, and the stirred mixture, which became faintly yellow, was kept at room temperature for 16 hr. It was then diluted with water, the toluene solution was washed and the solvent, unreacted phenol and a small amount of ethers removed by distillation *in vacuo*. The main fraction (659 g., 89%), b.p. 53–90° (0.1 mm.), $n^{25}\text{D}$ 1.539, $\lambda_{\max}^{\text{EtOH}-0.1\%\ \text{HOAc}}$ 225 mμ (log ε 3.9) and 279 mμ (log ε 3.3), mixed butenylphenols, was a colorless oil, completely soluble in aqueous alkali. The yellow flask residue consisted of dibutenylphenols and higher phenols and ethers.

The mixed butenylphenols (180 g.) were fractionated through a 10″ column into 5 fractions: A, 5 g., b.p. 53–55° (0.1 mm.), $n^{25}\text{D}$ 1.5377; B, 25 g., b.p. 55–60° (0.1 mm.), $n^{25}\text{D}$ 1.5380; C, 28 g., b.p. 60–63° (0.1 mm.), $n^{25}\text{D}$ 1.5385; D, 8 g., b.p. 63–69° (0.1 mm.), $n^{25}\text{D}$ 1.5390; and E, 9 g., b.p. 69–72° (0.1 mm.), $n^{25}\text{D}$ 1.5385; their infrared spectra are in accord with those of two-component mixtures, progressing steadily from A (strong band at 13.3 μ, mostly *o*-crotylphenol) to E (strong band at 12.1 μ, mostly *p*-crotylphenol). The colorless flask residue (103 g.) crystallized in the ice-box; two low temperature crystallizations from ligroin yielded 75 g. of soft needles, m.p. 39°, of **p-crotylphenol** (II); $\lambda_{\max}^{\text{EtOH}-0.1\%\ \text{HOAc}}$ 225 mμ (log ε 3.99), 279 mμ (log ε 3.29); $\lambda_{\min}$ 215 mμ (log ε 3.84), 247.5 mμ (log ε 2.10).

Anal.[22] Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found, mixed mono-phenols: C, 81.06; H, 8.04. Found, fraction C: C, 80.82; H, 8.25. Found, II: C, 81.22, 81.07; H, 8.37, 8.19.

The solid isomer, II, was characterized by a ***p*-nitrophenylurethan** which formed white needles from aqueous methanol, m.p. 139–140°, and by a **phenoxyacetic acid** which after two crystallizations from water melted sharply at 80°.

Anal. Calcd. for $C_{17}H_{16}O_4N_2$: C, 65.37; H, 5.16. Found: C, 65.30; H, 5.50. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.85; H, 6.90.

The exothermic reaction of the mixed sodium butenylphenoxides with chloroacetic acid yields a mixture of aryloxyacetic acids, of which one is easily separated through its insolubility in ligroin. Ultraviolet and infrared spectra suggested this to be ***o*-crotylphenoxyacetic acid** which crystallized from water in soft, white needles, m.p. 137°; $\lambda_{\max}^{\text{EtOH}-0.1\%\ \text{HOAc}}$ 215.0 mμ (log ε 3.94), 271.5 mμ (log ε 3.24), 277.5 mμ (log ε 3.20); $\lambda_{\min}$ 242.5 mμ (log ε 2.28), 275 mμ (log ε 3.17). Its infrared spectrum in Nujol mull showed a strong band at 10.3 μ, probably indicative of a *trans* double bond, RCH═CHR′.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.45; H, 7.04.

Reaction of fraction B with phenyl isocyanate gave a good yield of a crystalline phenylurethan which crystallized in fine needles from methanol, m.p. 65–66°, identical with *o*-crotylphenyl phenylcarbamate.[13]

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.18; H, 6.19.

Hydrogenation of II (methanol, Adams platinum oxide catalyst, 100°) quantitatively yielded ***p*-*n*-butylphenol**,[12] m.p. 20–21°, $n^{25}\text{D}$ 1.5176, characterized by a phenoxyacetic acid, m.p. 80–81°.

Hydrogenation of the mixed butenylphenols (50 g.) yielded mixed *n*-butylphenols (50 g.), $n^{25}\text{D}$ 1.517, which fractional distillation separated into 15 g. of *o*-*n*-butylphenol, b.p. 94–97° (8 mm.), $n^{25}\text{D}$ 1.518, characterized by a crystalline phenoxyacetic acid[23] (crystallized from ligroin), m.p. 104–105°; and 24 g. of *p*-*n*-butylphenol, b.p. 113–116° (8 mm.), $n^{25}\text{D}$ 1.518, characterized as above.

A small quantity of ethers (3–6%) is formed in this room temperature reaction; these distil with unreacted phenol and can be separated by their insolubility in alkali. Their boiling range (205–225°) and the physical constants of the higher b.p. fraction (b.p. 220–225°, $n^{25}\text{D}$ 1.530, $d^{25}{}_{25}$ 1.020) suggest that these ethers are a mixture of 2-ethylcoumaran and 2-methylchroman.[24]

The second catalyst of choice is a mixture of 85% phosphoric acid and concd. sulfuric acid. Adding a cooled solution of butadiene (60 g., 1.1 moles) in toluene (100 cc.) to a stirred mixture of phenol (94 g., 1 mole), toluene (100 cc.), 85% phosphoric acid (100 g.) and sulfuric acid (sp. gr. 1.84, 15 g.) and keeping the stirred mixture at 15–25° for 16 hr. yielded 115 g. (0.78 mole, 78%) of mixed butenylphenols a colorless oil, b.p. 80–120° (1.5 mm.), $n^{25}\text{D}$ 1.5385. The infrared spectrum of this mixture was similar to that of the mixed butenylphenols prepared with boron fluoride and phosphoric acid, and crystalline II was isolated from the higher b.p. fraction.

With 68% aqueous sulfuric acid and equimolar amounts of phenol and butadiene at 15°, the yield of mono-butenylphenols is 70%. Fractional distillation showed these to consist of *ca.* 60% *o*-crotylphenol and 30% of the crystalline isomer II.

The reactions catalyzed by boron fluoride, by the complex of phosphoric acid saturated with boron fluoride, by concd. sulfuric acid and by aluminum chloride are very exothermic and lead largely to higher phenols and ethers. Fair yields of butenylphenols are obtainable with polyphosphoric acid or, preferably, with mixtures of polyphosphoric acid and 85% phosphoric acid (2:1), titanium tetrachloride arenesulfonic acids and the aluminum chloride–alcohol and –ether complexes. Again, crystalline II was isolated by low temperature crystallizations from heptane from all mixed butenylphenols. Also, the higher b.p. liquid butenylphenol prepared by the procedure of Proell[8] crystallized at once on cooling and proved identical with II.

Zinc chloride and 85% phosphoric acid are inactive at 10–40°. Phosphoric acid (85%) becomes effective at 100–125°; at 140° the bulk of the product consists of ethers and higher phenols. Comparison of spectra showed that the maximum at 13.3 μ was more than that at 12.1 μ somewhat less intense than the corresponding maxima in the infrared spectra of mixed mono-butenylphenols prepared at lower temperatures, indicating somewhat more *p*-substitution in the latter.

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(19) L. P. Hammett and A. J. Deyrup, THIS JOURNAL, **54**, 2721 (1932); L. P. Hammett and M. A. Paul, *ibid.*, **56**, 827 (1934). I am much indebted to Mr. John E. Hyre for the determination of the acidity functions of the catalysts.

(20) I wish to thank Professor Paul D. Bartlett for this suggestion.

(21) 85% sirupy phosphoric acid exothermically absorbs approx its weight of boron fluoride.

(22) Analyses by the Micro-Tech Laboratories, Skokie, Ill.

(23) G Sandulescu and A. Girard, *Bull. soc. chim.*, [4] **47**, 1300 (1930).

(24) C. D. Hurd and W. A. Hoffman, *J. Org. Chem.*, **5**, 212 (1940); W. Baker and J. Walker, *J. Chem. Soc.*, 646 (1935).

From the product of the reaction described by Schaad[6] (77 g. of phenol, 20 g. of butadiene, 25 g. of U.O.P. polymerization catalyst #2, 200°, 4 hr.), there was obtained besides much unreacted phenol, 11 g. of a phenolic fraction, A, b.p. 65–130° (1 mm.), $n^{25}D$ 1.540; and 30 g. of dark, resinous material. The spectrum of A showed a strong band at 13.3 μ characteristic of *o*-substitution, only a weak band at 12.1 μ and no band at 10.35–10.40 μ, the position of one of the strongest bands of II, indicative of a symmetrically disubstituted *trans* double bond.

Acidity Functions.[19]—With anthraquinone as the Hammett indicator, the alkanesulfonic acid and polyphosphoric acid and the mixtures of 85% phosphoric acid and sulfuric acid and of polyphosphoric acid and phosphoric acid used as catalysts at 15–25° show acidity functions H_0 ranging from −6 to −7. The H_0 of 68–70% aqueous sulfuric acid is −5.0 to −5.2.

***p*-1-Butenylphenol (I).**—A mixture of 90 g. of II and 5 g. of 5% palladium-on-charcoal (Baker and Co., lot #785, activity 985) was refluxed under inert gas for 25 minutes when the reaction temperature had risen to 260°. The product was dissolved in ligroin and filtered, the solvent removed and the red, viscous oil (86 g.) distilled to yield a first fraction A (46 g.), b.p. 80–150° (0.5 mm.); a second fraction B (19 g.), b.p. 150–210° (0.5 mm.); and an orange resinous residue (18 g.). Crystallization of A from heptane yielded 5.5 g. of shiny, white platelets of the less soluble isomer I, identical with the compound prepared by alkali isomerization[1] of II. The infrared spectra of I and II in carbon disulfide are quite similar, except that I exhibits an intense band at 11.8 μ absent in the spectrum of II. The heptane mother liquor from I yielded 40 g. of unreacted II. Fraction B consisted largely of a colorless dimeric diphenol, b.p. 187–190° (0.4 mm.), which was accompanied by a fiery red impurity.

Anal. Calcd. $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.79; H, 8.13.

Butenylanisoles.—Anisole reacts much like phenol at 10–30°; mixed butenylanisoles were prepared in good yields with concd. sulfuric acid and with a 2:1 mixture of polyphosphoric acid and 85% phosphoric acid; b.p. 75–110° (10 mm.), $n^{25}D$ 1.519, strong bands at 12.1 and 13.3 μ, indicating *o*- and *p*-substitution.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.87; H, 9.00.

Acknowledgment.—I wish to thank Professors M. G. Ettlinger and C. D. Hurd for valuable ad vice.

MILWAUKEE, WISCONSIN

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Unsaturated Aromatic Amines; A Novel Synthesis of Indoles

By John E. Hyre and Alfred R. Bader

[Reprinted from the Journal of the American Chemical Society, **80**, 437 (1958).]

[Contribution from the Laboratories of the Pittsburgh Plate Glass Company, The Aldrich Chemical Company and Harvard University]

Unsaturated Aromatic Amines; A Novel Synthesis of Indoles

By John E. Hyre[1a] and Alfred R. Bader[1b]

Received June 14, 1957

Convenient preparations of N-allyl-, N-crotyl- and N-pentenylaniline are described. N-Crotylaniline reacts with polyphosphoric acid to yield 2,3-dimethylindole and a 2,3-dimethylindoline.

Our recent studies of unsaturated phenols[2] prompted a study of the preparations and reactions of simple unsaturated anilines.

N-Allylaniline,[3a–c,d] which had previously been

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[1] (a) Dept. of Chemistry, Harvard University; (b) Aldrich Chemical Company, Milwaukee, Wis.

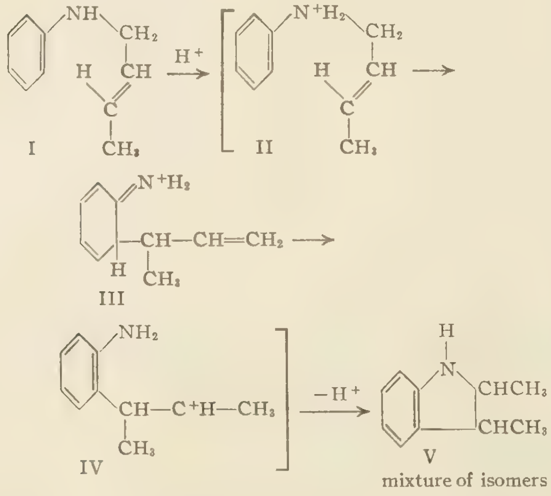
[2] A. R. Bader, This Journal, **78**, 1709 (1956).

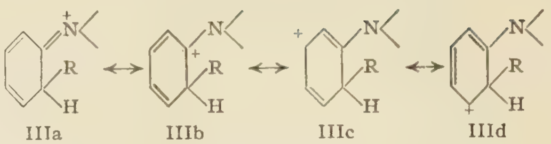
[3] (a) H. Schiff, *Ann. Suppl.*, **3**, 364 (1864); (b) F. B. Davis, R. Q Brewster, J. S. Blair and W. C. Thompson, This Journal, **44**, 2638 (1922); (c) F. L. Carnahan and C. D. Hurd, *ibid.*, **52**, 4586 (1930); (d) *cf.* also the paper by C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, **22**, 1418 (1957), which appeared while our paper was in press.

prepared only in low yields, is obtained conveniently and in 75–80% yields by the alkenylation of aniline with allyl chloride in non-polar solvents, under the conditions which favor C-alkenylation in phenols.[4] Hickinbottom[5] obtained *p*-crotylaniline, N-crotylaniline and less than 1% of 2,3-dimethylindole in the reaction of aniline with butadiene in the presence of aniline hydrochloride at 230–260°. N-Crotylaniline was prepared also by Arbuzov[6] in the reaction of 2-phenyl-3,6-dihydro-1,2,2H-oxazine with sodium in ethanol, and by Danforth[7] in the reaction of aniline with butadiene and sodium at 120°. Infrared spectra and hydrogenation to N-*n*-butylaniline indicate that the N-butenylaniline prepared by a modification of Danforth's method is predominantly N-crotylaniline. The analogous reaction of aniline with isoprene yields N-pentenylaniline.

When N-crotylaniline, I, was refluxed with polyphosphoric acid, 2,3-dimethylindole and a liquid amine, $C_{10}H_{13}N$, were isolated in *ca.* 32% yield each. The liquid amine was characterized by a benzenesulfonamide melting at 101–103° which differs from the benzenesulfonamide, m.p. 70–71°, of the 2,3-dimethylindoline prepared by the action of zinc dust and acid on dimethylindole.[8] The liquid amine contains two C-methyl groups, and is readily converted to 2,3-dimethylindole by the action of chloranil.[9] Thus, the liquid product is a 2,3-dimethylindoline which differs from the product of the zinc and acid reduction of 2,3-dimethylindole.

The formation of 2,3-dimethylindole and just one of the 2,3-dimethylindolines is of interest for at least two reasons. One is that we may be dealing with a *proton-catalyzed Claisen-type* rearrangement of N-crotylaniline,[10] the driving force being the resonance stabilization of the rearranged ion III; in the anilinium ion II the charge cannot be distributed by resonance.





The second point of interest is the isolation of only one of the indolines, suggesting that the other isomer may have been selectively, stereospecifically dehydrogenated. If, as seems plausible, the *trans* isomer is the form obtained by metal–acid reduction,[8] and this is also the precursor of the 2,3-dimethylindole obtained here, then we are dealing with a *concerted, acid-catalyzed trans-elimination* of an α- and a β-hydrogen.[11]

This hypothesis explaining the isolation of only one 2,3-dimethylindoline postulates the dehydrogenation of the *trans*-2,3-dimethylindoline present in the reaction mixture. Because of electron availability, the salt would be more difficult to oxidize, and the conversion of the indoline cation to that of the indole would be thermodynamically more difficult because the indoline is a much stronger base than the indole.

Experimental

N-Allylaniline.—To a stirred and cooled mixture of 227 g. (10 moles) of sodium sand, 1000 cc. of toluene and 932 g. (10 moles) of aniline, a solution of 765 g. (10 moles) of allyl chloride in 500 cc. of toluene was added slowly. The reaction is somewhat exothermic and the reaction temperature was kept below 25°. The mixture was stirred at room temperature overnight and then refluxed for 7 hours. Methanol and water were then added, and the washed organic layer was fractionated through a 20″ Stedman column. The product (407 g., 77% based on unrecovered aniline) is a colorless oil, b.p. 68–70° (1.3 mm.), $n^{25}\text{D}$ 1.5614, $d^{25}{}_{25}$ 0.9737.

Its toluenesulfonamide[8a] melts at 69°; the benzenesulfonamide forms needles from aqueous ethanol, m.p. 82–83°.

Anal. Calcd. for $C_{15}H_{15}NSO_2$: C, 65.94; H, 5.49. Found: C, 66.15; H, 5.42.

N-Allylacetanilide (acetic anhydride, sulfuric acid) forms needles from water, m.p. 46–47°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.43; H, 7.43. Found: C, 75.31; H, 7.53.

N-Crotylaniline.—A mixture of 448 g. (4.7 moles) of aniline, 334 g. (6.2 moles) of butadiene and 20 g. (0.87 moles) of sodium was heated in an autoclave at 120° for 18 hours. Methanol and water were added, and the washed organic layer was distilled *in vacuo* to yield 370 g. (79% based on unrecovered aniline) of N-crotylaniline, b.p. 81–82° at 1.7 mm.; $n^{25}\text{D}$ 1.5553; $d^{25}{}_{25}$ 0.9607; $\lambda_{\max}^{\text{EtOH}}$ 249 mμ (log *e* 4.10); 295 mμ (log *e* 3.30); $\lambda_{\min}^{\text{EtOH}}$ 273 mμ (log *e* 3.0). The infrared spectrum in CS_2 shows a strong band at 10.4 μ indicative of a *trans* disubstituted double bond, RCH=CHR′.

N-Butylaniline.—Hydrogenation of N-crotylaniline (methanol, Adams platinum oxide catalyst, 60 p.s.i.) quantitatively yielded N-*n*-butylaniline, b.p. 235–237°, $n^{25}\text{D}$ 1.5310, the infrared spectrum of which was identical with that of authentic N-*n*-butylaniline.

N-Pentenylaniline.—A mixture of 450 g. (4.7 moles) of aniline, 350 g. (5.1 moles) of isoprene and 20 g. of sodium similarly heated at 120° yielded N-pentenylaniline (216 g.), b.p. 94–95° at 1.7 mm., $n^{25}\text{D}$ 1.5502, $d^{25}{}_{25}$ 0.9507. The product's infrared spectrum shows a pronounced band at 11.22 μ ($R_1R_2C{=}CH_2$) and weaker bands at 11.6 and 12.35 μ ($R_1CH{=}CR_2R_3$) suggesting that the product is largely VI perhaps accompanied by some VII.

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(4) L. Claisen and E. Tietze, *Ber.*, **59B**, 2344 (1926).

(5) W. J. Hickinbottom, *J. Chem. Soc.*, 1981 (1934).

(6) Y. A. Arbuzov, *Doklady Akad. Nauk, S.S.S.R.*, **63**, 531 (1948).

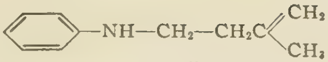
(7) J. Danforth, U. S. Patent 2,495,890 (Jan. 1950).

(8) A. Steche, *Ann.*, **242**, 371 (1887).

(9) P. L. Julian and H. C. Printy, THIS JOURNAL, **71**, 3206 (1949).

(10) For acid catalysis of the Claisen rearrangement, see W. Gerrard, M. F. Lappert and H. B. Silver, *Proc. Chem. Soc.*, 19 (1957).

(11) For a stereospecific amine dehydrogenation involving however nitrogen and an α-hydrogen, *cf.* F. L. Weisenborn and P. A. Diassi, THIS JOURNAL, **78**, 2022 (1956).



VI

VII

Anal. Calcd. for $C_{11}H_{15}N$: C, 81.93; H, 9.38. Found: C, 82.20, 82.10; H, 9.37, 9.50.

Reaction of Aniline with Butadiene at Higher Temperatures.—When aniline, butadiene and sodium are heated to a higher temperature, small quantities of N,N′-diphenylformamidine surprisingly are formed also. Thus, when a mixture of aniline (448 g., 4.7 moles), butadiene (358 g., 6.63 moles) and sodium (20 g., 0.87 moles) was heated at 170–190° for 18 hours, 4.2 g. of diphenylformamidine, m.p. 136–137° after crystallization from aqueous ethanol, was isolated by fractional distillation. The material ($\lambda_{\max}^{\mathrm{EtOH}}$ 282 mμ, log *e* 4.34; $\lambda_{\min}$ 240.5 mμ, log *e* 371) was identified by analysis and mixed melting point with authentic diphenylformamidine.[12]

Under similar conditions, (a) 100 g. of N-crotylaniline and 5 g. of sodium, (b) 29 g. of N-crotylaniline, 19 g. of aniline and 3 g. of sodium, (c) 19 g. of aniline, 15 g. of butadiene and 8 g. of sodium hydroxide, (d) 29 g. of N-crotylaniline, 19 g. of aniline and 8 g. of sodium hydroxide, and (e) 28 g. of N-crotylaniline, 18 g. of aniline, 4 g. of sodium hydroxide and 2 g. of sodium yielded no detectable diphenylformamidine.

The reaction of equimolar quantities of N-crotylaniline and potassium hydroxide at 220° for six hours yielded largely aniline, characterized through its benzenesulfonamide, and an insoluble black solid.

2,3-Dimethylindole and *cis*-2,3-Dimethylindoline.—A mixture of N-crotylaniline (100 g. 0.67 mole) and polyphosphoric acid (50 g.) was refluxed with stirring under inert gas for seven hours. The two phase mixture was hydrolyzed with 20% aqueous potassium hydroxide, and the product was extracted with ether, washed and fractionally distilled *in vacuo* to yield three fractions: A, b.p. 50–70° at 2 mm., 8 g.; B, b.p. 72–76° at 2 mm., 32 g., and C, b.p. 150–165° at 12 mm., 32 g. Fraction A, n^{25}_{D} 1.5802 consisted largely of aniline characterized by its benzenesulfonamide, m.p. 111–112°. Fraction B, n^{25}_{D} 1.5513, boiled sharply at 74° at 2 mm. on redistillation.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.63; H, 8.84. Found: C, 81.62, 81.76; H, 8.94, 9.04. Kuhn-Roth C-methyl, calcd. for one C-methyl group: 10.2%. Found: 12.0%. $\lambda_{\max}^{\mathrm{EtOH}}$ 242.5 mμ (log *e* 3.80); 294 mμ (log *e* 3.36); $\lambda_{\min}$ 272 mμ (log *e* 3.05).

Fraction B, *cis*-2,3-dimethylindoline, was characterized by its benzenesulfonamide which crystallized in needles from aqueous ethanol, m.p. 101–103°.

Anal. Calcd. for $C_{16}H_{17}NSO_2$: C, 66.87; H, 5.96. Found: C, 66.93, 67.00; H, 5.88, 5.72.

The infrared spectrum of *trans*-2,3-dimethylindoline,[8] b.p. 107–109° at 12 mm., differs from that of the *cis* isomer, and the *trans* isomer was characterized by a benzenesulfonamide melting at 70–71°.

Anal. Calcd. for $C_{16}H_{17}NSO_2$: N, 4.88. Found: N, 5.31, 5.28.

cis-2,3-Dimethylindoline was recovered unchanged after refluxing with polyphosphoric acid for 4 hours. Fraction C crystallized in the receiver, m.p. 103–104° after recrystallization from heptane.

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.71; H, 7.64; N, 9.65. Found: C, 82.76; H, 7.59; N, 9.65. $\lambda_{\max}^{\mathrm{EtOH}}$ 228.5 mμ (log *e* 4.50); 284 mμ (log *e* 3.84); 292 mμ (inflection, log *e* 3.79); $\lambda_{\min}$ 248 mμ (log *e* 3.27).

Its picrate[13] forms red needles from ethanol, m.p. 156–157°; its addition compound with picryl chloride[14] crystallizes in brown needles from ethanol, m.p. 135–136°.

Reaction of *cis*-2,3-Dimethylindoline with Chloranil.[9]—A mixture of *cis*-2,3-dimethylindoline (1 g.), xylene (50 cc.) and chloranil (2 g.) was refluxed for 4 hours, filtered, freed of solvent and the residue dissolved in ether. The ethereal solution was dried after extraction with dilute aqueous hydrochloric acid to remove the more strongly basic indoline, and distilled to yield 0.37 g. (38%) of 2,3-dimethylindole.

Acknowledgment.—We wish to thank Professors M. G. Ettlinger and C. D. Hurd for valuable advice.

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[12] W. Weith, *Ber.*, **9**, 457 (1876).

[13] L. Wolff, *ibid.*, **21**, 125 (1888).

[14] M. Padoa and C. Chiaves, *Gazz. chim. ital.*, **38I**, 236 (1908).

[Reprinted from the Journal of the American Chemical Society, 80, 3073 (1958).]

Unsaturated Phenols. V. The Reaction of Isoprene with Phenol

By Alfred R. Bader and William C. Bean

[Reprinted from the Journal of the American Chemical Society, **80**, 3073 (1958).]

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Unsaturated Phenols. V. The Reaction of Isoprene with Phenol[1]

BY ALFRED R. BADER AND WILLIAM C. BEAN

RECEIVED JANUARY 2, 1958

The reaction of isoprene with phenol, catalyzed by phosphoric acid, yields the *o*- and *p*-3-methylcrotylphenols IV and V, the γ-hydroxyisoamylphenols II and VIII, and the two chromans I and IX.

The reactions of isoprene with phenol have been studied briefly by Claisen[2] and by Pines and Vesely.[3] Claisen obtained 2,2-dimethylchroman (I) which proved identical with the ether synthesized by ring closure of the tertiary alcohol II prepared by the action of methylmagnesium iodide on ethyl dihydrocoumarate. Pines and Vesely, who used the alcohol and ether complexes of stannic chloride, and the ether complex of 85% phosphoric acid to prepare pentenylphenols, considered condensation to take place between phenol and the tertiary double bond of isoprene, but beyond that did not elaborate on the structures of the alkenylphenols formed. In the alkylation of phenol by the reso-

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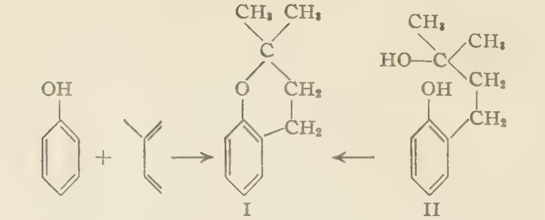
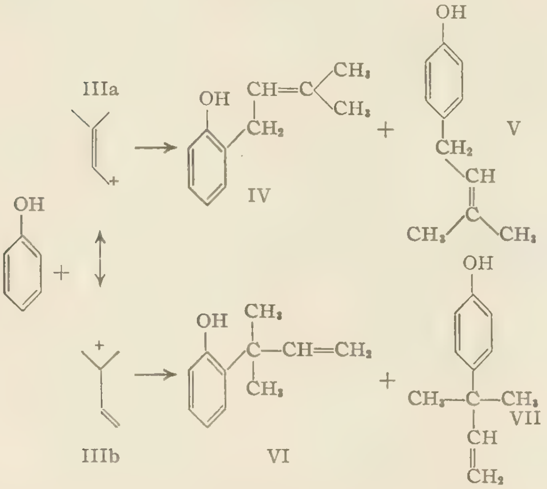
[1] For paper IV, see THIS JOURNAL, **79**, 6164 (1957).

[2] L. Claisen, *Ber.*, **54B**, 200 (1921); German Patent 374,142 (Dec., 1920).

[3] H. Pines and J. A. Vesely, U. S. Patents 2,553,470 and 2,578,206 (May and Dec., 1951).



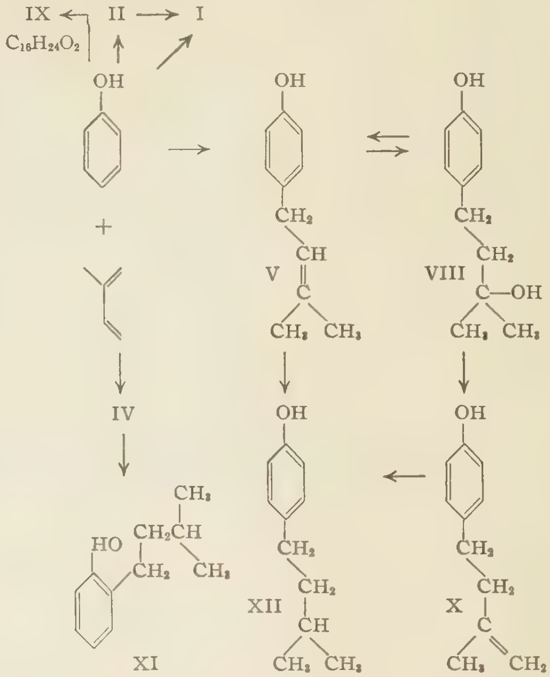
nant carbonium ion III one would *a priori* consider IV, V, VI and VII as possible products. However, alkenylations with butadiene,[1,4–6] isoprene[5,7,8] and



2,3-dimethylbutadiene[7] have shown that the products from the alkenylations with conjugated dienes are derived from that resonance hybrid of the carbonium ion which is *spatially most accessible;* compounds containing the crotyl, 3-methylcrotyl and 2,3-dimethylcrotyl groups are the predominant products in the alkenylations with butadiene, isoprene and 2,3-dimethylbutadiene respectively.

From the reaction of phenol with isoprene catalyzed by 71% phosphoric acid[9] at 20°, we obtained six products. The phenolic fraction yielded the 3-methylcrotylphenols IV and V and the crystalline tertiary alcohols II and VIII: the ethereal fraction consisted of 2,2-dimethylchroman I and an alcohol IX, $C_{16}H_{24}O_2$, melting at 51–52°.

That the pentenylphenols $C_{11}H_{14}O$ have structures IV and V rather than VI and VII was proved by (i) the hydrogenation of V to a *p*-amylphenol, m.p. 27–29°, different from the known *p-t*-amylphenol[10] melting at 94–95°; (ii) the infrared spectra of IV and V which did not contain bands at 910 and 990 cm.$^{-1}$ characteristic of —CH=CH$_2$[11]; and (iii) the alkali isomerizations[12] of IV and V to the corresponding conjugated phenols. Compounds such as VI and VII would not be expected to isomerize in alkali.



The 3-methylcrotylphenols IV and V prepared in these alkenylations could not be obtained crystalline. The *p*-isomer V, however, was easily characterized by its 2,6-bishydroxymethyl derivative, m.p. 110–111°, and the reaction of *p*-substituted phenols with formaldehyde appears to be one of the easiest means of characterization. Table I lists a number of similar dimethylol derivatives prepared. When V was treated with methanolic potassium hydroxide under the relatively mild conditions required to isomerize *o*-allyl- to *o*-propenylphenol, V remained non-conjugated, but the quite homogeneous phenol recovered crystallized easily, melted at 9–11°, and was characterized by the same bishydroxymethyl derivative melting at 110–111°. Apparently V is accompanied in the alkenylation by small amounts of an isomeric product, perhaps X, which prevents the crystallization of V, and which becomes isomerized to V in alkali.

The crystalline alcohol VIII, m.p. 134–135°, can be prepared also by the hydration of V, and is isolated particularly easily from the other products of the alkenylation because it is the only product sparingly soluble in toluene. The *o*-isomer II, m.p. 112°, had been prepared previously by Claisen[2]; its identity was proved by cyclization to I.

The dehydration of VIII yields one of two products, depending on conditions. In the presence of acid or iodine the predominant product is V characterized by its spectrum and bishydroxymethyl derivative. When, however, VIII is heated at atmospheric pressure without catalysts, dehy-

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(4) L. I. Smith and J. A. King, THIS JOURNAL, **63**, 1887 (1941).

(5) H. Pines, B. Kvetinskas, J. A. Vesely and E. Baclawski, *ibid.*, **73**, 5173 (1951).

(6) W. Proell, *J. Org. Chem.*, **16**, 178 (1951).

(7) L. F. Fieser, W. P. Campbell, E. M. Fry and M. D. Gates, THIS JOURNAL, **61**, 2559, 3216 (1939).

(8) L. I. Smith, H. W. Ungnade, H. H. Hoehn and S. Wawzonek, *J. Org. Chem.*, **4**, 311 (1939).

(9) For a method to determine the most convenient catalyst concentration by means of Hammett indicators, *cf.* paper IV.

(10) R. C. Huston and T. Y. Hsieh, THIS JOURNAL, **58**, 439 (1936).

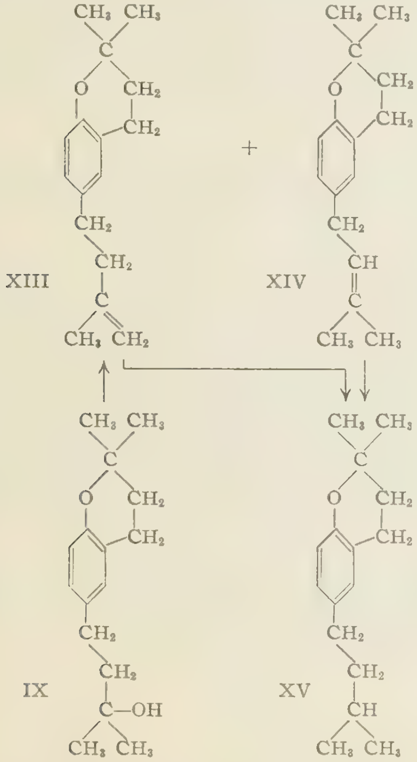
(11) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1412 (1948).

(12) A. R. Bader, THIS JOURNAL, **78**, 1709 (1956).

dration also occurs to a pentenylphenol melting at 9–12°. This product, however, depresses the m.p. of V, shows in the infrared a strong band at *ca.* 11.3 μ absent in the spectrum of V and characteristic of a double bond RR′C═CH$_2$,[11] cannot be characterized by a crystalline bishydroxymethyl derivative, and is assigned structure X.

The unsaturated phenols IV, V and X are easily hydrogenated to the isoamylphenols XI and XII melting at 12–14° and 27–29°, respectively. Such alkylphenols containing α-methylene groups are difficult to prepare by Friedel–Crafts reactions with alcohols, halides or alkenes, but are made conveniently by hydrogenation of the products of alkenylations with dienes.

The ether IX, $C_{16}H_{24}O_2$, is dehydrated easily either by heat or with 85% phosphoric acid at 25°, to yield the unsaturated ether XIII perhaps accompanied by some XIV. The infrared spectrum of IX in carbon disulfide shows a hydroxyl band at *ca.* 2.8 μ and a strong band at 12.2 μ characteristic of a substituted benzene ring bearing two adjacent hydrogen atoms. The spectrum of the dehydration product shows besides the band at 12.2 μ also a strong band at 11.25 μ characteristic of disubstituted terminal unsaturation. Hydrogenation of the unsaturated ether yields the chroman XV melting at 19–20°.



Experimental

Reaction of Isoprene with Phenol.—Preliminary experiments showed that 71% aqueous phosphoric acid corresponds in catalyst strength to the complexes used by Pines and Vesely,[3] and yields the same products. A cooled mixture of 125 g. (1.3 moles) of phenol, 90 g. (1.3 moles) of isoprene, 230 g. of toluene and 130 g. of 71% aqueous phosphoric acid was stirred at 20° for 16 hours. The reaction was somewhat exothermic. The reaction mixture was washed with water, and the toluene was distilled off *in vacuo*, leaving 212 g. of a faintly yellow oil. This mixture (200 g.) was stirred with aqueous potassium hydroxide solution to separate ethers from phenols. The ethers (24 g.) were fractionally distilled to yield 10 g. of **2,2-dimethylchroman** (I),[2] b.p. 224–226°, n^{25}D 1.524, and 10 g. of IX, b.p. 150–152° (0.8 mm.), n^{25}D 1.523; this crystallized slowly on standing and melts at 51–52°; λ_{max}^{EtOH} 220 mμ (log ε 3.92), 225 mμ (infl., log ε 3.89), 282 mμ (log ε 3.40), 291 mμ (log ε 3.34); λ_{min} 247.5 mμ (log ε 2.32), 289 mμ (log ε 3.32).

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.45; H, 9.82.

The phenolic fraction was distilled through a Stedman column to yield 28 g. of phenol; 23 g. of a fraction, b.p. 89–91° (1 mm.), n^{25}D 1.538, largely *o*-**3-methylcrotylphenol** (IV); 3 g. of a mixture of IV and V; 40 g. of a fraction b.p. 104–105° at 1 mm., n^{25}D 1.539, largely *p*-**3-methylcrotylphenol** (V)[13]; and 60 g. of yellow flask residue A; λ_{max}[14] of IV 275 mμ (log ε 3.36), λ_{min} 242.5 mμ (log ε 2.10); λ_{max} of V 225 mμ (log ε 3.96), 279 mμ (log ε 3.30); λ_{min} 219 mμ (log ε 3.91), 247.5 mμ (log ε 2.19).

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.69. Found: IV: C, 81.50; H, 8.97. Found V: C, 81.05; H, 8.36.

The infrared spectrum of IV in CS$_2$ shows a strong band at 13.3 μ characteristic of *o*-substitution and absent in the spectrum of V which shows a strong band at 12.2 μ characteristic of *p*-substitution and absent in the spectrum of IV. The spectrum of the fraction b.p. 104–105° at 1 mm. (largely V) showed a weak band at *ca.* 11.3 μ. When 30 g. of this fraction was refluxed with 30 g. of potassium hydroxide in methanol at 110° for six hours, no conjugation[12] had occurred, and the recovered phenol's b.p., refractive index and ultraviolet spectrum were identical with those of the starting material. Except for the disappearance of the weak band at *ca.* 11.3 μ, the infrared spectra were also identical. While the alkali-untreated *p*-substituted phenol could not be obtained crystalline, the product recovered from this alkali treatment crystallized in the ice-box and melted at 9–11°.

The *p*-3-methylcrotylphenol (V) (before and after the six-hour treatment with alkali) as well as other *p*-substituted phenols were characterized by their **2,6-bishydroxymethyl derivatives**. These are listed in Table I. A mixture of 4 g. of the phenol, 250 mg. of sodium hydroxide, 0.4 cc. of water and 4 g. of 37% formalin solution was let stand for 2 days. Toluene (10 cc.) and glacial acetic acid (3 cc.) were then added, the mixture was cooled thoroughly, and the crystalline product filtered and recrystallized.

A solution of flask residue A in toluene (200 ml.) was cooled, and the white solid, *p*-**(γ-hydroxyisoamyl)-phenol** (VIII) (12 g., m.p. 127–130°) was filtered and crystallized twice from xylene to yield 10 g. of flat needles, m.p. 134–135°; λ_{max} 224 mμ (log ε 3.83), 279 mμ (log ε 3.22); λ_{min} 245 mμ (log ε 1.68).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.48; H, 9.11.

The infrared spectrum of VIII in Nujol showed it to be *p*-substituted. It was characterized by a phenoxyacetic acid which, crystallized from water, melts at 101–102°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.80; H, 7.71.

The alcohol VIII can be obtained simply by diluting the initial reaction mixture with toluene (1:10) and filtering the almost pure VIII which crystallizes on standing.

The mother liquor from VIII was distilled *in vacuo*. The fraction, 30 g., b.p. 145–175° (0.8 mm.), crystallized partially on standing and after four crystallizations from heptane and ethanol yielded 7 g. of *o*-**(γ-hydroxyisoamyl)-**

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(13) In one experiment, W. C. B. obtained a crystalline *p*-substituted pentenylphenol, $C_{11}H_{14}O$ (*Anal.* Found: C, 81.52; H, 8 77) melting after one crystallization from heptane at 86°. Despite many attempts, we were not able to obtain this product again. The infrared spectrum of the compound (2% soln. in CS$_2$) showed between 10 and 13μ strong bands at 11.05, 11.55, 11.8, 12.25 and 12.45 μ; λ_{max} 217.5 mμ (log ε 3.75), 222.5 mμ (infl., log ε 3.71), 282.5 mμ (log ε 3.48); λ_{min} 245 mμ (log ε 2.02).

(14) Unless noted otherwise, the solvent in all ultraviolet spectrum determinations was 0.1% acetic acid in ethanol.

TABLE I

2,6-BISHYDROXYMETHYL DERIVATIVES

p-Substituent	Solvent of crystn.	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
2-Cyclopentenyl	Toluene	106	$C_{13}H_{16}O_3$	70.89	71.18	7.32	7.56
Crotyl	Aq. methanol	77–78	$C_{12}H_{16}O_3$	69.20	68.84	7.93	7.57
3-Methylcrotyl	Aq. methanol	110–111	$C_{13}H_{18}O_3$	70.24	70.44	8.16	8.27
Isoamyl	Aq. methanol	73–74	$C_{13}H_{20}O_3$	69.61	69.85	8.99	9.13
Crotyl allyl ether[a]	Toluene–heptane	80–81	$C_{15}H_{20}O_3$	72.55	72.59	8.12	8.27

[a] Made by the reaction of the sodium salt of 2,6-bishydroxymethyl-4-crotylphenol with allyl chloride.

phenol (II), m.p. 111–112°, which was characterized by cyclization to I;[2] λ_{max}[15] 274 mμ (log ε 3.35), 279 mμ (infl. log ε 3.32); λ_{min} 242.5 mμ (log ε 3.20).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.06; H, 9.09.

Hydrogenation of V (Adams platinum oxide catalyst, methanol, 80°) quantitatively yielded *p*-isoamylphenol (XII),[16] b.p. 103–105° (1 mm.), $n^{25}D$ 1.514, which crystallized in the ice-box, m.p. 27–29°.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 79.99; H, 10.19.

Similar hydrogenation of IV yielded *o*-**isoamylphenol** (**XI**), b.p. 85–86° (0.5 mm.), $n^{25}D$ 1.510, which crystallized in the ice-box, m.p. 12–14°.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.03; H, 10.10.

The phenol XI was characterized by a *p*-nitrophenylurethan which was crystallized from a mixture of heptane and toluene and melts at 90–92°.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: N, 8.53. Found: N, 8.83.

Hydration of V.—Stirring a heptane solution of V with 80% aqueous phosphoric acid at 25° for 4 hours gave a 90% yield of VIII.

Dehydration of VIII.—A mixture of 20 g. of VIII, 400 cc. of xylene and 1 cc. of 85% phosphoric acid was refluxed with water take-off under nitrogen for one hour. The mixture was washed with water and distilled *in vacuo* to yield 16 g. of a phenol, b.p. 101–103° (0.7 mm.), the infrared and ultraviolet spectra of which indicated it to be largely V with some X. This dehydration product was characterized by its 2,6-bishydroxymethyl derivative which melted at 109–110° after several crystallizations, and which did not depress the m.p. of the derivative of pure V.

The tertiary alcohol can also be dehydrated by refluxing its xylene solutions with iodine. A solution of 5 g. of VIII and 50 mg. of iodine in 100 cc. of xylene yielded, after refluxing with water take-off for 6 hours, 1.9 g. of unreacted VIII and 2.1 g. of unsaturated phenol, largely V. With 100 mg. of iodine, there was no unreacted VIII, 2.7 g. of crude V and 1.7 g. of higher boiling products. With larger quantities of iodine, more polymeric products and some conjugated phenols are obtained.

The dehydration of VIII also can be effected simply by refluxing or slow distillation in the absence of catalysts. The product X a colorless liquid, b.p. 107–110° (1.5 mm.), $n^{25}D$ 1.537, crystallizes in the cold, melts at 9–12° and depresses the m.p. of pure V. Hydrogenation of X also yielded XII. It does not form a crystalline 2,6-bishydroxymethyl derivative, and its infrared spectrum in CS_2 shows a strong band at *ca.* 11.3 μ absent in the spectrum of V.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.69. Found: C, 81.04; H, 8.70.

The Dehydration of IX.—Twenty grams of IX was refluxed under nitrogen for 3 hours, and distilled to yield some water and 16 g. of a colorless liquid, XIII perhaps with some XIV, b.p. 112–115° (0.5 mm.), $n^{25}D$ 1.525.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.60. Found: C, 83.07; H, 9.65.

Dehydration to the same product also can be effected by stirring a solution of IX in heptane with 85% phosphoric acid at 25°. Dehydration also takes place when a xylene solution of IX is refluxed with a small amount of 85% phosphoric acid. A molecular rearrangement must take place, however, as the product has a higher refractive index and a substantially different infrared spectrum. Also hydrogenation does not yield the crystalline chroman XV.

6-Isoamyl-2,2-dimethylchroman (**XV**).—Hydrogenation (Adams platinum oxide catalyst, methanol, 80°) of the unsaturated ether prepared by refluxing IX, or by treating it with phosphoric acid at 25°, yields a colorless liquid, b.p. 119–120° (1.7 mm.), $n^{25}D$ 1.510, which crystallizes on cooling and melts at 19–20°.

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.50; H, 10.31.

Acknowledgment.—We wish to thank Professor Martin G. Ettlinger for helpful advice.

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(15) The maxima at 224–225 mμ present in the spectra of V and VIII are absent in the spectra of the *o*-substituted II and IV.

(16) Z. M. Nazarova, *J. Gen. Chem. U.S.S.R*, **8**, 1336 (1938); *C. A.*, **33**, 4214 (1939) gives b.p. 245–250°, $n^{27}D$ 1.505.

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Indoles. II. The Acid-catalyzed Rearrangement of N-2-Alkenylanilines

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By Alfred R. Bader, Roden J. Bridgwater and Paul R. Freeman

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[CONTRIBUTION FROM THE LABORATORY OF THE ALDRICH CHEMICAL CO., MILWAUKEE 10, WIS.]

Indoles. II.[1a,1b] The Acid-catalyzed Rearrangement of N-2-Alkenylanilines

BY ALFRED R. BADER, RODEN J. BRIDGWATER AND PAUL R. FREEMAN

RECEIVED JULY 15, 1960

The acid-catalyzed rearrangement of N-2-alkenylanilines provides a convenient and simple method for the preparation of many indoles and indolines.

In studying the reactions of N-alkenylanilines, the observation was made[1b] that N-crotylaniline reacts with polyphosphoric acid to yield 2,3-dimethylindoline and 2,3-dimethylindole. Further work has shown that this proton-catalyzed Claisen-type rearrangement of N-crotylaniline is but one instance of a general reaction not limited either to polyphosphoric acid or to N-crotylaniline.

In the simplest case, N-allylaniline reacts with hydrochloric acid at 180° to yield 2-methylindoline and 2-methylindole, and as N-allylaniline can be made almost quantitatively by heating aniline with allyl chloride,[2] 2-methylindoline and 2-methylindole become easily accessible. Under the conditions used, N-allylaniline is in stoichiometric excess over hydrochloric acid, and the ratio of amine salt to free amine is approximately 2:1. The rearrangement of N-crotylaniline to yield 2,3-dimethylindoline and 2,3-dimethylindole proceeds so smoothly that refluxing of a mixture of excess aniline with crotyl chloride or bromide suffices. The rearrangement is quite exothermic, and an inert solvent such as 2-methylnaphthalene is helpful in controlling the reaction.

At least two competing reactions tend to reduce the yields of the simple indolines and indoles. Firstly, N-alkenylanilines are thermally unstable; thus while N-allylaniline can be distilled at atmospheric pressure, N-crotylaniline cannot, and in the reactions of N-allylaniline, N-crotylaniline and N-allyl-N-methylaniline with hydrochloric acid, some aniline is formed. Secondly, the disproportionation which yields aniline also liberates allyl moieties which alkylate the indoles further. Thus, in the simplest case, 2-methylindole is accompanied by 2-methyl-3-propylindole[3]; presumably the intermediate 2-methyl-3-allylindole is hydrogenated by the considerable quantities of hydrogen evolved. The identity of the 2-methyl-3-propylindole was proved by comparison with a sample prepared by the lithium aluminum hydride reduction of 2-methyl-3-propionylindole.

2-Methylindoline is converted slowly to 2-methylindole by the action of hydrochloric acid at 240°, and larger amounts of indoline and smaller of indole are isolated when the reaction mixture is not allowed to reflux after the initial exothermic reaction has subsided. Actually, even when the indoles rather than the indolines are wanted, it is easier to isolate the indolines, which are colorless, stable liquids, distilling without decomposition at atmospheric pressure, and then to dehydrogenate them. The simplest, quantitative mode of dehydrogenation is to heat the indoline with palladium-on-charcoal at 200° for 15–20 minutes.

The indolines can be characterized by solid derivatives such as arylsulfonamides and the high melting, easily purified diketolilolidines, formed in the reaction of indolines with diethyl malonate.[4] The easiest characterization of indolines is, however, their dehydrogenation to the crystalline indoles.

The rearrangement also can be applied to many ring-substituted anilines. Thus N-allyl-*o*-toluidine and N-allyl-*p*-toluidine yield 2,7- and 2,5-dimethylindole and 2,7- and 2,5-dimethylindoline, respectively, and the reaction of *o*-toluidine with crotyl chloride yields 2,3,7-trimethylindoline and 2,3,7-trimethylindole. The rearrangement is not confined to N-alkenylanilines monosubstituted on nitrogen; N-allyl-N-methylaniline rearranges easily

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(1) (a) Presented in part at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960. (b) For Paper I, see J. E. Hyre and A. R. Bader, *J. Am. Chem. Soc.*, **80**, 437 (1958).

(2) C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, **22**, 1418 (1957).

(3) A. E. Arbuzov, I. A. Zaitzev and A. I. Razumov, *Ber.*, **68B**, 1792 (1935); B. Oddo and C. Alberti, *Gazz. chim. ital.*, **63**, 236 (1933).

(4) E. Bamberger and H. Sternitzki, *Ber.*, **26**, 1300 (1895).

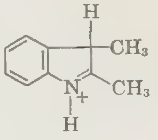
though less vigorously than N-allylaniline, and this preparation of 1,2-dimethylindole is much easier than either the alkylation of 2-methylindole with methyl iodide and sodium hydride or the Fischer indole synthesis.[5]

N-Allyl-*p*-fluoroaniline yields 5-fluoro-2-methylindoline and 5-fluoro-2-methylindole, and N-allyl-*p*-chloroaniline rearranges more vigorously to yield 5-chloro-2-methylindole[6] but no indoline. In each case the indole can be prepared from the aniline and allyl chloride without isolation of the intermediate N-allylaniline.

This general preparation of indoles is limited to those made from anilines sufficiently soluble to allow the preparation of the N-allylanilines and not cleaved by the strongly acidic conditions of the rearrangement. The N-allylanisidines and *p*-benzyloxyaniline, for instance, decompose under the reaction conditions and we have been unable to isolate methoxy- or benzyloxyindoles in the attempted rearrangement.

When first investigating[1b] the reaction of N-crotylaniline with polyphosphoric acid, we observed that the 2,3-dimethylindoline obtained in the rearrangement differed in spectra and solid derivatives from the 2,3-dimethylindoline obtained by the metal and acid reduction of the indole.[7] We then suggested the latter might be the *trans* isomer, and the dehydrogenation following this rearrangement might be stereospecific in such a manner that only the *trans*-indoline was dehydrogenated to the indole. A more careful investigation of the products of the metal and acid reduction of 2,3-dimethylindole and of this rearrangement has shown this not to be the case. The high pressure hydrogenation[8] of 2,3-dimethylindole is essentially stereospecific to yield the *trans*-2,3-dimethylindoline,[9] of lower density and lower refractive index[10] than the mixture of *ca.* 60% *cis*- and 40% *trans*-2,3-dimethylindoline obtained in the tin and hydrochloric acid reduction[7] of the indole. The lack of stereospecificity of the metal–acid reduction probably is due to the addition of hydrogen in separate steps perhaps involving the cation I as intermediate. The 2,3-dimethylindoline obtained in the rearrangement of N-crotylaniline contains, besides small amounts of other bases, *trans*- and *cis*-2,3-dimethylindolines in the ratio of 3 to 1.

Discussion of the mechanism of this reaction must include consideration of the interesting work of Hurd and Jenkins.[2] These workers found that N-allylaniline refluxed with zinc chloride in xylene gave a fair yield of *o*-allylaniline. The reaction of N-allylaniline with zinc chloride at 200–250° without solvent yielded aniline, some *p*-propylaniline, and gaseous hydrogen. The analogous reaction of N-cinnamylaniline yielded 2-phenylquinoline and *o*-cinnamylaniline. No indolines or indoles were found in any of these reactions.



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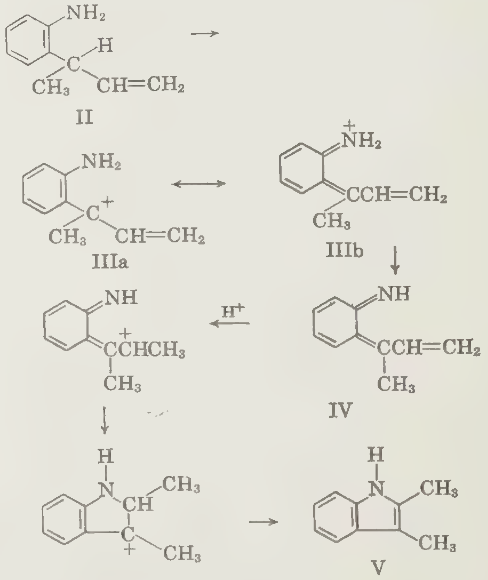
As *o*-allylaniline[2] yields 2-methylindoline when treated with hydrochloric acid at 190–200°, it seems likely that in the formation of 2-methylindoline discussed in this paper, *o*-allylaniline is an intermediate. However, to explain the formation of 2,3-dimethylindoline and 2,3-dimethylindole from N-crotylaniline, it is necessary to assume that the intermediate is *o*-(1-methylallyl)-aniline (II), rather than *o*-crotylaniline which would lead to 2-ethylindoline and 2-ethylindole or 2-methylquinoline derivatives. The rearrangement of N-crotylaniline takes place, therefore, by a Claisen-type mechanism with inversion,[11] whereas the rearrangement of N-cinnamylaniline under the conditions of Hurd and Jenkins proceeds without inversion.

An interesting feature of the reaction presented here is the dehydrogenation that produces indoles. Whereas 2-methylindoline heated with hydrochloric acid at 240° is dehydrogenated slowly to 2-methylindole, the 2,3-dimethylindolines are unaffected by such treatment. Therefore, presumably the dehydrogenation involved in the formation of indoles takes place before cyclization. Since N-crotylaniline, for instance, on direct loss of hydrogen, would give a Schiff base that would not lead



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[5] L. Marion and C. W. Oldfield, *Can. J. Research*, **25B**, 1 (1947).

[6] (a) E. B. Towne and H. M. Hill, U. S. Patent 2,607,779 (August 19, 1952); *C. A.*, **47**, 5452 (1953); (b) British Patent 773,440 (July 3, 1954); *C. A.*, **51**, 12147 (1957).

[7] A. Steche, *Ann.*, **242**, 371 (1887).

[8] H. Adkins and R. E. Burks, Jr., *J. Am. Chem. Soc.*, **70**, 4174 (1948).

[9] The usual rule that catalytic hydrogenation proceeds *cis* is not applicable in this case, as the vigorous hydrogenation[8] employed reaches a true equilibrium involving appreciable dehydrogenation of the indoline. Thus the indoline actually obtained is the more stable *trans* isomer.

[10] K. v. Auwers, *Ann.*, **420**, 84 (1920).

[11] Contrary to Hurd and Jenkins,[2] we think that the Claisen rearrangement does not necessarily involve electron transfer from the hetero-atom to the benzene ring but will be facilitated in amine salts compared to free amines because of delocalization of the positive charge in the transition state.[1b]

to an indole, it may be that the intermediate oxidized is *o*-(1-methylallyl)-aniline (II). Loss of hydride ion to some acid would give the cation III, which could proceed to the imine IV, and thence by normal, acid-catalyzed cyclization to 2,3-dimethylindole (V).

Experimental

2-Methylindole and 2-Methylindoline. (a) Without Solvent.—N-Allylaniline (350 g.) and concentrated hydrochloric acid (150 cc.) were heated with water removal. At *ca.* 180° the reaction became vigorously exothermic, considerable gas, largely hydrogen, was evolved, and the temperature spontaneously rose to 255°. When the reaction had subsided, the mixture was refluxed at 220° for 15 minutes, cooled, and separated into hydrochloric acid-soluble and -insoluble fractions. The acid-insoluble fraction (180 g.) on fractional distillation yielded 40 g. of a fraction A, b.p. 115–125° (1.5 mm.), which crystallized completely in the receiver, and 45 g. of a fraction B, b.p. 135–145° (1.5 mm.). Fraction A crystallized from ligroin in white platelets, m.p. 56–58° which did not depress the m.p. of authentic 2-methylindole.

Fraction B, 2-methyl-3-propylindole was redistilled, b.p. 131–132° (1.1 mm.), $\lambda_{\max}^{\mathrm{EtOH}}$ 225.5 mμ (log ϵ 4.49), shoulder 276 mμ (log ϵ 3.81), 281 mμ (log ϵ 3.83), shoulder 289.5 mμ (log ϵ 3.77), and characterized by a picrate, red-brown needles from methanol, m.p. 145–147°.

Anal. Calcd. for $C_{12}H_{15}N$ (fraction B): C, 83.24; H, 8.67; N, 8.09. Found: C, 83.09; H, 8.44; N, 8.53. Calcd. for $C_{18}H_{18}N_4O_7$ (picrate): C, 53.73; H, 4.50; N, 13.93. Found: C, 53.84; H, 4.33; N, 14.24.

The acid-soluble fraction (149 g.) on distillation yielded 48 g. of a fraction, b.p. 180–210°, largely aniline, and 82 g. of a fraction, b.p. 220–240°, largely 2-methylindoline. Redistillation of this fraction yielded 70 g. of 2-methylindoline, b.p. 226–230°, characterized by its dehydrogenation to 2-methylindole as described below, and by its reaction with diethyl malonate[4] to yield α′-methyldiketolilolidine, m.p. 298°.

Repeating the reaction as above, but refluxing the mixture for 8 hours instead of 15 minutes, gave more acid-insoluble product (234 g.) yielding 87 g. of a crystalline fraction, b.p. 115–125° (1.5 mm.), largely 2-methylindole, and 73 g. of a liquid fraction, b.p. 125° (0.8 mm.)–132° (0.3 mm.), largely 2-methyl-3-propylindole, characterized as above. The acid-soluble fraction (100 g.) again yielded aniline (50 g.) and a fraction (28 g.), b.p. 200–235°, from which no crystalline 2-methylindole could be obtained on dehydrogenation.

(b) With Solvent.—The same quantities of N-allylaniline and hydrochloric acid were heated in 500 g. of 2-methylnaphthalene. At 180° vigorous evolution of gas started, but the reaction was much more easily controlled than without solvent. Reflux was continued for 8 hours, during which time the reflux temperature rose from 220 to 232°. From the acid-soluble fraction (192 g.) there was obtained 55 g. of aniline and 101 g. of 2-methylindoline, characterized as above. From the acid-insoluble fraction (624 g.) there was obtained besides the solvent, 30 g. of 2-methylindole and 60 g. of 2-methyl-3-propylindole.

Other acids, for instance methanesulfonic acid, also react with N-allylanilines to yield the indoles and indolines, but seem to offer no practical advantages.

2 - Methyl - 3 - propylindole.[8]—2 - Methyl - 3 - propionylindole,[12] prepared from 2-methylindole, propionic anhydride and anhydrous sodium acetate analogous to the preparation of 3-acetyl-2-methylindole,[13] melts at 190–192° and strongly depresses the m.p. of 3-acetyl-2-methylindole. Reduction of 2-methyl-3-propionylindole (20 g.) suspended in ether with lithium aluminum hydride (10 g.) yielded an oil (14.5 g.), b.p. 131–135° (1 mm.), characterized by a picrate, m.p. 145–147°, which does not depress the m.p. of the picrate described above. The infrared and ultraviolet spectra of this oil and the 2-methyl-3-propylindole from the reaction of N-allylaniline with acid are identical.

2,3-Dimethylindole and 2,3-Dimethylindoline. (a) From Aniline and Crotyl Bromide.—To 559 g. (6 moles) of aniline, there was added gradually with stirring 402 g. (3 moles) of crotyl bromide. The mixture then was refluxed for 8 hours, the reaction temperature gradually rising to 186°. The mixture was cooled, and separated into a fraction soluble in dilute aqueous hydrochloric acid, and one insoluble. The acid-insoluble fraction (90 g.) on distillation yielded a crystalline fraction (66 g.), b.p. 120–130° (0.5 mm.), m.p. 70–80°, which after one crystallization from ligroin melts at 100–102° and does not depress the m.p. of authentic 2,3-dimethylindole.[14]

The acid-soluble fraction was made alkaline, extracted with toluene, the solvent removed and the residue (460 g.) distilled to yield 211 g. of a fraction boiling from 170 to 210°, mainly aniline, and a fraction (140 g.), b.p. 230–250°, a colorless liquid, n^{25}_{D} 1.554, mainly 2,3-dimethylindoline as indicated by its dehydrogenation to 2,3-dimethylindole as described below. The 2,3-dimethylindoline also was characterized by a benzenesulfonamide, m.p. 101–103°, identical with the benzenesulfonamides made from the indoline obtained in the reaction[1b] of N-crotylaniline with polyphosphoric acid, and the indoline obtained in the high-pressure hydrogenation of 2,3-dimethylindole. Vapor phase chromatographic examination (Apiezon L supported on Celite 545, 100–120 mesh, 130°, flow rate 35 ml./min.) of the 2,3-dimethylindoline fraction showed the presence of two major components, presumed to be the stereoisomeric 2,3-dimethylindolines (see below), and three unidentified compounds[15] present in lesser amounts. Other indolines formed similarly were also shown to contain minor impurities.

The reaction of crotyl chloride with aniline proceeds similarly.

(b) From Crotylaniline and Hydrochloric-Acid.—A mixture of N-crotylaniline[1b] (750 g., b.p. 95–100° (2.5 mm.))[16] and concentrated hydrochloric acid (300 cc.) was heated with water removal to 180° when an exothermic reaction raised the temperature to 220°. The mixture was refluxed at 220–230° for 4 hours, cooled and separated through its solubility in hydrochloric acid into an acid-insoluble fraction A (320 g.) and a soluble fraction B (340 g.). Fraction A on distillation yielded 160 g. of a fraction, b.p. 125–150° (1.5 mm.), which crystallized and which after one crystallization from ligroin melts at 95–98°, mixed m.p. with 2,3-dimethylindole not depressed. Fraction B yielded 170 g. of aniline and 95 g. of a fraction, b.p. 230–240°, which on redistillation boiled at 235–237° and was shown to be 2,3-dimethylindoline by its dehydrogenation to 2,3-dimethylindole.

2,3,7-Trimethylindole and 2,3,7-Trimethylindoline.—The reaction of *o*-toluidine and crotyl chloride yielded 2,3,7-trimethylindoline (presumably a mixture of *cis* and *trans* isomers), b.p. 238–242°, and 2,3,7-trimethylindole, crystallized from ligroin, m.p. 76–77°, characterized by a picrate, m.p. 155–157°.

Anal. Calcd. for $C_{11}H_{15}N$ (2,3,7-trimethylindoline): C, 81.95; H, 9.37; N, 8.68. Found: C, 81.91; H, 9.14; N, 8.51. Calcd. for $C_{11}H_{13}N$ (2,3,7-trimethylindole): C, 82.98; H, 8.23; N, 8.79. Found: C, 82.69; H, 8.06; N, 8.67. Calcd. for $C_{17}H_{16}N_4O_7$ (2,3,7-trimethylindole picrate): N, 14.43. Found: N, 14.40.

Dehydrogenation of the Indolines. (a) With Palladium-on-Charcoal.—When 10 g. of 2-methylindoline and 1 g. of 10% palladium-on-charcoal were heated at 200° for 30 minutes, vigorous evolution of gas occurred, and the mixture solidified completely on cooling, quantitatively yielding 2-methylindole. Similarly, each of the 2,3-dimethylindolines (the mixture of isomers prepared by tin and acid reduction[7] of 2,3-dimethylindole, the *trans* isomer prepared by high-pressure hydrogenation of the indole, and the mixture of isomers from the acid-soluble reaction product of aniline and crotyl bromide) gave 2,3-dimethylindole in high yield.

(b) With Acid.—A mixture of 50 g. of 2-methylindoline and 25 cc. of concentrated hydrochloric acid was heated with water removal to 240°, and refluxed for 2 hours. Separation

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(12) B. Oddo, *Gazz. chim. ital.*, **43II**, 208 (1913)

(13) E. Fischer, *Ann.*, **242**, 379 (1887)

(14) Examination of the mother liquors from the crystallization of 2,3-dimethylindole failed to show the presence of 2-ethylindole. Any 2-ethylindole formed may have been alkylated further, perhaps to 2-ethyl-3-butylindole analogous to the formation of 2-methyl-3-propylindole from N-allylaniline

(15) Perhaps 2-ethylindoline and 2-methyl-1,2,3,4-tetrahydroquinoline formed *via* *o*-crotylaniline are among these

(16) While N-allylaniline can be distilled at atmospheric pressure, N-crotylaniline decomposes considerably

through acid solubility yielded 14 g. of an acid-insoluble fraction, largely 2-methylindole, and 35 g. of an acid-soluble fraction, unreacted 2-methylindoline, characterized through its quantitative conversion by palladium-on-charcoal to 2-methylindole.

Similar treatment of the mixture of 2,3-dimethylindolines made by tin and acid reduction of the indole and of the mixture of 2,3-dimethylindolines made from N-crotylaniline and hydrochloric acid, with hydrochloric acid at 250° for 10 hours, yielded no 2,3-dimethylindole, the indolines being recovered unchanged.

N-Allyl-*o*-toluidine.—The reaction of *o*-toluidine (2 moles) with allyl chloride (1 mole) yielded N-allyl-*o*-toluidine, b.p. 236–238° (760 mm.).

Anal. Calcd. for $C_{10}H_{13}N$: N, 9.52. Found: N, 9.71.

2,7-Dimethylindoline and 2,7-Dimethylindole.—The reaction of 510 g. of N-allyl-*o*-toluidine and 275 ml. of concentrated hydrochloric acid became exothermic with gas evolution at 230°, and the mixture was refluxed at 250° for 15 minutes. The cooled mixture was separated into aqueous hydrochloric acid-soluble and insoluble fractions. The acid-soluble fraction (300 g.) yielded besides *o*-toluidine, 140 g. of 2,7-dimethylindoline, b.p. 240–245°, n^{22}D 1.563. Dehydrogenation with 10% palladium-on-charcoal yielded 2,7-dimethylindole, b.p. 112–116° (1 mm.) which crystallized on standing, m.p. 33–35°.

The acid-insoluble fraction (100 g.) yielded 30 g. of 2,7-dimethylindole, (identical with the above) which was characterized by a picrate, m.p. 154–156° crystallized from ethanol.

Anal. Calcd. for $C_{10}H_{13}N$ (2,7-dimethylindoline): C, 81.62; H, 8.85; N, 9.53. Found: C, 81.18; H, 9.18; N, 9.24. Calcd. for $C_{10}H_{11}N$ (2,7-dimethylindole); C, 82.69; H, 7.63; N, 9.64. Found: C, 82.14; H, 7.84; N, 9.59. Calcd. for $C_{16}H_{14}N_4O_7$ (2,7-dimethylindole picrate): C, 51.93; H, 3.77; N, 14.97. Found: C, 51.45; H, 4.16; N, 14.94.

2,5-Dimethylindoline and 2,5-Dimethylindole.—The reaction of N-allyl-*p*-toluidine and hydrochloric acid carried out analogously is strongly exothermic, and there were isolated 2,5-dimethylindole, m.p. 112–113°; 2,5-dimethyl-3-propylindole, a yellow oil, b.p. 155–160° (1.3 mm.), characterized by a picrate, m.p. 126°; and 2,5-dimethylindoline,[17] b.p. 239–240° at 760 mm., a colorless oil, characterized by its dehydrogenation to 2,5-dimethylindole.

Anal. Calcd. for $C_{10}H_{13}N$ (2,5-dimethylindoline): C, 81.58; H, 8.90; N, 9.52. Found: C, 81.46; H, 9.21; N, 9.58. Calcd. for $C_{13}H_{17}N$ (2,5-dimethyl-3-propylindole): C, 83.37; H, 9.15; N, 7.48. Found: C, 83.16; H, 9.19; N, 7.41. Calcd. for $C_{19}H_{20}N_4O_7$ (2,5-dimethyl-3-propylindole picrate): C, 54.80; H, 4.84; N, 13.46. Found: C, 54.46; H, 4.80; N, 13.72.

1,2-Dimethylindoline and 1,2-Dimethylindole.—The reaction of N-allyl-N-methylaniline, b.p. 213–214°, with hydrochloric acid is much less vigorous than the analogous reaction of N-allylaniline. Four hundred grams of the aniline and 200 cc. of concentrated hydrochloric acid were heated with water removal to 217° and refluxed for 4 hours. The cooled mixture was diluted with ligroin, and the crystalline solid (60 g.), aniline hydrochloride, m.p. 192–195°, filtered off. The filtrate was extracted with dilute hydrochloric acid. Distillation of the acid-insoluble fraction (53 g.) yielded 21 g. of a crystalline fraction, b.p. 90° at 0.2 mm. to 105° at 0.4 mm., m.p. 57–59° after one crystallization from aqueous methanol. This indole depresses the m.p. of 2-methylindole, and does not depress the m.p. of 1,2-dimethylindole made by the alkylation of 2-methylindole with methyl iodide and sodium hydride in dimethylformamide.

The acid-soluble product yielded 102 g. of a fraction, b.p. 225–235°, a colorless oil, which on redistillation gave 90 g. of 1,2-dimethylindoline,[18] b.p. 227–228°, characterized by its dehydrogenation to the crystalline 1,2-dimethylindole.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.20; H, 8.89; N, 9.91.

5-Chloro-2-methylindole.—A mixture of *p*-chloroaniline (1280 g.) and allyl chloride (840 g.) was refluxed for 3 hours, while 800 g. of 50% aqueous sodium hydroxide was added slowly. The mixture was cooled, concentrated hydrochloric acid (700 cc.) was added, and the mixture heated with water removal to 230° when vigorous exothermic reaction with evolution of hydrogen commenced. When the reaction had subsided, the mixture was cooled, and partitioned between aqueous hydrochloric acid and toluene. The acid-soluble fraction yielded only *p*-chloroaniline; no chloroindoline could be isolated. The acid-insoluble fraction was distilled to yield a fraction, b.p. 130–140° (0.1 mm.) (350 g.), which crystallized in the receiver. Recrystallization from petroleum ether yielded 260 g. of 5-chloro-2-methylindole, m.p. 114–116°.

Anal. Calcd. for C_9H_8ClN: C, 65.27; H, 4.87; N, 8.46. Found: C, 65.04; H, 5.03; N, 8.47.

The next fraction (100 g.), b.p. 154–160° (0.2 mm.) 5-chloro-2-methyl-3-propylindole, $\lambda_{\max}^{\mathrm{EtOH}}$ 232 mμ (log ϵ 4.51), shoulder 284 mμ (log ϵ 3.79), 290 mμ (log ϵ 3.82), shoulder 298 mμ (log ϵ 3.76), did not crystallize, and was characterized by a picrate, m.p. 135–136°.

Anal. Calcd. for $C_{12}H_{14}ClN$ (5-chloro-2-methyl-3-propylindole): C, 69.37; H, 6.79; N, 6.74. Found: C, 69.72; H, 7.28; N, 6.92. Calcd. for $C_{18}H_{17}ClN_4O_7$ (5-chloro-2-methyl-3-propylindole picrate): C, 49.50; H, 3.92; N, 12.82. Found: C, 49.63; H, 3.72; N, 12.92.

5-Chloro-2-methylindole also can be obtained from N-allyl-*p*-chloroaniline, b.p. 267–270° (760 mm.), but the isolation of this intermediate offers no practical advantages.

Anal. Calcd. for $C_9H_{10}ClN$: C, 64.48; H, 6.01. Found: C, 64.57; H, 6.12.

5-Fluoro-2-methylindole and 5-Fluoro-2-methylindoline.—The analogous one-step reaction of *p*-fluoroaniline with allyl chloride is less vigorous than the reaction of *p*-chloroaniline, and from the reaction mixture about equal amounts of 5-fluoro-2-methylindole, b.p. 112–120° (0.1 mm.), m.p. 99–101° after crystallization from heptane, and 5-fluoro-2-methylindoline, b.p. 225–227° (760 mm.), were obtained. A vapor phase chromatogram showed the latter to be 97% pure, but to contain eleven minor impurities.

Anal. Calcd. for C_9H_8NF (5-fluoro-2-methylindole): C, 72.47; H, 5.41. Found: C, 72.15; H, 5.36. Calcd. for $C_9H_{10}NF$ (5-fluoro-2-methylindoline): C, 71.50; H, 6.67; N, 9.27. Found: C, 71.40; H, 7.03; N, 9.50.

Both indole and indoline can be obtained also from N-allyl-*p*-fluoroaniline, b.p. 228–233°, but here also isolation of the intermediate offers no practical advantages.

Anal. Calcd. for $C_9H_{10}NF$: N, 9.27. Found: N, 8.91.

Dehydrogenation of 5-fluoro-2-methylindoline with palladium-on-charcoal quantitatively yielded 5-fluoro-2-methylindole.

2-Methylindoline from *o*-Allylaniline.—The reaction of *o*-allylaniline (200 g. prepared by the method of Hurd and Jenkins[2] and characterized by its benzenesulfonanilide, m.p. 83–84°, and its benzanilide, m.p. 122°) with hydrochloric acid (100 cc. of concentrated acid) at 190–200° for 2 hours yielded almost no acid-insoluble product, and from the acid-soluble fraction (170 g.), there was obtained 80 g. of a fraction, b.p. 226–234°, largely 2-methylindoline, as shown by its dehydrogenation to crystalline 2-methylindole in 90% yield.

The 2,3-Dimethylindolines.—The reduction[8,19] of 2,3-dimethylindole (86 g.) in dioxane at 170° in the presence of 17 g. of copper chromite and a maximum hot pressure of 18400 p.s.i. yielded 13 g. of unchanged 2,3-dimethylindole and 63 g. of an acid-soluble, colorless oil, b.p. 235°, *trans*-2,3-dimethylindoline, which a vapor phase chromatogram showed to be homogeneous. Its benzenesulfonamide, m.p. 101–103°, is identical with the benzenesulfonamide described above. The assignment of the *trans* configuration to this isomer is based on a comparison[10] of its refractive index and density with those of the mixtures of isomers described below. The 2,3-dimethylindoline from this hydrogenation has n^{25}D 1.551 and d^{25} 0.987; the molecular refraction is then 47.5 cc., calculated by group refractivities for 2,3-dimethylindoline, 47.5.

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[17] M. Treppenhauer, German Patent 623,693 (Dec. 31, 1935); *C. A.*, **30**, 4874 (1936); French Patent 792,064 (Dec. 21, 1935); *C. A.* **30**, 4181 (1936).

[18] D. A. Cockerill, Sir R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 4369 (1955).

[19] We sincerely thank Dr. William H. Jones for his help with this hydrogenation.

The reduction[7] of 2,3-dimethylindole with tin and hydrochloric acid yielded a colorless, acid-soluble oil, b.p. 234–236°, $n^{25}\text{D}$ 1.556, d^{25} 0.994, which a vapor phase chromatogram showed to contain *ca.* 60% *cis*- and *ca.* 40% *trans*-2,3-dimethylindoline. The benzenesulfonamide[1b] of the *cis* isomer isolated from this mixture melts at 70–71°.

The acid-soluble product of the reaction of aniline with crotyl bromide was fractionated. As shown by vapor phase chromatogram, the fraction b.p. 230–240°, $n^{25}\text{D}$ 1.554, d^{25} 0.990, contained besides three other compounds, *ca.* 55% *trans*-2,3-dimethylindoline and *ca.* 19% *cis*-2,3-dimethylindoline.

Acknowledgment.—We wish to thank Professor Martin G. Ettlinger for valuable advice.

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Hydrogen Peroxide–Vanadium Pentoxide Oxidation of Cyclohexenes

E. J. Eisenbraun, A. R. Bader, J. W. Polacheck, and E. Reif

[Reprinted from the Journal of Organic Chemistry, **28**, 2057 (1963).]

Hydrogen Peroxide–Vanadium Pentoxide Oxidation of Cyclohexenes[1a]

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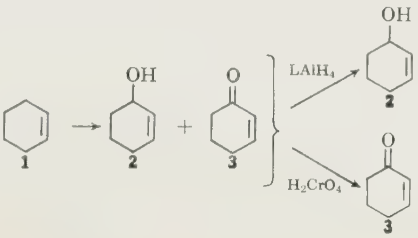
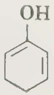
Received January 14, 1963

A re-examination of the oxidation of cyclohexene (**1**) with hydrogen peroxide–vanadium pentoxide (HP–VP, peroxyvanadic acid) revealed 2-cyclohexen-1-ol (**2**) to be a major reaction product. This contradicts an earlier report[2] claiming exclusive formation of 2-cyclohexen-1-one (**3**) as the volatile product. Similar oxidative experiments with the isomeric methylcyclohexenes (**7**, **13**, and **17**) demonstrate the reaction to be essentially nonselective as to site of oxidation and that both alcohols and ketones appear in the volatile products, these being a mixture of direct oxidation products and products derived from allylic shifts.

Treibs[2] and co-workers claimed 2-cyclohexen-1-ol (**2**) to be absent from the products of the oxidation of cyclohexene (**1**) with HP–VP and 2-cyclohexen-1-one (**3**) was reported to be the exclusive low boiling product (40% yield). *trans*-1,2-Cyclohexanediol (**6**) and adipic acid were reported as higher boiling products (9% yield for both). These authors considered 2-cyclohexen-1-one (**3**) to be present in part as the enol **4** to account for the formation of a borate ester.

We have demonstrated that 2-cyclohexen-1-ol (**2**)





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[1] (a) Presented before the Organic Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.; (b) Department of Chemistry, Oklahoma State University, Stillwater, Okla.; (c) Heidenheimer Chemisches Laboratorium, Heidenheim an der Brenz, Germany.

[2] W. Treibs, G. Franke, G. Leichsenring, and H. Roder, *Ber.*, **86**, 616 (1953).

is a major product of the oxidation of cyclohexene with HP–VP, and that it actually exceeds 2-cyclohexen-1-one (**3**) in the product mixture by a ratio of 2.3:1. The oxidation was repreated several times according to the published procedure,[2] and each experiment gave essentially the same product boiling at 61–63° (14 mm.) in reasonable agreement with the reported value. However, gas chromatographic studies show the presence of two sharply defined and completely separated peaks. The mixture of volatile products shows a maximum $\lambda_{\max}^{\mathrm{EtOH}}$ 225 mμ (ϵ 3905) while the reported[3] maximum for **3** is 225 mμ (ϵ 11,270). Strong hydroxyl group absorption was noted in the infrared spectrum of the mixture. These data suggested the mixture to be **2** and **3**. Attempts to separate the mixture by fractional distillation through a spiral column and by preferential reaction with semicarbazide hydrochloride were ineffective. Accordingly, the products were directly interconverted and the identity of the components established through isolation of the individual pure compounds by oxidation to **3** and reduction to **2**.

A Jones' oxidation[4] with chromic acid in acetone solution readily converted the entire mixture to **3**. The course of the reaction was followed conveniently with gas chromatographic analyses at regular intervals. The peak of the gas chromatogram of the reaction product at termination of the oxidation coincides exactly with the smaller and second peak of the chromatogram of the original mixture. The oxidation product was identified as **3** through its ultraviolet spectrum, in agreement with Woodward's rules,[5] its ininfrared spectrum, and the melting point of its red 2,4-dinitrophenylhydrazone.[6] Other syntheses of **3**, each by a different procedure, have been reported.[7]

Reduction of the original volatile oxidation mixture with lithium aluminum hydride in ether solution gave a single product. This product shows no carbonyl band in its infrared spectrum but shows strong absorption in the hydroxyl and double bond regions. These data and the melting point of the phenylurethane derivative,[6] 107–109°, established the identity of the product as 2-cyclohexen-1-ol (**2**).

A reconstituted mixture (70% **2** and 30% **3**) prepared from pure **2** and **3** gives essentially identical spectra (ultraviolet and infrared) and gas chromatographic curve as those from the original mixture obtained by oxidizing cyclohexene with HP–VP.

Pure 2-cyclohexen-1-ol (**2**) was oxidized with HP–VP under the same conditions used for the oxidation of cyclohexene. The steam volatile products from this reaction were shown through gas chromatographic analyses to be a mixture of **2** and **3** in a ratio of 7.3:1. This experiment suggests **2** to be one of the precursors of **3**.

Several routes may exist for the formation of the various products obtained from the oxidation of cyclohexene with HP–VP. 2-Cyclohexen-1-ol (**2**) and 2-cyclohexen-1-one (**3**) may be rationalized as being formed from cyclohexene hydroperoxide by the indicated routes in Fig. 1. *trans*-1,2-Cyclohexanediol (**6**) may arise from cleavage of cyclohexene oxide which has been reported along with **2** as a product of the bimolecular epoxidation of cyclohexene by cyclohexene hydroperoxide.[8,9]

cis-1,2-Cyclohexanediol (**5**) and adipic acid are formed by direct oxidation of the double bond of cyclohexene. We suggest that peroxyvanadic acid, $H_3[V(O_2)O_3]$,[10] attacks the double bond of cyclohexene to form a cyclic ester of peroxyvanadic acid in a reaction reminiscent of the osmic ester formation of olefins.[11,12] The cyclic ester may then be hydrolyzed to *cis*-1,2-cyclohexanediol (**5**) or undergo cleavage to adipic aldehyde in the manner of periodate oxidation of 1,2-glycols.[13] The aldehyde is oxidized in turn to adipic acid. This rationalization suggested the possible presence of some *cis*-1,2-cyclohexanediol (**5**) in the reaction products. The diol **5** is not formed as a major product but we were able to establish its presence through gas chromatographic studies by enrichment of the crude reaction product with authentic *cis*-diol **5**. The diols **5** and **6** are present in the crude reaction product in the ratio of 1:15. The presence of the *trans*-diol **6** was established readily through gas chromatographic studies and direct isolation from the reaction products. Distillation and recrystallization afforded a pure sample of the diol **6** which shows no depression in melting point on admixture with authentic *trans*-1,2-cyclohexanediol (**6**). The proposed routes permit accumulation of *trans*-diol **6** with simultaneous formation of adipic acid.

Milas[14] reported that the HP–VP oxidation of cyclohexene in *t*-butyl alcohol gives a small amount of *cis*-1,2-cyclohexanediol (**5**), an unidentified aldehyde, and considerable quantities of adipic acid. This suggests that it may be possible to control selectively direct attack on the double bond over allylic attack by altering the reaction conditions.

An interesting parallel to the HP–VP oxidation of cyclohexene is provided by the work of Farmer and Moore.[15] These investigators demonstrated that both 2-cyclohexen-1-ol (**2**) and 2-cyclohexen-1-one (**3**) are formed (ratio 6:1) when cyclohexene (**1**) is oxidized with *t*-butyl hydroperoxide at 140°. These authors also demonstrated that oxidation of 1-methyl-1-cyclohexene (**7**) with *t*-butyl hydroperoxide yielded both ketones and alcohols among the products and that all possible allylic positions except on the methyl group were attacked. This is to be expected for a nonselective oxidation process and was rationalized through a free radical mechanism with a hydroperoxide and an olefin radical as intermediates.

The effect of change in concentration of hydrogen peroxide on the composition of the products from the oxidation of cyclohexene was studied with gas chromatography. We found an increase of hydrogen peroxide

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[3] H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953).

[4] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

[5] R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).

[6] F. C. Whitmore and G. W. Pedlow, Jr., *ibid.*, **63**, 758 (1941).

[7] For a reference list of other preparations of 2-cyclohexen-1-one, see K. I. Williamson, R. T. Keller, G. S. Fonken, J. Szmuszkovicz, and W. S Johnson, *J. Org. Chem.*, **27**, 1612 (1962).

[8] R. Criegee, H. Pilz, and H. Flygare, *Ber.*, **72**, 1799 (1939).

[9] E. H. Farmer and A. Sundralingam, *J. Chem. Soc.*, 121 (1942).

[10] N. V. Sidgwick, "Chemical Elements and Their Compounds," Vol. 1, Oxford University Press, New York, N. Y., 1950, p. 810.

[11] R. Criegee, *Ann.*, **522**, 75 (1936).

[12] N. A. Milas and S. Sussmann, *J. Am. Chem. Soc.*, **58**, 1302 (1936).

[13] E. L. Jackson, "Organic Reactions," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 341.

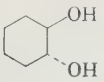
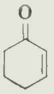
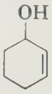
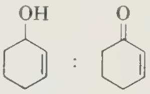
[14] N. A. Milas, *J. Am. Chem. Soc.*, **59**, 2342 (1937).

[15] E. H. Farmer and C. G. Moore, *J. Chem. Soc.*, 149 (1951).

concentration from $^1/_6$ to $^1/_3$ and $^1/_2$ mole caused an increase in yield of **2** and **3**. However, additional increase of hydrogen peroxide failed to increase the yield, and not all the peroxide was consumed during the reaction. The results of these studies on $^1/_6$, $^1/_3$, and $^1/_2$ mole of hydrogen peroxide per mole of cyclohexene are presented in Table I. Thus, the maximum yields of the mixture of **2** and **3** may be obtained with the $^1/_2$ mole ratio.

TABLE I[a]

SUMMARY OF CYCLOHEXENE OXIDATIONS WITH HYDROGEN PEROXIDE

Moles of hydrogen peroxide per mole cyclohexene	Ratio of peak areas			Ratio
	 :	 :		
1/6	1	1.9	3.2	1.7
1/3	1	2.8	5.0	1.8
1/2	1	3.0	4.1	1.3

[a] These data are the average of two analyses.

To account for formation of a borate ester Treibs,[2] *et al.*, stated that 2-cyclohexen-1-one (**3**) exists in part as the enol **4**. In our hands, pure 2-cyclohexen-1-one (**3**) failed to give significant yields of borate ester since major portions of unchanged boric acid and 2-cyclohexen-1-one (**3**) were recovered (84 and 67%, respectively). We were, however, able to isolate a low yield (3.2%) of 2-cyclohexen-1-one (**3**) by steam distilling the pot residue after unchanged **3** had been distilled at 25–35° (0.05 mm.). To isolate **3** from the pot residue suggests that some **3** may have reacted with boric acid through the enol **4**. However, under identical conditions, 2-cyclohexene-1-ol reacted completely with boric acid, and a 78% yield of borate ester was isolated.

The HP–VP oxidations of each of the methylcyclohexenes (**7**, **13**, and **17**) in acetone were studied to determine whether the methyl substituent has any steric effect or directive influence on the site of the oxidation and, hence, the isomer composition. The gas chromatogram of the reaction products from 1-methyl-1-cyclohexene (**7**) showed seven *major* components of which five have been identified by successive enrichment with authentic products. The identified products from the oxidation of 1-methyl-1-cyclohexene (**7**) are **8**–**12** (see Table II).

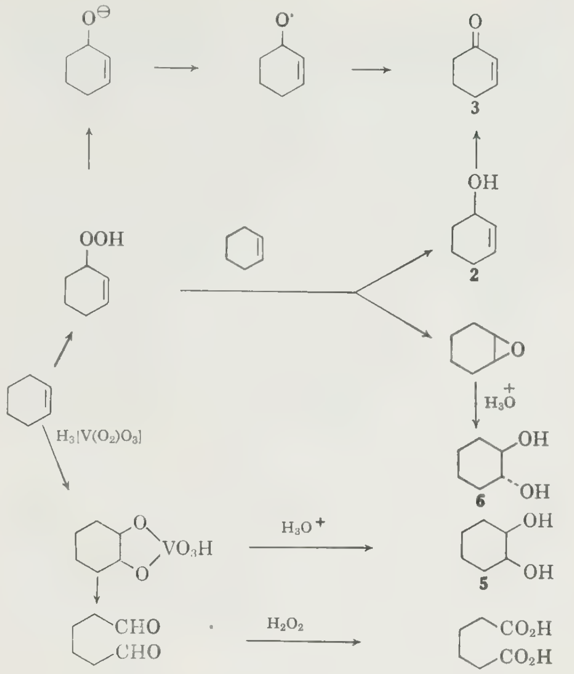
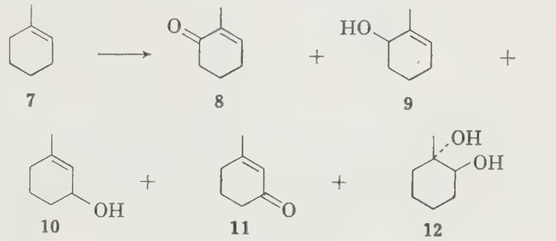


Figure 1



Reduction of the reaction mixture containing **8**, **9**, **10**, **11**, and **12** with lithium aluminum hydride caused

TABLE II

GAS CHROMATOGRAPHIC ANALYSES OF HP–VP–METHYLCYCLOHEXENE OXIDATION PRODUCTS

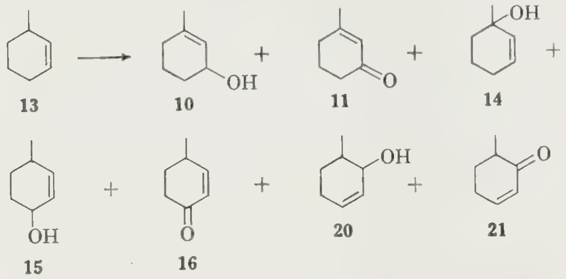
Starting material	Moles of hydrogen peroxide per mole of methylcyclohexene	Column	Oxidation products (time of emergence in min.; relative area)							
7	1/6	Carbowax[a]	Unknown alc.	Unknown ketone (2.8; 1.6)	**8** (5.9; 1)	**9** (8; 3.2)	**10** (8.8; shoulder)	**11** (12; 1.6)	**12** (22.2; 6.6)	
7	1/6	PDEAS[b]	Unknown (2.1; 1.2)	**10** (3.2; 1)	**9** (4.5; 3.3)	**8** (5.4; 1.2)	**11** (12.2; 1.4)	**12** (24.8; 10.7)		
13	1/6	PDEAS[c]	Unknown alc. (1.0; 1.3)	**14** (2.1; 3.3)	**20** (3.2; 5.7)	**15** (5.0; 3.2)	**10** (6.2; 6.3)	**21** (6.5; shoulder)	**16** (8.0; 1.0)	**11** (15; 2.1)
17	1/6	PDEAS[d]	Unknown (5.5; 1.4)	**20** (6.1; 5.3)	Unknown (6.7; shoulder)	**18** (7.0; 2.9)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 2.8)		
17	1/3	PDEAS[d]	Unknown (5.5; 0.7)	**20** (6.1; 2.8)	Unknown (6.7; shoulder)	**18** (7.0; 1.2)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 4.0)		
17	1/2	PDEAS[d]	Unknown (5.5; 0.5)	**20** (6.1; 3.6)	Unknown (6.7; shoulder)	**18** (7.0; 1.5)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 4.2)		

[a] 10% Carbowax 20M on alkaline firebrick; $^1/_4$ in. × 5 ft.; temperature programmed from 130–200°; helium flow, 80 ml./min. [b] 15% PDEAS on acid-washed firebrick; $^1/_4$ in. × 5 ft.; 140°; [c] Same as *b*, except 135°. [d] 15% PDEAS on acid-washed firebrick; $^1/_4$ in. × 4 m.; 160°; helium flow, 65 ml./min. [e] From PDEAS the alcohol **10** emerges with the ketone **21**; these can, however, be separated on Carbowax at 115°. A quantitative estimation is, however, difficult because **21** polymerizes on the alkaline support.

disappearance of **8** and **11**, and an increase of **9** and **10**; this latter compound is present as a minor component in the crude oxidation product. Oxidation of the mixture containing **8**, **9**, **10**, and **11** with Jones' reagent in acetone solution[4] caused disappearance of **9** and **10** with simultaneous increase of **8** and **11**.

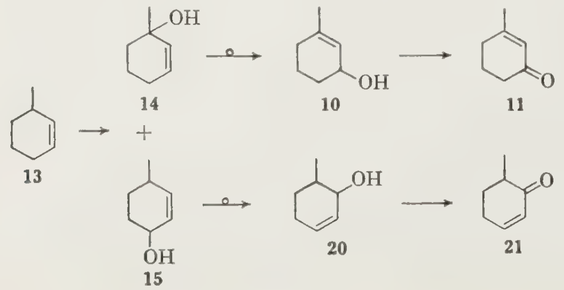
1-Methyl-1-cyclohexene (**7**) was oxidized with chromium trioxide in acetic acid, according to the method of Whitmore and Pedlow,[6] to determine whether this closely related reaction gives the reported mixture of 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexen-1-one (**11**) in the ratio of 1:9.6. We obtained a ratio of 1:7.8. Gas chromatographic analyses also showed the presence of five additional, minor products.

3-Methyl-1-cyclohexene (**13**) was oxidized with the HP–VP oxidant, and the crude product steam distilled to minimize high boiling products (presumed to be diols). These were observed as six minor peaks appearing late in the gas chromatogram. The gas chromatogram of the steam-distilled mixture showed eight peaks, of which seven have been identified (see Table II). The presence of the expected oxidation products **14**, **15**, and **16** from **13** was established by gas chromatographic studies of samples successively enriched with authentic materials.

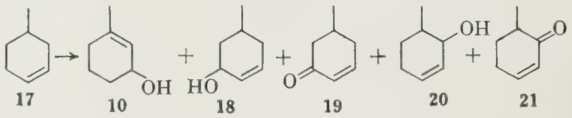


The identities of the remaining peaks were established in a circuitous manner. The total mixture was oxidized with Jones' reagent to a mixture of three ketones with gas chromatography peaks in the ratio 1.0:1.7:3.0. These peaks were shown to be due to ketones **21**, **16**, and **11** in this order, by collecting the ketones in a 2,4-dinitrophenylhydrazine solution as they emerged from the column. The 2,4-dinitrophenylhydrazones were recrystallized and melted at 147–151°, 164–165°, and 176–178°, respectively. An admixture with authentic 2,4-dinitrophenylhydrazones showed no depression in melting point. The presence of the alcohols **10** and **20** was then shown in the HP–VP oxidation mixture by enrichment with authentic materials.

The presence of the abnormal oxidation products **10**, **11**, **20**, and **21** among the expected allylic oxidation products suggested that allylic rearrangement takes place during the HP–VP oxidation of 3-methyl-1-cyclohexene (**13**). The products **10**, **11**, **20**, and **21** are presumed to form as shown (bottom, col. 1).



4-Methyl-1-cyclohexene (**17**) was oxidized similarly and five of the seven major steam-volatile products were identified by enrichment of the product mixture with authentic materials (see Table II). The presence of the unexpected alcohol **10** was confirmed by oxidizing the mixture with Jones' reagent, and showing the presence of **11** in the product by enrichment with authentic **11** in gas chromatographic studies, and by isolating the 2,4-dinitrophenylhydrazone of **11** as it emerged from the column.



While **13** yields both the normal oxidation products, **15** and **16**, and the products of the allylic shift, **20** and **21**, we were unable to detect **15** and **16**, the corresponding products produced by allylic shift accompanying **18** and **19** in the oxidation of **17**.

Experimental

Starting Materials.—The cyclohexene (**1**) used for the HP–VP oxidation was homogenous by gas chromatography (Ucon Polar column at 40°). 1-Methyl-1-cyclohexene (**7**), b.p. 110.3°, showed a single gas chromatographic peak (Ucon Polar column at 50°). 3-Methyl-1-cyclohexene (**13**), b.p. 102.5°, was obtained by fractional distillation from a mixture of 1-methyl-1-cyclohexene (**7**) and 3-methyl-1-cyclohexene (**13**). The gas chromatographic curve (200-ft. squalane capillary column at 26°, hydrogen flame detector) of the fractionated 3-methyl-1-cyclohexene showed 3-methyl-1-cyclohexene (**13**) to be 99% pure. Under these conditions 3-methyl-1-cyclohexene (**13**) and 4-methyl-1-cyclohexene (**17**) showed separation. 4-Methyl-1-cyclohexene (**17**), b.p. 102.7°, was shown to be 99% pure through the same gas chromatographic procedure as described for 3-methyl-1-cyclohexene.

Oxidations with HP–VP.[2] **(a) Cyclohexene, $^{1}/_{6}$ Mole Hydrogen Peroxide.**—To an 8-l. vessel equipped with stirrer, condenser, and dropping funnel were added 500 g. (6.1 moles) of cyclohexene (**1**) and 5.0 l. of acetone. To the well stirred mixture was added the catalyst prepared by mixing 20 ml. of 30% hydrogen peroxide and 2.0 g. of vanadium pentoxide at 5–10° and diluting with 200 ml. of precooled (−10°) acetone. The catalyst mixture was filtered as rapidly as possible so that the temperature did not rise above −2° during preparation. The flask was cooled in a water bath and 100 ml. (*ca.* 1 mole total) of 30% hydrogen peroxide was added to the agitated mixture over about 30 min. The reaction was maintained at 30°. After about 10 ml. of hydrogen peroxide was added, the color changed from orange to green. If the color change did not take place, an additional 5.0 ml. of hydrogen peroxide was added. The mixture was stirred an additional hour and then allowed to stand overnight. The reaction mixture was then held at reflux for 1 hr. with stirring and checked for hydrogen peroxide with titanium sulfate solution (if hydrogen peroxide was present, more cyclohexene was added and the reaction held at reflux for an additional hour). If peroxide was absent, acetone and excess cyclohexene were distilled (4 to 4.5 l.), the distillate diluted with water, and about 100 g. of cyclohexene was recovered from the water-insoluble layer. The residue was dried over anhydrous sodium sulfate, filtered, and distilled at 61–63° (14 mm.) to give 42–45 g. of a mixture of 2-cyclohexen-ol (**2**) and 2-cyclohexen-1-one (**3**). Gas chromatographic studies on 15% phenyldiethanolamine succinate (PDEAS) substrate supported on a column of 60–80-mesh acid-washed firebrick ($^{1}/_{4}$ in. × 5 ft.) showed the presence of two sharply defined, completely separated peaks (2 min. at 140°; 80 ml. helium/min.; Wilkens Model A-90P, thermal conductivity detector). A cleaner product containing less impurities in the gas chromatogram was obtained if the crude product was steam distilled before final distillation. The distilled product gave λ_{max}^{EtOH} 225 mμ (ϵ 3905)[16]; $\lambda_{max}^{CS_2}$ 3.0 and 5.95 μ.

(b) **Cyclohexene, $^1/_3$ Mole Hydrogen Peroxide and (c) Cyclohexene, $^1/_2$ Mole Hydrogen Peroxide.**—These oxidations were carried out essentially as described for part a. The yield of product boiling at 61–64° (14 mm.) was 63–65 g. for $^1/_3$ mole and 78–80 g. for $^1/_2$ mole. Gas chromatographic data on parts a, b, and c are summarized in Table I and described as part of the Jones' oxidation procedure.

(d) **1-Methyl-1-cyclohexene (7).**—The oxidation of **7** was similar to part a and was carried out in a 2-l., three-necked flask containing 1 l. of acetone and 96 g. (1 mole) of **7**. The catalyst was prepared from 0.4 g. of vanadium pentoxide and 2 ml. of cold 30% hydrogen peroxide and diluted with 30 ml. of acetone after 2–3 min.; see Table II for gas chromatographic data of the steam-distilled product mixture. 1-Methyl-*trans*-1,2-cyclohexanediol (**12**) crystallized directly from the reaction mixture and was also isolated as a high boiling fraction, b.p. 100° (12 mm.), m.p. 84–86°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.53; H, 10.83. Found: C, 64.51; H, 10.59.

(e) **3-Methyl-1-cyclohexene (13) and (f) 4-Methyl-1-cyclohexene (17).**—These olefins were oxidized in the same manner as described in part d, and the results are tabulated in Table II.

Oxidation of 1-Methyl-1-cyclohexene (7) with Chromic Acid.—1-Methyl-1-cyclohexene (**7**) (96 g. 1.0 mole), was oxidized according to the precedure of Whitmore and Pedlow[6] except that the reaction mixture was steam distilled rather than extracted. The steam distillate was saturated with salt, extracted with ether, the ether dried over anhydrous magnesium sulfate, filtered, and distilled. The distillation residue was directly injected onto a $^1/_4$ in. × 5 ft. gas chromatographic column containing 15% PDEAS on 60–80-mesh acid-washed firebrick. Flow rate was 80 ml. helium/min. and column temperature was 140°. Two major peaks in the ratio of 1:7.8 were observed. These were established as 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexene-1-one (**11**) by successively enriching the reaction product with authentic ketones **8** and **11** and analyzing by gas chromatography.

Jones' Oxidations[4] of the Reaction Products from HP–VP Oxidations. (a) Crude Mixture of 2-Cyclohexen-1-ol (2) and 3-Cyclohexen-1-one (3).—The crude reaction product from the oxidation of cyclohexene with HP–VP[2] was steam distilled, the steam distillate saturated with salt, extracted with ether, the ether layer dried over anhydrous magnesium sulfate, filtered, and the ether distilled slowly under water aspirator vacuum. The concentrate (424 g.) was dissolved in 5 l. of redistilled acetone and oxidized by dropwise addition of Jones' reagent[4] to the well stirred solution. The reagent is a mixture of 267 g. of chromium trioxide and 230 ml. of sulfuric acid (Spectro Grade 1.84) made up to 1.0 l. with distilled water.[4] The temperature of the reaction was maintained at 20–30° by cooling in a water bath. Progress of the oxidation (2 hr.) was followed by occasionally withdrawing a 1-ml. sample to which was added about 25 mg. of sodium bicarbonate and the pH checked to ensure neutrality. The sample was shaken; the solution decanted and dried over anhydrous magnesium sulfate. The supernatent liquid was directly injected onto the PDEAS column at 140°. Two peaks were observed before oxidation was begun. As the oxidation proceeded, the second peak grew at the expense of the first peak until at termination only the second peak remained. The orange-yellow end point was maintained for about 10 min. This end point is demonstrated easily with a drop of Jones' reagent in a few mililiters of acetone. A few drops of isopropyl alcohol will consume the excess reagent. The reaction product was decanted and the suspension of green salts rinsed with a few mililiters of acetone. Sodium bicarbonate (50 g.) was added to reaction mixture, suspension filtered, anhydrous magnesium sulfate (500 g.) added, the suspension filtered once more, and the acetone distilled through a Vigreux column. On occasion it was necessary once more to dry the product with anhydrous magnesium sulfate before final distillation. Distillation at 61° (14 mm.) gave 371 g. of 2-cyclohexen-1-one (**3**); λ_{max}^{EtOH} 224 mμ (ϵ 11,716) and $\lambda_{max}^{CS_2}$ 5.95 μ.[16] The red 2,4-dinitrophenylhydrazone was recrystallized from isopropyl alcohol and melts at 166–167°.[3,6]

(b) **Products from 1-Methyl-1-cyclohexene (7).**—The crude reaction product obtained from the HP–VP oxidation of 1-methyl-1-cyclohexene (**7**) was steam distilled, the steam distillate saturated with salt, extracted with ether, the ether separated and concentrated by distillation. The concentrate was oxidized with Jones' reagent in a manner similar to part a but on a smaller scale. The oxidation product was isolated by steam distillation, extracted with ether, and the dried ether concentrate injected onto an alkaline Carbowax 20M gas chromatographic column, temperature programmed from 30–200°.

The peaks represented by 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexen-1-one (**11**) were identified by enriching the reaction product sample with authentic materials. The peaks due to the alcohols **9** and **10** were not present in the gas chromatogram.

(c) **Products from 3-Methyl-1-cyclohexene (13).**—The Jones' oxidation of the products from HP–VP oxidation of **13** was conducted in the same manner as for part b. The gas chromatogram (PDEAS column at 135°) showed three peaks in the ratio of 1.0: 1.7:3.0. The ketones were collected from the PDEAS column in a 2,4-dinitrophenylhydrazine solution. The resulting red 2,4-dinitrophenylhydrazone derivatives were collected, recrystallized, and found to melt at 147–151°, 164–165°, and 176–178°. Admixtures of these red 2,4-dinitrophenylhydrazones with 2,4-dinitrophenylhydrazones derivatives of authentic 6-methyl-2-cyclohexen-1-one (**21**), 4-methyl-2-cyclohexen-1-one (**16**), and 3-methyl-2-cyclohexene-1-one (**11**), respectively, show no depression in melting point. The ketones from the individual peaks were collected in ether as they emerged from the column and used to identify peaks in the chromatogram of the crude reaction product and as a source for lithium aluminum hydride reduction to obtain the respective alcohols.

(d) **Products from 4-Methyl-1-cyclohexene (17).**—The Jones' oxidation of **17** was carried out as in part b. The presence of **11**, which emerged last on the PDEAS column, was shown by enrichment with authentic **11** and by the isolation of its red 2,4-dinitrophenylhydrazone derivative, m.p. 176–178°, which does not depress the melting point of the 2,4-dinitrophenylhydrazone of authentic 3-methyl-2-cyclohexen-1-one (**11**).

Lithium Aluminum Hydride Reductions. (a) Mixture of 2-Cyclohexen-1-ol (2) and 2-Cyclohexen-1-one (3).—To a 5-l., three-necked flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel with pressure equalizing side arm, containing 42 g. lithium aluminum hydride dissolved in 3 l. of anhydrous ether, was added a 300-g. sample of a mixture comprised of 37% 2-cyclohexen-1-one (**3**) and 63% 2-cyclohexen-1-ol (**2**) at a rate to maintain gentle reflux. Two hours were required for addition. The reaction mixture was stirred an additional 4 hr. at reflux temperature and water was added dropwise until evolution of gases ceased. The suspension was allowed to settle; the ether solution was decanted and tested with water to ensure complete destruction of lithium aluminum hydride. The suspended salts were rinsed twice with 200-ml. portions of ether and the combined ether solution dried over anhydrous magnesium sulfate, filtered, and ether distilled. The concentrate was distilled at 64–65° (10.5 mm.) to give 240 g. of 2-cyclohexen-1-ol (**2**) whose infrared spectrum showed $\lambda_{max}^{CS_2}$ 3.0 and 6.08 μ. The gas chromatogram (PDEAS at 115°) showed a single major peak and no peak corresponding to 2-cyclohexen-1-one (**3**). The phenyl urethane melts at 107–109°.[6]

(b) **Crude Products from 1-Methyl-1-cyclohexene (7).**—The crude HP–VP products of 1-methyl-1-cyclohexene (**7**) were reduced with lithium aluminum hydride as described under part a. The products were isolated by steam distillation. The steam distillate was saturated with salt and extracted with ether; the ether layer was separated and washed with small portions of water, dried over anhydrous magnesium sulfate, filtered, and distilled. The concentrate was analyzed with gas chromatography (PDEAS column at 130°). The peaks corresponding to the ketones **8** and **11** were completely absent. The peaks corresponding to the alcohols **9** and **10** were found to have increased.

Borate Ester Preparation. (a) From 2-Cyclohexen-1-ol (2).—A mixture of 49.0 g. (0.5 mole) of 2-cyclohexene-1-ol (**2**), 8.4 g. (0.136 mole) boric acid, and 100 ml. of dry benzene was heated at reflux temperature for approximately 2 hr. until water–benzene azeotrope (7.0 ml. total) no longer collected in the Dean–Stark separator. The boric acid completely dissolved within a few minutes after reflux was attained. Most of the benzene (75 ml.) was distilled at atmospheric pressure and the product distilled through a short-path Vigreux column at 30–115° (0.04 mm.). The benzene forerun was discarded and the product fractionated

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[16] D. Dusterhoft of Lakeside Laboratories kindly carried out these determinations.

through a spiral column to give 15.8 g. recovered **2** and 32.0 g. (0.133 mole, 78% yield based on boric acid) of colorless boric acid ester, b.p. 133–145° (0.2 mm.). A center cut, b.p. 142–145° (0.2 mm.), was used for analyses and infrared spectrum; $\lambda_{\max}^{\text{neat}}$ 2.95, 6.08, 7.05, 7.24, 7.60, 8.00, 9.60, 9.40, 9.56, 10.42, 10.76, 11.11, and 13.80 μ.

Anal. Calcd. for $C_{18}H_{27}BO_3$: B, 3.57. Found: B, 3.73.

A 14.9-g. (0.049 mole) sample of the borate ester of **2** was steam distilled, the distillate extracted with ether, the ether extract dried over anhydrous magnesium sulfate, filtered, and the ether distilled to give 12.3 g. (85% recovery) of regenerated 2-cyclohexen-1-ol (**2**). The infrared spectrum and gas chromatogram (PDEAS at 140°) were identical with those of original **2**. The contents of the steam distillation reaction flask were colorless.

(b) **From 2-Cyclohexen-1-one (3).**—Under conditions similar to part a, 2-cyclohexen-1-one (**3**) (0.5 mole) and boric acid (0.136 mole) in 100 ml. of benzene gave 2 ml. of water–benzene azeotrope. The dark-colored reaction product was filtered to yield 7.1 g. (84% recovery) of unchanged boric acid. The filtrate was distilled at 25–35° (0.05 mm.) to give 32.1 g. (66% recovery) of 2-cyclohexene-1-one whose gas chromatogram (PDEAS at 125°) and infrared spectrum were identical with those of original ketone **3**.

The dark-colored, viscous pot residue was steam distilled to give 1.6 g. (0.016 mole, 3.2%) of regenerated 2-cyclohexen-1-one (**3**) whose infrared spectrum, gas chromatogram (PDEAS at 125°) and gas chromatogram of an admixture with **3** were identical with 2-cyclohexene-1-one (**3**). A dark-colored tar remained in the steam distillation flask.

Preparation of Comparison Compounds. (a) ***cis*-1,2-Cyclohexanediol (5).**—A sample of a mixture of *cis*-1,2-cyclohexanediol (**5**) and *trans*-1,2-cyclohexanediol (**6**) was separated by gas chromatography on PDEAS at 162° and collected in ethyl acetate. The retention times were 11.5 and 12.4 min., respectively.

(b) **2-Methyl-2-cyclohexen-1-one (8).**—2-Methyl-2-cyclohexen-1-one (**8**) was obtained by dehydrohalogenation[17] of 2-chloro-2-methylcyclohexanone[18] with lithium bromide and lithium carbonate in dimethylformamide. The ketone **8**, $n^{23}D$ 1.4852, $\lambda_{\max}^{\text{neat}}$ 6.05 μ, gives a single peak on the PDEAS gas chromatographic column at 145°. Its red 2,4-dinitrophenylhydrazone crystallized from isopropyl alcohol melts at 207–209°.[19]

(c) **2-Methyl-2-cyclohexen-1-ol (9).**—The alcohol **9** was obtained from the ketone **8** *via* lithium aluminum hydride reduction in ether solution followed by steam distillation. The product shows a single gas chromatographic peak on the PDEAS column at 145°.

(d) **3-Methyl-2-cyclohexen-1-ol (10).**—A sample of 3-methyl-2-cyclohexen-1-one (**11**) was reduced with lithium aluminum hydride in ether to give 3-methyl-2-cyclohexen-1-ol (**10**), $n^{23}D$ 1.4835, b.p. 82–84° (15 mm.,) and $\lambda_{\max}^{\text{neat}}$ 3.07 and 6.08 μ. Gas chromatographic analysis on PDEAS at 140° shows a single peak.

(e) **3-Methyl-2-cyclohexen-1-one (11).**—A 182-g. (1.0 mole) sample of 4-carbethoxy-3-methyl-2-cyclohexen-1-one,[20] $n^{23}D$ 1.4842, was hydrolyzed by steam distilling from 1 l. of 15% sulfuric acid. The steam distillate was saturated with salt and extracted with ether; the ether layer was washed with water, dried over anhydrous magnesium sulfate, filtered, and distilled to give 87 g. (0.79 mole, 79% yield) of 3-methyl-2-cyclohexene-1-one (**11**), b.p. 80–95° (9 mm.,) $n^{25}D$ 1.4910, and $\lambda_{\max}^{\text{neat}}$ 6.05 and 6.2 μ. The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate melts at 176–178°.

(f) **1-Methyl-2-cyclohexen-1-ol (14).**—A 24-g. sample (0.25 mole) of 2-cyclohexen-1-one was added to 2 equivalents of methylmagnesium iodide contained in a 1-l., three-necked flask equipped with stirrer, condenser protected with a calcium chloride tube, and dropping funnel. The 2-cyclohexene-1-one was added to the chilled (−5°) reaction flask over a 2-hr. period. The reaction mixture was allowed to come to room temperature and then heated at reflux temperature for 0.5 hr. The reaction mixture was then poured onto 500 g. of ice, and the product was directly steam distilled without addition of ammonium chloride or acid. [It was intentional that acid was avoided to minimize isomerization of 1-methyl-2-cyclohexen-1-ol (**14**) to 3-methyl-2-cyclohexen-1-ol (**10**).] The steam distillate (1 l.) was saturated with salt, extracted with 200 cc. of ether, and washed with two small portions of water; the ether layer separated, dried over anhydrous magnesium sulfate, filtered, and the ether distilled. The concentrate was analyzed with gas chromatography (PDEAS column at 100°) and found to be a mixture of 36% 1-methyl-2-cyclohexen-1-ol (**14**),[6] 58% 3-methylcyclohexanone,[6] and 6% 3-methyl-2-cyclohexen-1-ol (**10**).[6] The 3-methylcyclohexanone and the alcohol **10** were identified by enriching the total reaction product with authentic materials and analyzing by gas chromatography. A pure sample of the alcohol **14** was obtained by collection from the PDEAS column at 125°.

(g) **4-Methyl-2-cyclohexen-1-ol (15).**—The ketone **16** was reduced with lithium aluminum hydride in ether to give 4-methyl-2-cyclohexen-1-ol (**15**) which shows essentially a single gas chromatographic peak; the yield of **15** was 71%.

(h) **4-Methyl-2-cyclohexen-1-one (16).**—A procedure similar to j was employed in the preparation of 4-methyl-2-cyclohexen-1-one (**16**) from 4-methylcyclohexanone. The ketone **16** gave a red 2,4-dinitrophenylhydrazone which melts at 168–169° on recrystallization from isopropyl alcohol.

(i) **5-Methyl-2-cyclohexen-1-ol (18).**—A sample of 5-methyl-2-cyclohexen-1-one (**19**) was purified by gas chromatography on PDEAS, reduced by lithium aluminum hydride, and the product isolated by steam distillation. The product, 5-methyl-2-cyclohexen-1-ol (**18**), shows a single peak on the PDEAS gas chromatographic column.

(j) **5-Methyl-2-cyclohexen-1-one (19).**—A 112-g. sample of *dl*-3-methylcyclohexanone was chlorinated with sulfuryl chloride in carbon tetrachloride solution.[19] The chlorocyclohexanone was distilled at 35–87° (0.1 mm.) and shown by gas chromatography on PDEAS at 170° to contain 3-methylcyclohexanone in the initial cut. Center cuts, b.p. 50–80° (0.1 mm.), were free of 3-methylcyclohexanone but appeared to be a mixture of 2-chloro-3-methylcyclohexanone and 2-chloro-5-methylcyclohexanone since double peaks were observed in the gas chromatogram on PDEAS at 170° column temperature.

Dehydrohalogenation[17] in the presence of lithium bromide and lithium carbonate in dimethylformamide solvent was carried out on a 50-g. sample of the mixture of chloro ketones. The product was isolated by steam distillation and extraction of the steam distillate with ether. Dimethylformamide was removed from the ether extract by washing with water. The product, b.p. 34–54° (0.1 mm.), was shown by gas chromatography on PDEAS at 170° to be a mixture containing the desired product, 5-methyl-2-cyclohexen-1-one (**19**) (3.5 min. retention time), as well as 3-methyl-2-cyclohexen-1-one (**11**) and 3-methylphenol (6.2 and 14 min., respectively). The latter compounds were identified by enriching the mixture with authentic materials. A pure sample of 5-methyl-2-cyclohexen-1-one (**19**) was obtained by collecting the ketone as it emerged from the column. An orange 2,4-dinitrophenylhydrazone was prepared from the collected sample and found to melt at 148–149°[21] after recrystallization from methanol.

(k) **6-Methyl-2-cyclohexen-1-ol (20).**—A sample of 6-methyl-2-cyclohexen-1-one (**21**) was purified through gas chromatography (PDEAS column at 150°) by collecting in ether solution. The ether solution was added dropwise to a stirred solution of lithium aluminum hydride in ether. The reaction was heated at reflux temperature for approximately 0.5 hr., cooled, and the excess lithium aluminum hydride cautiously destroyed by the dropwise addition of water. Additional water was added and the reaction product steam distilled. The alcohol **20** was isolated from the steam distillate by extraction with ether, the ether solution dried, concentrated, and analyzed by gas chromatography (PDEAS column at 120°) which showed essentially a single peak with a slight trailing shoulder. This shoulder was assumed to be due to the presence of *cis* isomer. The yield of **20** was 72%. The alcohol **20** was added to a sample of the HP–VP oxidation product of 4-methyl-1-cyclohexene (**17**) and this enrichment established the presence of **20** in the reaction mixture.

(l) **6-Methyl-2-cyclohexen-1-one (21)** was generously donated by D. R. Coulson and E. J. Warawa of Columbia University. Reduction with lithium aluminum hydride gave 6-methyl-2-cyclohexen-1-ol (**20**).

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[17] R. Joly, J. Warnaut, G. Nomine, and D. Bertin, *Bull. soc. chim. France*, 360 (1958).

[18] Generously donated by J. Levy and H. L. Goering of the University of Wisconsin.

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The Oxidation of Dunnione with Alkaline Hydrogen Peroxide

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The Oxidation of Dunnione with Alkaline Hydrogen Peroxide*

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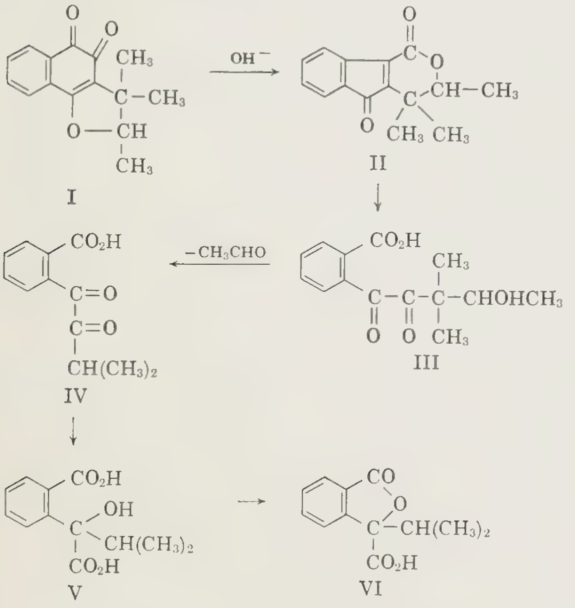
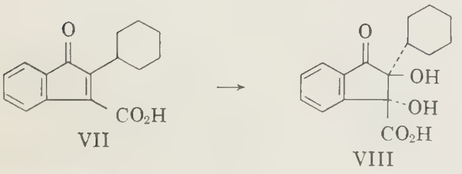
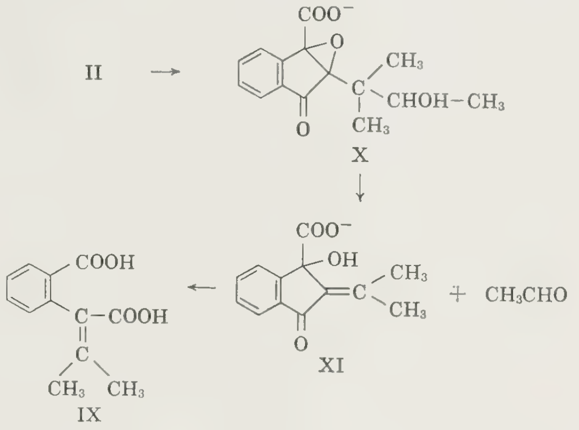
Dunnione, the orange-red pigment of *Streptocarpus dunnii* Mast., has been shown by degradation[1,2] and synthesis[3,4] to be the *o*-naphthoquinone I. Treatment of I with alkali yields allodunnione (II) *via* a rearrangement common to all 2-hydroxy-3-alkyl-1,4-naphthoquinones.[5] The oxidation of dunnione and of allodunnione in alkali with hydrogen peroxide yields[1,2] acetaldehyde, phthalic acid, and a white, crystalline acid, $C_{12}H_{12}O_4$, m.p. 205–206°, formulated as the five-membered lactonic acid VI. This acid was presumed to be formed from allodunnione (II) by oxidation and loss of acetaldehyde from III by a reverse aldol condensation, followed by a benzilic acid rearrangement of IV and ring closure of V to VI. The alkaline hydrogen peroxide oxidation of indenonecarboxylic acids similar to allodunnione yields[6] diols such as VIII from VII, and as Price and Robinson[1,2] had not shown the $C_{12}H_{12}O_4$ oxidation product to be lactonic, we reinvestigated this substance.





Following the published procedure[1] for the oxidation of natural dunnione, we obtained the crystalline acid, the infrared spectrum of which has its carbonyl absorptions between 5.9 and 6.0 μ, thus excluding VI for the structure of this oxidation product. This appeared to be a dicarboxylic acid and comparison with the known[7] α-isopropylidenehomophthalic acid (IX) by mixture melting point and by ultraviolet and infrared spectra established their identity. The structure of IX was confirmed by n.m.r. spectra of the acid and its dimethyl ester.

Presumably the oxidations of allodunnione and VII proceed *via* the epoxides, but while the epoxide of VII is simply hydrolyzed to the diol, the epoxide X more easily cleaves to acetaldehyde and XI. Such cleavages of derivatives of 1,3-diols are well known.[8] The formation[8d] of merolimonol from limonol appears particularly like the present example.



Paths for the oxidation of XI to IX can be written either by way of 2-isopropyl-1,3-indandione and V or through diverse rearrangements of known type,[9] some involving ring contraction to benzocyclobutenes. The degradation is certainly interesting, but since evidence is lacking, we refrain from further details of possible mechanisms.

Experimental

The oxidation of natural dunnione exactly as described[1] yields a crystalline, optically inactive solid, the melting point of which varies somewhat with the rate of heating from 205 to 215°; $\lambda_{\max}^{\mathrm{MeOH}}$ 204 mμ (log ϵ 4.40) and 278 mμ (log ϵ 3.18).

α-Isopropylidenehomophthalic acid[7] made *via* its monomethyl ester, m.p. 141°, has infrared and ultraviolet spectra superimposable on those of the oxidation product. The melting point of a mixture is not depressed.

Proton magnetic resonance spectra for the isopropylidenehomophthalic acid were kindly obtained by Mr. H. E. Miller at Rice University with a Varian A-60 spectrometer (60 Mc.). The acid dissolved with sodium carbonate in deuterium oxide showed only a multiplet from aryl hydrogen atoms centered

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* To Professor Louis F. Fieser

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[8] (a) A. Eschenmoser and A. Frey, *Helv. Chim. Acta*, **35**, 1660 (1952); (b) S. Searles and M. S. Gortatowski, *J. Am. Chem. Soc.*, **75**, 3030 (1953); (c) R. Lukes and J. Plesek, *Collection Czech. Chem. Commun.*, **21**, 1305 (1956); *Chem. Abstr.*, **51**, 12901 (1957); (d) D. Arigoni, *et al.*, *Experientia*, **16**, 41 (1960); D. L. Dreyer, *ibid.*, **20**, 297 (1964); A. D. Cross, *Quart. Rev.* (London), **14**, 317 (1960).

[9] (a) G. B. Payne, *J. Org. Chem.*, **26**, 4793 (1961); (b) G. B. Payne and C. W. Smith, *ibid.*, **22**, 1680 (1957); (c) C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 5352 (1952).

157 c.p.s. below absorption from protons in the water and two equal singlets for the allylic methyl groups at 168 and 193 c.p.s. above the solvent peak. The spectrum of the crude dimethyl ester, prepared with diazomethane in ether and examined in deuteriochloroform, was composed of two singlets for the allylic methyl groups at 95 (presumably *cis* to aryl) and 139 c.p.s. below the tetramethylsilane reference signal, two singlets, also from three protons each, for the carbomethoxyl groups at 217 and 230, a multiplet from three aryl protons at 425–455, and a multiplet from one aryl proton (presumably *ortho* to carbomethoxyl) at 475–487 c.p.s.

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6-Trimethylammoniopurinide

Rainer Klemm, Helmut Schulze, Martin G. Ettlinger, and Alfred R. Bader

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6-Trimethylammoniopurinide[1]

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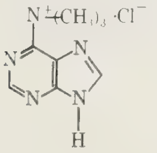
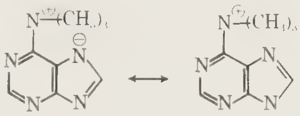
Current clinical interest[2] in the carcinostatic activity of the antimetabolite 6-purinyltrimethylammonium chloride[3] (I) led us to investigate methods for the purification of this salt. Precipitation of its aqueous solution by organic solvents consistently yielded products low in chlorine.[4] During further study, an aqueous solution of I was passed through an anion-exchange column in its hydroxide form, yielding on evaporation a new substance, mp 190–192°, which was chlorine free and had structure II (see Experimental Section).


I


II etc.

Experimental Section

Purin-6-yltrimethylammonium chloride (I) was prepared by the method of Horwitz and Vaitkevicius.[3] Small quantities of crude I were purified by solution in cold water and quick precipitation with acetone; pure I melts at 191–192°.

6-Trimethylammoniopurinide (II).—A solution of 170 g of I in 1 l. of water was passed through an ion-exchange column with 1.5 l. of Dowex 1-X8 (hydroxyl form), and the column was then washed thoroughly with water. The combined eluates were then evaporated to dryness *in vacuo* at 50°, and the product crystallized from water and was dried *in vacuo* (P_2O_5) to yield 112 g of II, mp 190–192°.

Anal. Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.30, 54.30; H, 6.03, 6.20; N, 39.18, 39.49.

Structure II is supported by the nmr spectrum[5] in D_2O which shows, besides two equal peaks at 221 and 212 cycles below the signal from solvent protons, only one, much more intense, peak at 59 cycles above solvent reference. The dipolar salt II has the same melting point as 6-dimethylamino-1-methylpurine[6] (III), and the melting points of the respective picrates are also similar. However, the mixture melting point of II and III is depressed, the maximum of the ultraviolet spectrum of II is at much lower wavelength than that of III, and the nmr spectrum of III shows two well-separated methyl group signals. Electrometric titration shows that II is a weak base and the pK_a of the conjugate acid I is 6.8. This value appears reasonable, for purine has $pK_a = 8.9$,[7] and the trimethylammonium group would lower the pK.[8]

Similarly, the ultraviolet spectrum of II appears reasonable [$\lambda_{max}^{H_2O}$ (pH 10) 274 mμ (log ϵ 3.86)] when compared with that of purine anion[9] [λ_{max} (pH 11) 271 mμ (log ϵ 3.88)]; the trimethylammonium group, being nonconjugating, would be expected to have little effect. The spectrum of II at pH 1 (that is, of I), with λ_{max} 265 mμ (log ϵ 3.94), is also close to that of neutral purine [λ_{max} 263 mμ (log ϵ 3.90)].

Saline solutions of I and II are indistinguishable.

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(1) Alpurine (Trademark applied for).

(2) V. K. Vaitkevicius and M. L. Reed, *Proc. Am. Assoc. Cancer Res.*, **7**, 72 (1966).

(3) J. P. Horwitz and V. K. Vaitkevicius, *Experientia*, **17**, 552 (1961).

(4) Similar material, which can now be construed as a solvated equimolar mixture of I and II, was obtained by E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3274 (1962).

(5) We wish to thank Dr. George Slomp for determining the nmr spectrum of II.

(6) (a) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Am. Chem. Soc.*, **86**, 5320 (1964); (b) B. C. Pal and C. A. Horton, *J. Chem. Soc.*, 400 (1964); (c) we wish to thank Professor R. K. Robins for a sample of III.

(7) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

(8) H. C. Brown, D. H. McDaniel, and O. Häflinger in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press Inc., New York, N. Y., 1955, p 592.

(9) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

Alfred **Bader** (New York), Robert **Rosner** (Vienna) and Paul **Shore** (St. Louis)*

ANTI-SEMITISM, TOLERANCE, AND THE POLITICS OF CHEMISTRY IN NINETEENTH CENTURY VIENNA

Introduction

No city in Europe in the nineteenth century had a history as deeply intertwined with the careers of its Jews as Vienna. No city has had more great Jewish scientists and artists, and none has harbored more virulent anti-Semitism.[1] The long history of the Jews in Vienna covers periods of prosperity and persecution which depended on the needs and whims of the Habsburg monarchy. During wars against Protestants or the Turks, whenever there was pressing need for their support as financiers and suppliers of food and munitions for the army, the wealthier Jews were protected by Imperial policy. When need for organized support lessened or opposition from the Catholic Church and from popular demonstrations increased, they suffered suppression and even expulsion. The Empress Maria Theresia (1740–80), like most of her Habsburg ancestors, despised the Jews and restricted the number living in Vienna to wealthy bankers and their families. Of a total of 350,000 Jews living in the entire Austrian Empire in 1779, only about 500 lived within the city.

Maria Theresia's son, Joseph II, driven by the desire to make his dominions more efficient and prosperous, made great efforts to centralize and modernize the Habsburg empire. In 1782, one year after his ascension to the throne, he issued the *Toleranzpatent*, which made it easier for the Jews to settle in

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* The writers gratefully acknowledge the assistance of Professor Edward Timms.

[1] For overviews, see:
- (a) R. S. *Wistrich*, „The Jews of Vienna in the Age of Franz Joseph", Oxford University Press, 1990;
- (b) G. E. *Berkley*, „Vienna and Its Jews: The Tragedy of Success, 1880–1980's", Abt Books, Cambridge, Massachusetts, 1988;
- (c) B. *Pauley*, „From Prejudice to Persecution: A History of Austrian Antisemitism", The University of North Carolina Press, 1992;
- (d) M. L. *Rozenblit*, „The Jews of Vienna 1867–1914: Assimilation and Identity", The State University of New York Press, Albany, 1983;
- (e) P. J. *Shore*, „Jews at the University of Vienna, 1782–1822", Öst. Ges. Wissenschaftsgeschichte, 15, 43 (1995);
- (f) R. *Rosner*, „Die Chemie in Österreich zur Zeit der Veröffentlichung von Josef Loschmidt's Chemische Studien", ADEVA Archiv der Universität Graz, 1997.

Vienna and removed some of the worst restrictions under which they suffered.[2] They were encouraged to engage in agriculture and to learn trades. Most importantly, Jews were permitted to attend schools and universities and could receive doctorates in the faculties of Medicine and Law.[3] The edict's goal was: *To make the Jewish nation useful and serviceable to the state, mainly through education and enlightenment of the Jews as well as by directing them to the sciences, the arts and the crafts.*

This ordinance was strongly criticized by the conservative members of the Catholic clergy, led by Christoph Anton Cardinal Migazzi, the Archbishop of Vienna, and many others. After Joseph's death in 1790, new regulations were issued by his successors, Leopold (1790–1792) and Francis I (1792–1835) which again made it more difficult for Jews to stay in Vienna and the neighboring provinces of Upper and Lower Austria. But in spite of all the restrictions, a growing number of Jews did settle in Vienna in the first decades of the 19th century and start businesses.

Some of these were related in one way or another to chemistry. A survey of the development of industry in 1825 reported that production of acetic acid had begun in Mödling, a town near Vienna, according to the process developed by „Ehrenfels the Israelite".[4] Several patents for novel methods of producing acetic acid and for tanning and similar trades were granted to Jews coming from the Eastern part of the empire, but such business activities were often feared by Gentile competitors who tried to oppose the licensing of Jewish merchants, and were willing to go to the authorities to prevent such competition.[5]

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[2] The legal and political background of emancipation in the Habsburg lands is outlined in „Joseph and the Jews: The Origins of the Toleration Patent of 1782," Austrian History Yearbook, 4, 101–119.

[3] Joseph's decree of January 12, 1782 states „...His Majesty has most graciously resolved that as children of Jews are permitted to attend all schools of higher learning apart from those of Theology, provided they exhibit excellence through talent and application in the sciences, have passed all preliminary examinations and fulfilled all requirements, they may attain the title of Doctor in Law and in Medicine ..." [Translated from the decree in the archives of the University of Vienna]

[4] S. von *Keess*, Beschreibung der Fabikate, die in den Fabriken des österreichischen Kaiserstaates erzeugt werden. Vol. 2, p. 356. J. Wellishauser, Vienna, 1820–1823. Anton Ehrenfeld, whose father was „*Essigfabrikant*" (producer of acetic acid), was a student at the Polytechnical Institute in 1819–20.

[5] Competition between Gentile and Jewish merchants had long antecedents in the Habsburg empire. See Tomas *Pekny*, Historie Židú v Čechách a na Moravě. Sefer, Praha 1993, p. 220ff.

Regulations for the establishment of such businesses were very restrictive, and the Professor of Chemistry of the Polytechnic Institute (today the Technical University) in Vienna was often consulted before any chemistry-related business could be established.[6] Professor Paul Traugott Meissner (1778–1864), a native of Transylvania, who held this position from 1816 to 1845, met fierce opposition when he tried to help Jews.

P. T. Meissner's The Emancipation of the Jews

Meissner was a man of unique character and great wit and therefore popular with his students. He was known for his experimental skill and for the development of novel chemical equipment, but he was very obstinate and sometimes quarrelsome. He clung to theories which had been discarded by most other scientists and developed his own system of chemistry, for which he was strongly criticized by Justus von Liebig, the most outstanding German organic chemist of his time.

Meissner's greatest claims to fame came through two totally different events. His invention of a practical heating system for buildings in Austria endeared him to the upper classes. Yet Meissner had his enemies. Liebig's attack on him in an article on chemistry in Austria described his incompetence as a teacher of chemistry and finally led to his forced retirement:[7]

... in the most important and most influential institute, we see a man of whom we can honestly say that he has harmed his country immeasurably. His tremendous memory is like the stomach of one who eats everything that is offered. Food is gobbled up along with bits of glass and stones, but nothing of

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[6] The Polytechnical Institute was divided into a commercial and a technical division. From its very beginning, there were Jews, mainly from Hungary, Bohemia, Moravia and Triest, enrolled in each division. The exact number cannot be determined. The records of some students were clearly labeled *'Israelit'*. Others indicate that the student came from the *'Israelitische Schule in Prag'*. Yet others gave the father's profession as *'Handelsjude'*. In some instances, only the names – e. g. Wertheimstein in 1816, Eduard Lewy and Joseph Muttersgleich in 1817 – suggest that they were Jews.

It is interesting to note that many Moravian Jews obtained patents related to the production of alcohol and acetic acid. Albert Lewin and Moses Trebitsch from Nikolsburg received a patent in 1824 for improved distillation equipment, as did Wolf Tauber from Leipnitz in 1825 and Isaak Kohn from Jamnitz in 1826. Before Ehrenfels the Israelite produced acetic acid in Mödling in 1825, Rubin Friedman and Albert Simon Kohn had received patents for improved acetic acid production in 1823. [S. von *Keess* and W. C. W. *Blumenbach*, Systematische Darstellung der neuesten Fortschritte in den Gewerben und Manufakturen, Vol. 2, pp. 198–209. Carl Gerold, Vienna, 1830.]

[7] J. *Liebig*, Annalen der Pharmazie, 25, 339 (1838).

what he devours goes into his bloodstream. His strength is not increased but rather diminished. In all his organs there is irritability and weakness, his nerves are jangled, his impressions are all wrong, his eyes cannot distinguish between colors, his feelings are dulled. Read his books: every letter therein is typically Meissner.

... Take a young man who has studied under Meissner: he is stuffed with the most desperate and pretentious views. He has learned nothing about real chemistry ... Nonetheless, Meissner had many students: He was straightforward and totally without Viennese charm and hypocrisy. They loved him despite his being a Protestant – a rarity among Austrian academics – despite his absurd chemical ideas and his boring lectures – he usually read from a chemical textbook he had written and rarely demonstrated experiments.

He considered himself „a strict Communist". Today we would call him an idealistic socialist. Perhaps his experiences in a minority religious group influenced his hopes for fair treatment for all. When, after the revolution of March 1848, censorship was abolished in Austria and everyone could express his views freely, Meissner wrote a book *(fig. 1)* of 177 pages proposing a constitution for an imaginary newly-populated island.[8] Almost at the end of this „last epistle to his former students" are his thoughts about Jews, expressed in vignettes:

The Emancipation of the Jews

My father had a large dairy farm in the suburbs. On the farm was a distillery where there was an old Jew named Abraham, a thoroughly honest fellow. He had a daughter called Salome. Salome had married Ephraim and the two had a son who was to be named Isaac.

Old Abraham had invited me to this celebration, but before the ceremony, the future little Isaac had a very human accident. I chanced to come along just as he was taken out of the bathtub and, cleaned up after this little mishap, was about to be tidied and made ready to appear before the Rabbi. I happened to notice for the first time that little Jewish babies looked exactly like little gypsies, ordinary Christians and even the babies of the nobility.

After this discovery in natural history had established itself in my mind, we moved on to the sacred business of changing the future Isaac into the present Isaac. Oh, even now, after sixty-two years, my mouth waters and I remember with pleasure how good the cookies were that old Martha gave me, which looked much like vetchbeans but were nicely brown and very sweet. Just as this delicacy was most luscious, little Isaac suddenly cried out at the very instant when he had turned into the Isaac of the present. I rushed towards

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[8] P. T. *Meissner*, „Des alten Schulmeisters Glossen über die neuen Verfassungs-Experimente", Vienna, 1848.

him but couldn't see anything because of the rabbi's long caftan. Children, however, are careful observers, and also streetwise. Before a fortnight had passed, the secret was out, and from then on I couldn't stand the old rabbi with his long ugly beard. I really don't approve that man should want to correct God's work, just as is now the case with celibacy and was years ago – in honor of God – in the boys' choir of the Holy Father in Rome.

From then on, my childish ideas about Jews stood corrected. I then knew, through having seen this with my own eyes, that Jews were human beings, and I tried as best I could to help my father when he got angry, when he fought with the entire city because they would not allow him to keep old Abraham living at his dairy.

However, there were many occasions when I got angry by myself and argued pretty hard on my own account, quarreling with other people about the Jews, because no matter where my fate sent me, everywhere I found the same hostile spirit against this terribly downtrodden people.

From the frying pan into the fire – by chance I got my appointment where I was meant to act as a brake to keep the Jews down. I am speaking of the post as teacher of chemistry in the Polytechnic Institute, a post which involved me in refereeing trade disputes, particularly those dealing with licensing – all behind the scenes and clearly for the convenience of those in power.

In this position, I simply couldn't avoid a fight. I just had to choose between helping to keep these severely repressed Jews down or making a number of enemies. I chose to follow my conscience and so had to fight a good deal, and even in just causes was rewarded only with trouble and jealousy. Yes, it even came to the point that I was accused of accepting bribes, and the Minister President shouted to my face, „Well, we know that you are a patron of the Jews."

From these facts, you can see, my friends, that I more than many another, had the opportunity to study the full extent of the pressure on the Jews, and I have therefore had occasion, more than others, to think seriously about the Jewish Question.

You may also conclude from this how happy I was later, that the old prejudices against this poor oppressed people slowly declined and were replaced by friendlier thoughts.

Finally, you will understand how sad I am nowadays to see this good feeling declining. Why is this happening? Because now and then a Jew in this period of free speech is speaking too loudly, and perhaps has even done something bad. Is that enough reason to hate the entire people, the people that has been treated more miserably than any other? I believe not.

Look here, my friends, this is the point we have now reached. Should the Jews be partially or completely emancipated?

By way of reply, I offer only the short account of the case in which I defended myself when I was called a patron of the Jews. What happened was the following. At the time of the famine of 1817, two hard-working Jewish brothers who wanted to work, not just as traders, had established a factory in Vienna in which a good many men found employment. Soon, however, Christian manufacturers of the same product complained and demanded their expulsion. During the investigation by the commission, and to its astonishment, it was found that most of the Christian manufacturers who were complaining had dismissed their workers because everything had become so expensive, whereas the Jewish manufacturers had kept their workers on – Christian workers, mind you – even though they could not sell their goods. And despite considerable sacrifice and troubles they continued to pay them. Hence, my conscience forced me to stand up for these good brothers, and this was why I was accused of being a patron of the Jews.

My defense was as follows: It is quite true that Jews have several bad traits, often, for instance, bargaining so hard that I could not possibly defend it. However, it is undoubtedly equally true that Jews have been forced out of all other means of earning a living and the only thing they could do was to trade. This has been so for the last 1800 years and has forced the Jews to become what they now are.

If this really is the case – and surely no sensible person can deny it – then we are the real cause of this, and we have the absolute obligation to give these miserably treated Jews all rights, without exception, just as we have them. Then we should wait for another 1800 years to see whether they change.

If the Jews don't change in 1800 years, then there is proof that they are absolutely no good, and we have the right to drive all of them out of the world. I prophesy, however, that the emancipated Jews, once they live among us, will be ashamed of their repulsive peculiarities and customs and will lose these. Yes, I even prophesy that emancipation is the surest means of letting the Jews disappear completely from the world as a peculiar people, because, through marriage they will intermingle with other people.

„You are certainly mistaken in that," the President shouted, „because a Jew will never marry a Christian." My reply was, „Your Excellency, I don't depend on the Jew at all. My hope rests on the Christian son. The young scamp will look over the fence and discover that the daughter of Israel is a very pretty child. He will chat up pretty Judith and poor old Israel will have to recognize his fate. That is what my calculation is based on."

That was my opinion then and still is and will remain so, because I am convinced that God is such a great monopolist, that despite our different Gods, once God's patience is at an end, he will chase us with the broom of common sense into a single and united church.

Now, however, my Old Testament friends, a word to you: „Look, you cannot imagine how much I have had to bear because of and for you these 40 years. Inquire and you will learn that even at the time when it was still customary, I never accepted the ducats offered by your brothers. However, I certainly deserved thanks, and now in these new times, I demand it. Therefore I ask you for two things:

Firstly, restrain your hotheads so that they do not inflame other people too much. Be assured that it does no good. It alienates many a person who felt warmly toward you, and it can only do harm.

Secondly, I still do not accept money from you; however, speak to your rabbis for me. They are in the position to do me a great favor. What is that? I don't have to tell you. The rabbis are educated people. They will discover for themselves what they should, or rather, what they should not do.

Now, however, another word to you, my Christian friends – a little story. A few days ago, at the Schottenhof, I met an old butcher whom I have known for 34 years and who feels kindly towards me. Meaning well, I spoke very strongly to this fellow about these hotheads. Think carefully about his answer. „Dear sir," he said, „when a man has had nothing to eat for a long time and then comes to a laden table, he thinks that he simply cannot get enough, and so he sometimes eats too much. You shouldn't take that amiss." Isn't the old butcher a clever man? Should we be less clever than that old butcher?

While Meissner was arraigned as an incompetent chemist, he nevertheless was idealistic and tolerant at a time of widespread intolerance. It is worth noting, however, that Meissner did express the hope, common to many Gentiles educated after the Enlightenment, that the Jews would ultimately „change" and thereby become better citizens.[9]

Viennese society, and university academic culture in particular, were slow to accept even the cautious tolerance of Meissner. Although the first Jewish students entered the medical school in Vienna in 1782 and received their degrees in 1789, study and advancement, particularly in the academic world, was extremely difficult until late in the next century.[10] The careers of Wilhelm and Theodor Wertheim illustrate the problems Jews faced.

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[9] Enlightenment intellectuals, almost without exception, tempered their toleration of Jews with the hope that contact with Gentiles would ultimately „improve" them. See Jonathan *Hess*, „Progress, Violence and the Jewish Question: Christian Wilhelm Dohm and the Debate on Jewish Emancipation in Eighteenth-Century Germany," Proceedings of the East-West Seminar, Berlin, 1997 (in press).

[10] Max *Neuberger*, „Die ersten an der Wiener medizinischen Fakultät promovierten Ärzte jüdischen Stammes," Monatschrift für Geschichte und Wissenschaft des Judentums 62, 219–222.

The Careers of the Wertheim Brothers

The father of Wilhelm and Theodor, Zacharias Wertheim, descendant of a Viennese Jewish family of '*Hofjuden*' (protected Jews) who had been prominent for centuries, had graduated from the medical school in 1802 at age 22. Wilhelm and Theodor were particularly attracted to physics and chemistry, fields which Jewish students were entering in greater numbers in the decades after 1815. Both were taught in the medical faculty at the University of Vienna until 1849, when they came under the faculty of philosophy. After receiving his M.D., Wilhelm went to Berlin to continue studying physics and chemistry with Mitscherlich. Theodor, the younger brother, followed him to Berlin before his graduation, despite their father's protests.[11]

Wilhelm, a physicist, then moved to Paris to accept a position at the Ecole Polytechnique. Theodor, who concentrated on organic chemistry, returned to Austria to work with Redtenbacher, a Liebig student, who had become Professor of Chemistry in Prague. Redtenbacher helped him obtain a grant for his research, which enabled Wilhelm Wertheim to publish a paper, praised by Liebig and Berzelius, on the chemistry of oils of garlic and mustard. In 1848, the year of great revolutionary hope for reform, both Wertheim brothers were elected members of the newly-formed Vienna Academy of Sciences. There was no possibility of academic advancement in Austria, however, for only members of the Catholic church were normally appointed as university professors.[12] After the death of their father in 1852, Theodor converted and was offered a professorship in Pest in 1854, where he taught in German until 1860. After 1860, because of Hungarian nationalist demands, he was required to lecture in Hungarian, although they would have made an exception and allowed him to teach in Latin, the traditional language of education and politics in that country. Unwilling to do this, Theodore moved to Graz in 1861, where he was successful, becoming dean in 1862, a position he held until his death in 1864.

Wilhelm would not consider conversion and remained in Paris, where Jews had enjoyed relatively better opportunities since the reforms initiated by

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[11] Biographical sketches of the Wertheim family are found in C. von *Wurzbach*, „Biographisches Lexicon des Kaiserthums Österreich“, Vol. 53, 113–121 (1886), Vienna; and Siegfried *Plaschkes*, „Die ersten jüdischen Ärzte der Wiener Universität und ihre Schicksale,“ Bulletin des Leo Baeck Instituts, 5 (1962), p. 207.

[12] As early as 1806 a Protestant had been appointed to the Faculty of Philosophy, but the culture of the University of Vienna for many decades slowed the admission of non-Catholics, Protestant or Jewish, to university posts. See *Shore*, op. cit., p. 62. The issue of how academic prejudice in Austria against non-Catholics in general related to widely held societal attitudes of anti-Semitism merits further investigation.

Napoleon.[13] Yet despite being greatly appreciated there, he wanted to return to his native Austria. In 1851, he did go briefly to Vienna, hoping to obtain some position commensurate with his abilities but was offered only a „Docentur“ at the university, the equivalent of an assistant professorship, which was itself considered a special concession. Frustrated, Wilhelm ultimately returned to Paris, where he became a French citizen and received many further honors for his outstanding work during the next ten years. Yet he was not happy, sank into a deep depression and committed suicide in 1861.

Wilhelm Wertheim's obituary was written by Anton Schrötter, Meissner's successor as professor of chemistry at the Polytechnic Institute in Vienna and secretary of the Academy of Sciences. Schrötter regretted the fact that no matter how outstanding, no Jew was ever given a professorship at an Austrian university[14]:

Thus passed a man of rare talent in the full flower of his powers, in a foreign land which had welcomed him, while his fatherland has only the consolation that hopefully the times have gone forever when a flawless character and outstanding scientific ability are not the deciding factors in the choice of a teacher.

Schrötter was overly optimistic in thinking that flawless character and scientific ability would eventually outweigh questions of religion. Anti-Semitism had continued and as the nineteenth century preoccupation with nationalism increased, had became more racial than religious.

Since the revolution of 1848, liberalism had been the dominant ideology of intellectuals and scientists in Austria as in most other European countries. But Austrian liberalism was not merely anti-clerical as elsewhere. With the growing demand by other nationalities within the Habsburg empire for the same rights as the German-speaking population, the Austrian liberals became increasingly German nationalists and anti-Slav. Significantly, their attitude was shared for some time by most Jewish intellectuals who were German-speaking. These Jews chafed under the humiliating sanctions placed on them and identified with the desire for constitutional freedom and equality, considering themselves not only Austrians in terms of political identity but Germans in terms of culture.

Some Austrian Jews had played a prominent part in the Revolution, for which they were blamed by the establishment and the Catholic Church, which was

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[13] See Abram Leon *Sachar*, A History of the Jews. New York: Alfred A. Knopf, 1964, pp. 281–283. Napoleon's reforms were preserved, at least on paper, first by the Bourbons and then by subsequent French regimes throughout the nineteenth century.

[14] A. *Schrötter*, „Berichte des General-Sekretärs“, p. 188, Almanach, Academy of Sciences, Vienna, 1861.

alarmed by the prospect of equal rights for Jews. However, government restrictions were finally removed by the Constitution of 1867. Enacted primarily to appease Hungarian demands for equality, it „abolished all disabilities on grounds of religious differences“. As a result, the number of Jews in Vienna increased rapidly.

By 1885, 35% of students at the University of Vienna were Jews.[15] Although this number decreased in the following years, fear of competition and Jewish domination of finance fostered a spread of racial anti-Semitism throughout the university. Many Jews had assimilated and intermarried and many others had converted, but to the anti-Semites, the conversion of a Jew to Christianity did not alter his ‘race’, in increasingly secular and ethnicity-conscious Austrian society the defining characteristic of a Jew. Even the famous surgeon, Theodor Billroth, later one of the non-Jewish founding members of the League Against Anti-Semitism, warned in a book[16] in 1876 against having too many „members of the Jewish race“ in the medical profession. Defined in these ominous terms the „Jewish Question“ became one of the main topics in the political life of Vienna, particularly in the University.

Billroth, Loschmidt and the Jewish Question

Billroth’s comments exemplify the opinions of many well-educated intellectuals:

Many young people, mainly Jews from Galicia and Hungary, come to Vienna absolutely penniless, with the crazy idea that they can earn a living (through giving lessons ...) and study medicine at the same time.[17]

Billroth stressed that he did not wish to be mistaken for

One of those modern Jew-bashers (Judenschimpfer) who are so popular these days... Thanks to their active imagination, Jews often have talent for science and medicine. And thanks to the sharpness of their minds, their energy and their tireless capacity for work, even with limited material means, success is generally assured. So they are often able to achieve the highest. And, in fact, the distinguished among the Jews are usually visionaries, idealists and humanists at the same time, often in the spirit of the Nazarene who stands above us all.

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[15] Bruce *Pauley*, „From Prejudice to Persecution: A History of Austrian Anti-Semitism“, University of North Carolina Press, Chapel Hill, 1992, p. 31.

[16] T. *Billroth*, Über das Lehren and Lernen der medizinischen Wissenschaften, pp. 148–153, Carl Gerold’s Sohn, Vienna, 1876.

[17] It is interesting to reflect that penniless Eastern European youngsters could go to Vienna and study medicine at the University. It would have been much more difficult for sons of peddlers on the Lower East Side in New York to attend Columbia University.

Like so many Jews in Vienna (and elsewhere in Western Europe), Billroth looked down especially on the 'depraved' Eastern European Jews whose cultural norms were especially distant from those evident in the Imperial capital:

It seems to me that the Hungarian and Galician Jews have severely degenerated through constant inter- and early marriages (bridegrooms of 17 and brides of 12 are not rare) and in some areas are well on their way towards a certain physical and mental degeneracy.

He continued:

There is a widespread error, to speak of Jews as Germans or Hungarians or Frenchmen, who just happen to have a religion different from the other inhabitants of Germany, Hungary or France. One forgets completely that Jews are a clearly defined nation, and that a Jew can no more become a German than can a Persian, a Frenchman, a New Zealander or an African. What one calls Jewish Germans are Jews who just happen to speak German, who happen to have been brought up here, even though they may think and write poetry in better and more beautiful German than some Germans of the purest water. They lose their national tradition as little as Germans lose theirs among other nations such as Transylvania or America.

Note Billroth's identification of distant (New Zealand) or „savage" (African) cultures as examples of societies irretrievably remote from German *Kultur*, as well as his regret at the isolation of ethnic German groups in Transylvania and America. Yet „isolated" German speaking communities were often the most nationalist in their outlook. German nationalism was especially strong amongst German speakers in Bohemia and Moravia, even among those who were partly of Czech origin, and many of these opposed Slav demands for equal rights. In this complex situation some German nationalists looked on German-speaking Jews as their allies, while others were so anti-Semitic that they could not consider cooperation with Jews.

One of the latter was the influential scientist, Gustav Tschermak (1836–1927), a chemist who later became professor of mineralogy in Vienna. A German nationalist from Moravia, he changed the spelling of his name from Czermak to mask (not very effectively) his Czech origin. Whenever the appointment of a Jew was proposed by the members of the faculty of philosophy at the University, Tschermak opposed it. Seldom was his opposition overridden. In 1873, Adolf Lieben was proposed for the chair of the second of the two Chemical Institutes of the University of Vienna. Lieben was one of Austria's best-educated chemists. He had worked with Wurtz in Paris and with Cannizzaro in Palermo, and he had held the chairs in Turin and Prague, where he was one of the first Jewish professors. Despite Tschermak's objections, he was appointed and led this most important institute for organic chemistry until his retirement in 1906, but even this success, in a climate intolerance and nationalism, had few positive consequences for the promotion of other Jews. Meanwhile the anti-Semitic atmosphere, particularly at the provincial universities throughout the Austrian Empire, became so pervasive that the Ministry of Education took „the Jewish question“ into account whenever a professor had to be appointed.[18] Only in Prague was it somewhat easier for a Jew to become a university professor because there Jews were considered to be allies against the Czechs.

Tschermak opposed the appointment of Guido Goldschmiedt in Vienna in 1885. In 1887 a new head of the chemistry department was to be appointed in Graz. Although Goldschmiedt was one of the ablest senior chemists suitable for the post and had strong support from Josef Loschmidt[19], who was Professor at the University of Vienna and on the Senate there, anti-Semitism prevailed. It was feared that a Jewish professor would not be accepted by the students and staff, so the appointment was given to Zdenko Hans Skraup, a German nationalist of Czech origin. Eventually Goldschmiedt did receive the chair of organic chemistry in Prague where he was also elected dean. Only in 1910, four years after Lieben's retirement, was Goldschmiedt, then 61 years old, finally invited to Vienna. Tschermak similarly opposed the appointment of another very able organic chemist, Josef Herzig.

The delayed career of Josef Herzig, a very able organic chemist, is an exemplary illustration of both the problems Jews experienced at the university and the way that the authorities under Francis Joseph dealt with these problems. At the time the University of Vienna had two chemical institutes, both headed by organic chemists. The head of the „Second Chemical Institute“ until 1906 was Adolf Lieben, as noted earlier. When the head of the „First Chemical Institute“ died in 1899, the most senior chemist there was Josef Herzig, a Jew born in Galicia, who carried on as temporary head. In the prevailing atmosphere of anti-Semitism at the university, the authorities were afraid of having Jews head

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[18] A well documented example for this was the appointment of a professor of chemistry in Innsbruck in 1902. As customary, the faculty made several proposals for the appointment: I. loco: Friedrich Emich (Graz) and Josef Herzig (Vienna); II. loco: Karl Brunner (Prague). In the report to the Emperor, the Minister of Education, Dr. Wilhelm von Hartel, said that he shared the doubts of the faculty regarding the acceptance of Herzig in Innsbruck, due to his Jewish religion. As Emich was still required in Graz, he proposed the appointment of Karl Brunner, who was appointed. (University Archives, Philosophical Faculty 639/1902 quoted in „Die Fächer Mathematik, Physik und Chemie an der Philosophischen Universität zu Innsbruck bis 1945“, edited by Franz *Huter*, Innsbruck 1971 p.191)

[19] In an unpublished letter of March 4, 1888, Loschmidt wrote to Ludwig Boltzmann strongly supporting Goldschmiedt: *„Among Austrian chemists who are not yet professors, Goldschmiedt is the most outstanding.“* (Archives of Graz University)

both chemical institutes. The Ministry of Education therefore decided to appoint a physical chemist as the head of the „First Chemical Institute“ (which ever since has been known as the Institute for Physical Chemistry). In 1906 Josef Herzig was appointed head of a newly created department for Pharmaceutical Chemistry, a post he held until 1923.

An interesting contrast to Tschermak's aversion to Jews is presented by Loschmidt[20]. Born in a small village in Bohemia, he would have had his first contact with Jewish students at the University of Prague where he studied from 1837–41. From there he went to Vienna in 1841 and worked with Meissner and Schrötter, both of whom as we have seen favored a fairer treatment of Jews. Loschmidt spent one summer at the home of Meissner. In his posthumously published notes[21], he described in detail Meissner's last lecture at the Polytechnic Institute in February 1845, the students' uproar that their beloved teacher was to retire, and the difficulties Schrötter had in his first lecture. Undoubtedly Loschmidt knew Meissner's essay about the Jews, published in 1848.

Loschmidt had considerable experience working with Jews. In Schrötter's laboratory, he and his friend, Benedict Margulies, later a Jewish convert to Protestantism, had developed a practical scheme for the conversion of sodium nitrate into potassium nitrate, required in gunpowder, and the two started a factory near Vienna. At first business went well, but the economic upheaval during the war in Hungary in 1849 led to the company's bankruptcy. In 1852 and 1853, Loschmidt worked in a chemical factory in Brünn (modern day Brno) owned by L. Kohn, presumably a Jew. He continued working with Margulies as we see from a joint patent application for an aeromotor filed in 1865. We know that the families remained close friends from correspondence between the wives and the inscription in a visitor's book on Loschmidt's death: *„Dem unvergesslichen Freunde (to a never to be forgotten friend) Benedict u. Anna Margulies“*. Loschmidt clearly had other Jewish friends, as the Margulies' inscription is followed by *„In Treuer Erinnerung, Oscar u. Hermine Bernheimer“*, another typically Jewish name.

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[20] For a review of J. Loschmidt's life and chemistry, see W. J. *Wiswesser*, „Johann Josef Loschmidt (1821–1895): a forgotten genius“, Aldrichimica Acta, 22, [1] 17 (1989), and „Pioneering Ideas for the Physical and Chemical Sciences: Josef Loschmidt's Contributions and Modern Developments in Structural Organic Chemistry, Atomistics, and Statistical Mechanics“, Proceedings of the Josef Loschmidt Symposium, held June 25–27, 1995, in Vienna, Austria, Plenum Press, New York and London, 1997.

[21] J. *Loschmidt*, „Zur Erinnerung an Anton Ritter Schrötter von Kristelli“, published posthumously, Vienna, 1906; A. *Bauer*, „Zur Erinnerung an Paul Traugott Meissner“, Naturhistorisch-Biographische Essays, Vienna, 1911.

As well as his business associations and friendships, Loschmidt knew many Jewish students and their parents because he lived and taught for nine years (1856–1865) in the Leopoldstadt, which had Vienna's largest concentration of Jews. Of the school's 250 students, 40% were Jews, over 50% were Catholics, and only 2% were Protestants. It is interesting to note that his weekly teaching load was 6 hours of chemistry, 5 of physics, and 3 of arithmetic, economics and bookkeeping, which would have brought him into close contact with his pupils.[22]

Loschmidt was interested in the social and political issues of his day. Therefore, it is not surprising that at a time when the „Jewish Question" was considered in Vienna to be a major issue, he gave some thoughts to the problem and put them down in a private note, which was found in his papers *(fig. 2)*.

The Voice of the People is the Voice of God

The inundation by the Semitic race is no figment of the imagination. Public intuition carries the day against all the humanistic unction of popular literature. The danger threatens not only the lower echelons of society who feel the pressure firsthand, but also the state. It is both a social and a political tragedy. Every division that separates subjects of a state is a thorn in the flesh to the politician – he perceives it as a direct weakening of the strength of the state. It is no wonder that he brings his statesmanship to bear upon curing this attrition. It could be that the roots of the conflict lie in religion, or in language or in race [yet] *it is always perceived as a misfortune and the solution has always been to cure the ill with whatever means are permissible – and probably also ones that are not permissible. Mostly – but not always, it is with miserable success. In world history, the attempt to come up with a state religion or the attempt to sustain one. Triumphs: the Spanish Inquisition, the Drayonnades in France, the Counter-Reformation in Austria. No longer suitable today, the cure worse than the disease. On the other hand, the work of changing language was carried out in a more gentle and often more enduring way.* [Stricken by author: *In Germany against the Slavs ... too often with a bitter end, when force*] *There are enough renowned examples to show that the multi-lingual issue is a real evil for a large empire, at least if one language is not the state language of the vast majority.*

The implication of „Vox populi, vox Dei", a quotation attributed to the Medieval scholar Alcuin, with which Loschmidt begins, is that most people in Vienna hate the Jews and the voice of the people is the voice of God. But a careful analysis combined with our knowledge of Loschmidt's friendship with Jews leads to the conclusion that this essay, written late in Loschmidt's life, is

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[22] Religiöse Zusammensetzung der Schüler in der Unterrealschule: Programm der Unterrealschule St. Johann in der Jägerzeile, Jg. 4 (1859), p. 26.

not an expression of virulent anti-Semitism. Loschmidt's reasoning about anti-Semitism is reminiscent of his scientific arguments. Compare this, for instance, with his most studied analysis, that of the structure of benzene[23]. There he stated that one might be tempted to think of benzene as a diallene, or possessing a bicyclic structure, but then chose a monocyclic structure for all his aromatic compounds. About the „Jewish Question", he felt that two or more languages, religions and cultures threaten the efficiency of any empire, and the essay shows to what extent the position of Jews in a multi-ethnic and multi-national state was considered a very important topic. His method in both cases – benzene and anti-Semitism – was to begin with what seemed reasonable – the diallene structure and 'The Voice of the People' – and then to take critical issue with them. Indeed, Loschmidt's ideas were not very different from those of many Jews themselves. Baron Maurice de Hirsch, who gave over $100 million to Jewish philanthropy in 1896, wrote, „All our misery comes from Jews who want to climb too high. We have too many intellectuals. I want to prevent the Jews from pushing ahead too much."[24]

What can we learn from all this? Perhaps most importantly, the danger of generalizing about cultural attitudes. Scholars such as Daniel J. Goldhagen assert that anti-Semitism was part and parcel of the emotional makeup of Germans and Austrians.[25] Goldhagen writes:

Anti-Semitism in Germany was such that when Germans, participants or bystanders, learned that the Jews were to be killed, they evinced not surprise, not incredulity, but comprehension. Whatever their moral or utilitarian stances toward the killing were, the annihilation of the Jews made sense to them.[26]

If anything, the Viennese turned out to be even worse than the Germans. Hermann Göring commended them in the autumn of 1938 for having learned in only five months how to „deal" with their Jews, when it had taken Germans five years to learn[27].

Goldhagen's thesis raises most serious questions. On the one hand, he demonstrates beyond doubt that many Germans were not only anti-Semitic, but also approved of Hitler's plan to kill all Jews. And he acknowledges that „By no means should this [indictment] be understood that a timeless German character exists."[28] On the other hand, by minimizing the virulent anti-Semitism of other countries – Poland and the Ukraine had pogroms of unspeakable

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[23] *Wiswesser*, op. cit.

[24] *Berkley*, op cit., p. 56.

[25] D. J. *Goldhagen*, „Hitler's Willing Executioners", A. A. Knopf, New York, 1996.

[26] Ibid., p. 403.

[27] Quoted in *Pauley*, op. cit., p. 285.

[28] *Goldhagen*, op cit., p. 594, footnote 53.

cruelty before Hitler, and anti-Semitism in Poland was spread more widely than in Germany – he points to a generalization regarding the prevalence of Anti-Semitism in German speaking lands, both in the twentieth and nineteenth centuries whose limits are not known[29]. It is not simply that we can identify those rare individuals who later would openly oppose Nazi policies[30]. We must also consider the complexities of the debates concerning „the Jewish question“ that went on for more than a century before the Holocaust, and seek to understand what the participants were striving, sometimes in deliberately indirect ways, to say. Meissner's and Loschmidt's writings do not invalidate what we already know about attitudes held by Austrian university teachers, but they contribute to a more nuanced picture of the intellectual climate of the time.

To analyze the views of four Viennese chemists – Meissner, Schrötter, Loschmidt, and Tschermak – does not give a statistically valid overview of anti-Semitism among Austrian chemists in the 19th century, but it does show what diversity existed within an environment which is sometimes dealt with in broad brushstrokes and may tempt us to demonize an entire *Zeitgeist*. Anti-Semitism undoubtedly was a significant, even dominant feature of intellectual life at the University of Vienna. Yet the stated positions of Meissner and Schrötter suggest that there were variations and subtleties among the attitudes held by members of the academic community that have not always been appreciated from the distance of a century and a half or more. The surviving writings of these men also raise the possibility that other heretofore unknown documentation of varying viewpoints of Austrian academics on „the Jewish question“ awaits discovery in university archives and elsewhere. What is certain is that the arguments such as Meissner's and Schrötter's in favor of more opportunities for Jews, were part of the prelude to the remarkable efflorescence of Austrian arts and science before 1938, tragically the final moment of cross-fertilization between Jewish and Gentile intellectual traditions in that country's universities.

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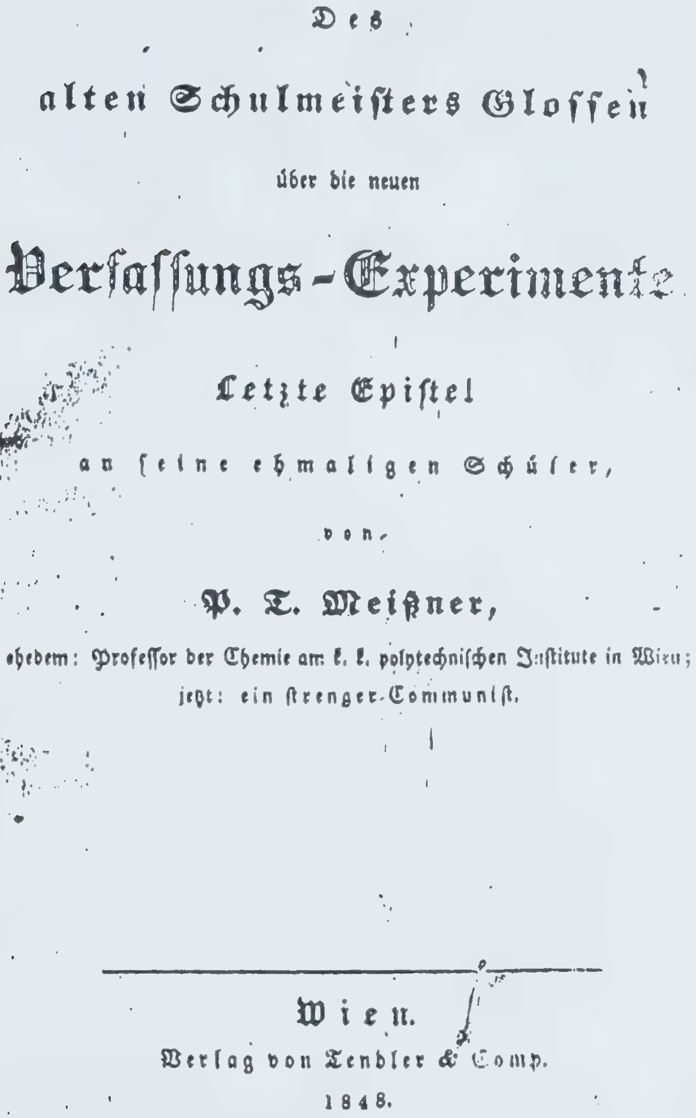
[29] Some of the clearest accounts of how widespread anti-Semitism was in Poland are given by concentration camp survivors, in Chapter 1, Pre-War Years, in Martin *Gilbert's* „The Boys. Triumph over Adversity“, Weidenfeld & Nicolson, London, 1996.

[30] *Goldhagen* cites examples of almost unbelievable courage. A hospital chaplain in France, Walter Höchstädter, secretly printed his scathing protest against anti-Semitism and sent a thousand copies through the military mail to soldiers at the front (pp. 431–32). As early as 1935, Marga Meusel, a Protestant social worker in Berlin, warned, *„It is not an exaggeration when one speaks of the attempt to annihilate the Jews.“* She continues, *„What shall we one day answer to the question, where is thy brother Abel? The only answer that will be left to us as well as the to the Confessing Church is the answer of Cain“* (pp. 437–38).

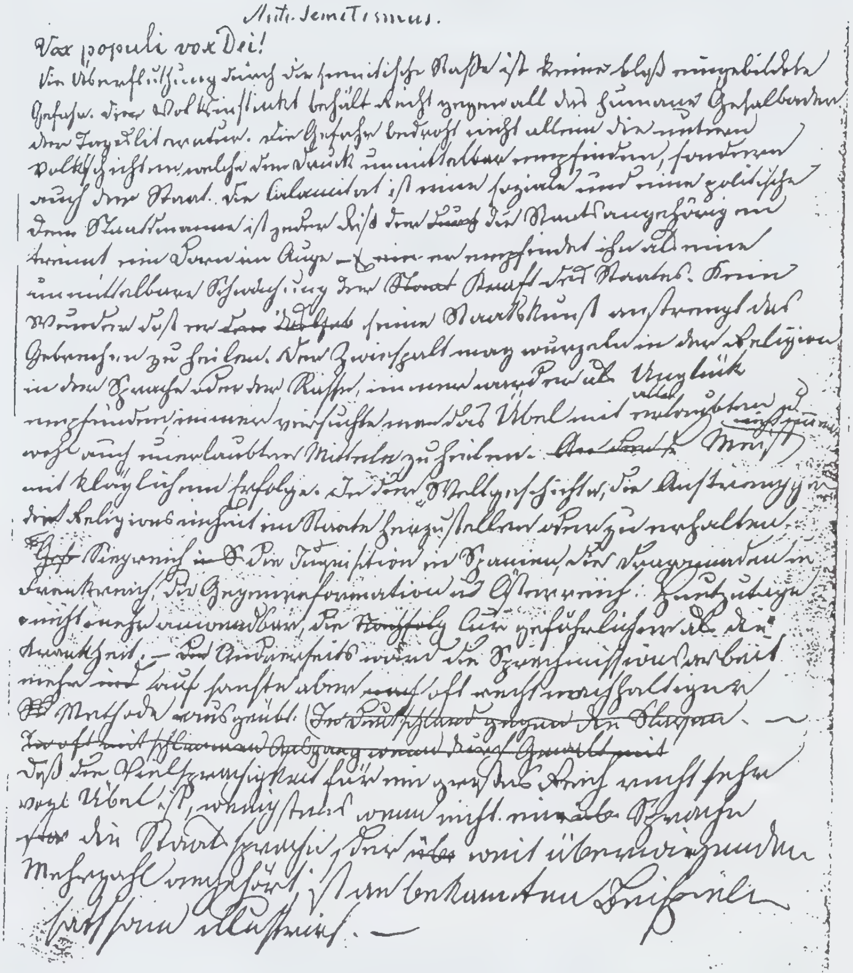
Figure 1



Des
alten Schulmeiſters Gloſſen
über die neuen
Verfaſſungs-Experimente
Letzte Epiſtel
an ſeine ehmaligen Schüler,
von
P. T. Meißner,
ehedem: Profeſſor der Chemie am k. k. polytechniſchen Inſtitute in Wien;
jetzt: ein ſtrenger Communiſt.

Wien.
Verlag von Tendler & Comp.
1848.

Figure 2



Anti-Semitismus.

Vox populi vox Dei!

[Reprinted from the Journal of the American Chemical Society, 79, 6164 (1957).]

Unsaturated Phenols. IV. Crotylphenols

By Alfred R. Bader

[Reprinted from the Journal of the American Chemical Society, **79**, 6164 (1957).]

[CONTRIBUTION FROM THE LABORATORIES OF THE PITTSBURGH PLATE GLASS CO. AND THE ALDRICH CHEMICAL CO.]

Unsaturated Phenols. IV.[1] Crotylphenols

BY ALFRED R. BADER[2]

RECEIVED JUNE 20, 1957

Butadiene reacts with phenol in the presence of some Friedel-Crafts catalysts to yield largely a mixture of butenylphenols, with some higher phenols and ethers. *o*- and *p*-crotylphenol have been characterized. A correlation between the acidity functions of acid actalysts and their activity is discussed.

Although the synthesis of compounds related to the tocopherols has prompted studies of the reactions of phenols, specifically hydroquinones, with butadiene,[3] isoprene,[4] 2,3-dimethylbutadiene[4] and phytadiene,[5] the reaction of the simplest phenol with the simplest diene has been described only briefly. A patent[6] has alleged that *p*-crotylphenol is the major component of the monoalkenylphenolic fraction formed in 36% yield in the high temperature reaction of phenol with butadiene catalyzed by solid phosphoric acid.[7] Proell[8] has described the reaction of butadiene with phenol catalyzed by alkanesulfonic acid yielding a mixture of butenylphenols. Claisen[9] had previously described the preparation of chromans from phenol and dienes such as isoprene, and the preparation of pentenylphenols from these reactants under milder conditions has been studied by Pines and Vesely.[10]

The reaction of phenol with 1,3-butadiene at

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(1) For paper III, see THIS JOURNAL, **78**, 1709 (1956).

(2) Aldrich Chemical Co., Milwaukee 12, Wisconsin.

(3) L. I. Smith and J. A. King, THIS JOURNAL, **63**, 1887 (1941).

(4) L. F. Fieser, W. P. Campbell, E. M. Fry and M. D. Gates, *ibid.*, **61**, 3216 (1939).

(5) L. E. Smith, H. E. Ungnade, H. H. Hoehn and S. Wawzonek, *J. Org. Chem.*, **4**, 311 (1939).

(6) R. E. Schaad, U. S. Patent 2,283,465 (May, 1942).

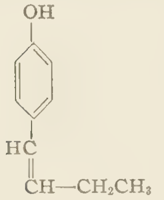
(7) V. N. Ipatieff, U. S. Patents 1,993,512 and 1,993,513 (March, 1935).

(8) W. Proell, *J. Org. Chem.*, **16**, 178 (1951).

(9) L. Claisen, *Ber.*, **54**, 200 (1921); German Patent 374,142 (April, 1923).

(10) H. Pines and J. A. Vesely, U. S. Patents 2,553,470 and 2,578,206 (May and December, 1951). Details of the reaction of phenol with isoprene will be described in paper V of this series.

room temperature in the presence of relatively mild Friedel–Crafts catalysts yields largely butenylphenols accompanied by only small amounts of ethers and higher phenols. Fractionation of the butylphenols obtained on hydrogenation showed the presence of *o*- and *p*-*n*-butylphenols, identified by physical constants and solid derivatives. Thus the possible structures for the original reaction products are *p*-1-butenylphenol (I), *p*-crotylphenol (II), *p*-3-butenylphenol (III) and the three corresponding *o*-substituted isomers. The absence of conjugated isomers such as I was shown by ultraviolet spectra and infrared spectra of the mixed butenylphenols and of cuts obtained by fractional distillation indicated the presence mainly of *o*- and *p*-crotylphenol.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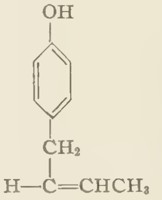
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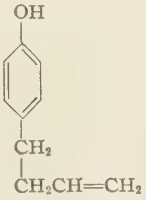
III

Low temperature crystallizations of the highest boiling butenylphenol fraction yielded a crystalline solid, m.p. 39°, the infrared spectrum of which shows a strong band at 10.35 μ, indicative of a symmetrically disubstituted *trans* double bond and no bands at 10.1–10.2 and 11.0 μ, characteristic of the vinyl group $RCH{=}CH_2$.[11] The spectrum of this crystalline isomer also shows an intense band at 12.1 and no absorption at 13.3 μ, and this evidence for *p*-substitution is in accord with this isomer's quantitative hydrogenation to the known[12] *p*-*n*-butylphenol. Assignment of structure II to this solid isomer was confirmed by its ultraviolet spectrum and by its isomerization by palladized charcoal to the conjugated isomer I, m.p. 85–86°.[1]

Fractionation of the non-crystallizable monobutenylphenols boiling over a 20° range and examination of the fractions' infrared spectra showed that the intensities of the band at 12.1 μ increased and those of the band at 13.3 μ decreased with increasing b.p., indicating increasing ratios of *p*-butenylphenols in the higher b.p. fractions. The presence of *o*-crotylphenol in an intermediate fraction was confirmed by the preparation of its phenylurethan melting at 65–66°, identical with the derivative of authentic *o*-crotylphenol.[13]

When titanium tetrachloride, alkanesulfonic acids or the aluminum chloride solvates were the catalysts, the non-crystallizable butenylphenol fractions showed no bands at 10.25 and 10.95 μ, whereas weak bands were present at those wave lengths in the spectra of the butenylphenols obtained with the other catalysts. Theoretically, *n*-butenylphenols with terminal unsaturation as in III are improbable as products of alkenylation,[14] and the weak bands at 10.25 and 10.95 μ may be caused by small amounts of methallyl- or *cis*-crotylphenols.[15]

Butadiene is less reactive than cyclopentadiene, and 85% phosphoric acid, the preferred[14] catalyst for the cycloalkenylation of phenol at 25°, is ineffective with butadiene at that temperature. As has been pointed out by Price,[16] only few direct comparisons of the relative activities of Friedel–Crafts catalysts are recorded in the literature. The composition of the products of the reaction of butadiene with phenol varies greatly with different catalysts, and it seemed of interest to compare the activities of a number of catalysts in this reaction. Comparison is complicated by the involvement of two reactions in the formation of 1:1 adducts, *i.e.*, the alkenylation and the acid-catalyzed ring closure of the *o*-isomer[17] and by further reactions of the alkenylphenols by oxidation and condensation.

Axe[18] has implied that the complex prepared by *saturating* phosphoric acid with boron fluoride, which is an effective catalyst in the butenylation of benzene, also can be used in the alkenylation of phenol. Actually, the use of this as of other strong Friedel–Crafts catalysts such as aluminum chloride and concentrated sulfuric acid leads almost exclusively to ethers and resinous products. The saturated BF_3–phosphoric acid catalyst diluted with an equal weight of 85% phosphoric acid is, however, one of the catalysts of choice; with it or with a mixture of phosphoric and sulfuric acids the mixed butenylphenols are accompanied by only small amounts of ethers and higher phenols. Aqueous sulfuric acid, titanium tetrachloride, alkanesulfonic acids,[8] arenesulfonic acids, aluminum chloride alcoholate and etherate and mixtures of polyphosphoric acid and phosphoric acid also catalyze the mono-butenylation at 15–25°.

The reaction temperature and the catalyst composition direct the orientation. With the complex of phosphoric acid and boron fluoride or with alkanesulfonic acids, *p*-substitution predominates at 15–25°, whereas II constitutes only 30% of the mono-butenylphenols when aqueous sulfuric acid is used at that temperature. This dependence of the product composition on the negative ion associated with the carbonium ion suggests that alkenylations do not involve simply the electrophilic attack on phenol of the diene's free, resonant carbonium ion.

The ranges of composition of the effective cat-

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[11] (a) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1412 (1948); (b) N. Sheppard and G. Sutherland, *Proc. Roy. Soc.* (*London*), **A196**, 195 (1949); (c) D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, 915 (1950).

[12] E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 265.

[13] L. Claisen and E. Tietze, *Ber.*, **59B**, 2351 (1926).

[14] A. R. Bader, THIS JOURNAL, **75**, 5967 (1953).

[15] H. Pines, B. Kvetinskas, J. A. Vesely and E. Baclawski, *ibid.*, **73**, 5173 (1951), have claimed on the basis of infrared spectra and hydrogenation to 2-*n*-butylthiophene that the products of the reaction of thiophene with butadiene are 2-(3-butenyl)-thiophene and 2-crotylthiophene. The evidence for the presence of the former was two bands at 910 and 970 cm.$^{-1}$, thought to be indicative of a vinyl group. However, the band at 970 cm.$^{-1}$ (10.3 μ) is at too long a wave length to be indicative of a vinyl group which never absorbs even in allylic substitution products[11c] and in 2-vinylthiophene with a conjugated, possibly perturbed group at more than 10.2 μ. Perhaps the lower boiling butenylthiophene is 2-*cis*-crotylthiophene.

[16] C. C. Price in R. Adams, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 2.

[17] See D. S. Tarbell, *ibid.*, Vol. II, pp. 18, 27.

[18] W. N. Axe, U. S. Patent 2,471,922 (May, 1949).

alyst mixtures are quite narrow, particularly with sulfuric acid (68–70% at 15–25°). Except for aqueous sulfuric acid, the acid catalysts effective for the mono-butenylation at room temperature have acidity functions[19] H_0 of *ca.* −6 to −7, corresponding to 77–83% aqueous sulfuric acid. It may be that but for its oxidizing action, say, 80% aqueous sulfuric acid would be the optimum concentration, and that 68–70% is the highest concentration not causing oxidation of the α-methylene group and the lowest catalyzing the alkenylation.[20] Once one effective catalyst is known in a given reaction, the determination of its acidity function appears helpful in suggesting the most convenient catalyst of similar H_0 to be tried.

Weaker catalysts such as 85% phosphoric acid become effective at higher temperatures; the resulting products contain largely *o*-substituted phenols. The reaction at 200° following the procedure of Schaad[6] yielded only a small amount of mixed mono-butenylphenols from which no *p*-crotylphenol could be isolated. The infrared spectrum of the mixture suggested that it consisted largely of *o*-substituted phenols.

Experimental

Butenylphenols.—To a stirred and cooled mixture of 940 g. (10 moles) of phenol, 1000 cc. of toluene, 100 g. of the complex prepared by saturating[21] 85% phosphoric acid with gaseous boron fluoride and 100 g. of 85% phosphoric acid, there was added slowly a cold solution of 270 g. (5 moles) of butadiene in 1000 cc. of toluene. The reaction was slightly exothermic, and the stirred mixture, which became faintly yellow, was kept at room temperature for 16 hr. It was then diluted with water, the toluene solution was washed and the solvent, unreacted phenol and a small amount of ethers removed by distillation *in vacuo*. The main fraction (659 g., 89%), b.p. 53–90° (0.1 mm.), n^{25}D 1.539, $\lambda_{\max}^{\mathrm{EtOH}-0.1\%\ \mathrm{HOAc}}$ 225 mμ (log ϵ 3.9) and 279 mμ (log ϵ 3.3), mixed butenylphenols, was a colorless oil, completely soluble in aqueous alkali. The yellow flask residue consisted of dibutenylphenols and higher phenols and ethers.

The mixed butenylphenols (180 g.) were fractionated through a 10″ column into 5 fractions: A, 5 g., b.p. 53–55° (0.1 mm.), n^{25}D 1.5377; B, 25 g., b.p. 55–60° (0.1 mm.), n^{25}D 1.5380; C, 28 g., b.p. 60–63° (0.1 mm.), n^{25}D 1.5385; D, 8 g., b.p. 63–69° (0.1 mm.), n^{25}D 1.5390; and E, 9 g., b.p. 69–72° (0.1 mm.), n^{25}D 1.5385; their infrared spectra are in accord with those of two-component mixtures, progressing steadily from A (strong band at 13.3 μ, mostly *o*-crotylphenol) to E (strong band at 12.1 μ, mostly *p*-crotylphenol). The colorless flask residue (103 g.) crystallized in the ice-box; two low temperature crystallizations from ligroin yielded 75 g. of soft needles, m.p. 39°, of **p-crotylphenol** (II); $\lambda_{\max}^{\mathrm{EtOH}-0.1\%\ \mathrm{HOAc}}$ 225 mμ (log ϵ 3.99), 279 mμ (log ϵ 3.29); $\lambda_{\min}$ 215 mμ (log ϵ 3.84), 247.5 mμ (log ϵ 2.10).

Anal.[22] Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found, mixed mono-phenols: C, 81.06; H, 8.04. Found, fraction C: C, 80.82; H, 8.25. Found, II: C, 81.22, 81.07; H, 8.37, 8.19.

The solid isomer, II, was characterized by a *p*-**nitrophenylurethan** which formed white needles from aqueous methanol, m.p. 139–140°, and by a **phenoxyacetic acid** which after two crystallizations from water melted sharply at 80°.

Anal. Calcd. for $C_{17}H_{16}O_4N_2$: C, 65.37; H, 5.16. Found: C, 65.30; H, 5.50. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.85; H, 6.90.

The exothermic reaction of the mixed sodium butenylphenoxides with chloroacetic acid yields a mixture of aryloxyacetic acids, of which one is easily separated through its insolubility in ligroin. Ultraviolet and infrared spectra suggested this to be *o*-**crotylphenoxyacetic acid** which crystallized from water in soft, white needles, m.p. 137°; $\lambda_{\max}^{\mathrm{EtOH}-0.1\%\ \mathrm{HOAc}}$ 215.0 mμ (log ϵ 3.94), 271.5 mμ (log ϵ 3.24), 277.5 mμ (log ϵ 3.20); $\lambda_{\min}$ 242.5 mμ (log ϵ 2.28), 275 mμ (log ϵ 3.17). Its infrared spectrum in Nujol mull showed a strong band at 10.3 μ, probably indicative of a *trans* double bond, RCH=CHR′.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.45; H, 7.04.

Reaction of fraction B with phenyl isocyanate gave a good yield of a crystalline phenylurethan which crystallized in fine needles from methanol, m.p. 65–66°, identical with *o*-crotylphenyl phenylcarbamate.[13]

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.18; H, 6.19.

Hydrogenation of II (methanol, Adams platinum oxide catalyst, 100°) quantitatively yielded ***p*-*n*-butylphenol**,[12] m.p. 20–21°, n^{25}D 1.5176, characterized by a phenoxyacetic acid, m.p. 80–81°.

Hydrogenation of the mixed butenylphenols (50 g.) yielded mixed *n*-butylphenols (50 g.), n^{25}D 1.517, which fractional distillation separated into 15 g. of *o*-*n*-butylphenol, b.p. 94–97° (8 mm.), n^{25}D 1.518, characterized by a crystalline phenoxyacetic acid[23] (crystallized from ligroin), m.p. 104–105°; and 24 g. of *p*-*n*-butylphenol, b.p. 113–116° (8 mm.), n^{25}D 1.518, characterized as above.

A small quantity of ethers (3–6%) is formed in this room temperature reaction; these distil with unreacted phenol and can be separated by their insolubility in alkali. Their boiling range (205–225°) and the physical constants of the higher b.p. fraction (b.p. 220–225°, n^{25}D 1.530, d^{25}_{25} 1.020) suggest that these ethers are a mixture of 2-ethylcoumaran and 2-methylchroman.[24]

The second catalyst of choice is a mixture of 85% phosphoric acid and concd. sulfuric acid. Adding a cooled solution of butadiene (60 g., 1.1 moles) in toluene (100 cc.) to a stirred mixture of phenol (94 g., 1 mole), toluene (100 cc.), 85% phosphoric acid (100 g.) and sulfuric acid (sp. gr. 1.84, 15 g.) and keeping the stirred mixture at 15–25° for 16 hr. yielded 115 g. (0.78 mole, 78%) of mixed butenylphenols a colorless oil, b.p. 80–120° (1.5 mm.), n^{25}D 1.5385. The infrared spectrum of this mixture was similar to that of the mixed butenylphenols prepared with boron fluoride and phosphoric acid, and crystalline II was isolated from the higher b.p. fraction.

With 68% aqueous sulfuric acid and equimolar amounts of phenol and butadiene at 15°, the yield of mono-butenylphenols is 70%. Fractional distillation showed these to consist of *ca.* 60% *o*-crotylphenol and 30% of the crystalline isomer II.

The reactions catalyzed by boron fluoride, by the complex of phosphoric acid saturated with boron fluoride, by concd. sulfuric acid and by aluminum chloride are very exothermic and lead largely to higher phenols and ethers. Fair yields of butenylphenols are obtainable with polyphosphoric acid or, preferably, with mixtures of polyphosphoric acid and 85% phosphoric acid (2:1), titanium tetrachloride arenesulfonic acids and the aluminum chloride–alcohol and –ether complexes. Again, crystalline II was isolated by low temperature crystallizations from heptane from all mixed butenylphenols. Also, the higher b.p. liquid butenylphenol prepared by the procedure of Proell[8] crystallized at once on cooling and proved identical with II.

Zinc chloride and 85% phosphoric acid are inactive at 10–40°. Phosphoric acid (85%) becomes effective at 100–125°; at 140° the bulk of the product consists of ethers and higher phenols. Comparison of spectra showed that the maximum at 13.3 μ was more than that at 12.1 μ somewhat less intense than the corresponding maxima in the infrared spectra of mixed mono-butenylphenols prepared at lower temperatures, indicating somewhat more *p*-substitution in the latter.

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[19] L. P. Hammett and A. J. Deyrup, THIS JOURNAL, **54**, 2721 (1932); L. P. Hammett and M. A. Paul, *ibid.*, **56**, 827 (1934). I am much indebted to Mr. John E. Hyre for the determination of the acidity functions of the catalysts.

[20] I wish to thank Professor Paul D. Bartlett for this suggestion.

[21] 85% sirupy phosphoric acid exothermically absorbs approx its weight of boron fluoride.

[22] Analyses by the Micro-Tech Laboratories, Skokie, Ill.

[23] G. Sandulescu and A. Girard, *Bull. soc. chim.*, [4] **47**, 1300 (1930).

[24] C. D. Hurd and W. A. Hoffman, *J. Org. Chem.*, **5**, 212 (1940); W. Baker and J. Walker, *J. Chem. Soc.*, 646 (1935).

From the product of the reaction described by Schaad[9] (77 g. of phenol, 20 g. of butadiene, 25 g. of U.O.P. polymerization catalyst #2, 200°, 4 hr.), there was obtained besides much unreacted phenol, 11 g. of a phenolic fraction, A, b.p. 65–130° (1 mm.), n^{25}D 1.540; and 30 g. of dark, resinous material. The spectrum of A showed a strong band at 13.3 μ characteristic of *o*-substitution, only a weak band at 12.1 μ and no band at 10.35–10.40 μ, the position of one of the strongest bands of II, indicative of a symmetrically disubstituted *trans* double bond.

Acidity Functions.[10]—With anthraquinone as the Hammett indicator, the alkanesulfonic acid and polyphosphoric acid and the mixtures of 85% phosphoric acid and sulfuric acid and of polyphosphoric acid and phosphoric acid used as catalysts at 15–25° show acidity functions H_0 ranging from -6 to -7. The H_0 of 68–70% aqueous sulfuric acid is -5.0 to -5.2.

***p*-1-Butenylphenol (I).**—A mixture of 90 g. of II and 5 g. of 5% palladium-on-charcoal (Baker and Co., lot #785, activity 985) was refluxed under inert gas for 25 minutes when the reaction temperature had risen to 260°. The product was dissolved in ligroin and filtered, the solvent removed and the red, viscous oil (86 g.) distilled to yield a first fraction A (46 g.), b.p. 80–150° (0.5 mm.); a second fraction B (19 g.), b.p. 150–210° (0.5 mm.); and an orange resinous residue (18 g.). Crystallization of A from heptane yielded 5.5 g. of shiny, white platelets of the less soluble isomer I, identical with the compound prepared by alkali isomerization[1] of II. The infrared spectra of I and II in carbon disulfide are quite similar, except that I exhibits an intense band at 11.8 μ absent in the spectrum of II. The heptane mother liquor from I yielded 40 g. of unreacted II. Fraction B consisted largely of a colorless dimeric diphenol, b.p. 187–190° (0.4 mm.), which was accompanied by a fiery red impurity.

Anal. Calcd. $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.79; H, 8.13.

Butenylanisoles.—Anisole reacts much like phenol at 10–30°; mixed butenylanisoles were prepared in good yields with concd. sulfuric acid and with a 2:1 mixture of polyphosphoric acid and 85% phosphoric acid; b.p. 75–110° (10 mm.), n^{25}D 1.519, strong bands at 12.1 and 13.3 μ, indicating *o*- and *p*-substitution.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.87; H, 9.00.

Acknowledgment.—I wish to thank Professors M. G. Ettlinger and C. D. Hurd for valuable ad vice.

MILWAUKEE, WISCONSIN

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Hydrogen Peroxide–Vanadium Pentoxide Oxidation of Cyclohexenes

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[Reprinted from the Journal of Organic Chemistry, **28**, 2057 (1963).]

Hydrogen Peroxide–Vanadium Pentoxide Oxidation of Cyclohexenes[1a]

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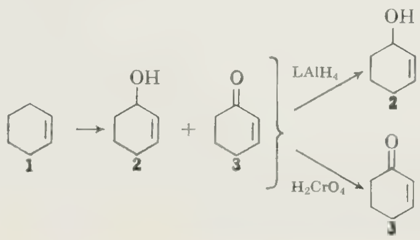
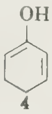
Received January 14, 1963

A re-examination of the oxidation of cyclohexene (1) with hydrogen peroxide–vanadium pentoxide (HP–VP, peroxyvanadic acid) revealed 2-cyclohexen-1-ol (2) to be a major reaction product. This contradicts an earlier report[2] claiming exclusive formation of 2-cyclohexen-1-one (3) as the volatile product. Similar oxidative experiments with the isomeric methylcyclohexenes (**7**, **13**, and **17**) demonstrate the reaction to be essentially nonselective as to site of oxidation and that both alcohols and ketones appear in the volatile products, these being a mixture of direct oxidation products and products derived from allylic shifts.

Treibs[2] and co-workers claimed 2-cyclohexen-1-ol (**2**) to be absent from the products of the oxidation of cyclohexene (**1**) with HP–VP and 2-cyclohexen-1-one (**3**) was reported to be the exclusive low boiling product (40% yield). *trans*-1,2-Cyclohexanediol (**6**) and adipic acid were reported as higher boiling products (9% yield for both). These authors considered 2-cyclohexen-1-one (**3**) to be present in part as the enol **4** to account for the formation of a borate ester.

We have demonstrated that 2-cyclohexen-1-ol (2)





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[1] (a) Presented before the Organic Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.; (b) Department of Chemistry, Oklahoma State University, Stillwater, Okla.; (c) Heidenheimer Chemisches Laboratorium, Heidenheim an der Brenz, Germany.

[2] W. Treibs, G. Franke, G. Leichsenring, and H. Roder, *Ber.*, **86**, 616 (1953).

is a major product of the oxidation of cyclohexene with HP–VP, and that it actually exceeds 2-cyclohexen-1-one (**3**) in the product mixture by a ratio of 2.3:1. The oxidation was repreated several times according to the published procedure,[2] and each experiment gave essentially the same product boiling at 61–63° (14 mm.) in reasonable agreement with the reported value. However, gas chromatographic studies show the presence of two sharply defined and completely separated peaks. The mixture of volatile products shows a maximum $\lambda_{\max}^{\text{EtOH}}$ 225 mμ (ϵ 3905) while the reported[3] maximum for **3** is 225 mμ (ϵ 11,270). Strong hydroxyl group absorption was noted in the infrared spectrum of the mixture. These data suggested the mixture to be **2** and **3**. Attempts to separate the mixture by fractional distillation through a spiral column and by preferential reaction with semicarbazide hydrochloride were ineffective. Accordingly, the products were directly interconverted and the identity of the components established through isolation of the individual pure compounds by oxidation to **3** and reduction to **2**.

A Jones' oxidation[4] with chromic acid in acetone solution readily converted the entire mixture to **3**. The course of the reaction was followed conveniently with gas chromatographic analyses at regular intervals. The peak of the gas chromatogram of the reaction product at termination of the oxidation coincides exactly with the smaller and second peak of the chromatogram of the original mixture. The oxidation product was identified as **3** through its ultraviolet spectrum, in agreement with Woodward's rules,[5] its ininfrared spectrum, and the melting point of its red 2,4-dinitrophenylhydrazone.[6] Other syntheses of **3**, each by a different procedure, have been reported.[7]

Reduction of the original volatile oxidation mixture with lithium aluminum hydride in ether solution gave a single product. This product shows no carbonyl band in its infrared spectrum but shows strong absorption in the hydroxyl and double bond regions. These data and the melting point of the phenylurethane derivative,[6] 107–109°, established the identity of the product as 2-cyclohexen-1-ol (**2**).

A reconstituted mixture (70% **2** and 30% **3**) prepared from pure **2** and **3** gives essentially identical spectra (ultraviolet and infrared) and gas chromatographic curve as those from the original mixture obtained by oxidizing cyclohexene with HP–VP.

Pure 2-cyclohexen-1-ol (**2**) was oxidized with HP–VP under the same conditions used for the oxidation of cyclohexene. The steam volatile products from this reaction were shown through gas chromatographic analyses to be a mixture of **2** and **3** in a ratio of 7.3:1. This experiment suggests **2** to be one of the precursors of **3**.

Several routes may exist for the formation of the various products obtained from the oxidation of cyclohexene with HP–VP. 2-Cyclohexen-1-ol (**2**) and 2-cyclohexen-1-one (**3**) may be rationalized as being formed from cyclohexene hydroperoxide by the indicated routes in Fig. 1. *trans*-1,2-Cyclohexanediol (**6**) may arise from cleavage of cyclohexene oxide which has been reported along with **2** as a product of the bimolecular epoxidation of cyclohexene by cyclohexene hydroperoxide.[8,9]

cis-1,2-Cyclohexanediol (**5**) and adipic acid are formed by direct oxidation of the double bond of cyclohexene. We suggest that peroxyvanadic acid, $H_3[V(O_2)O_3]$,[10] attacks the double bond of cyclohexene to form a cyclic ester of peroxyvanadic acid in a reaction reminiscent of the osmic ester formation of olefins.[11,12] The cyclic ester may then be hydrolyzed to *cis*-1,2-cyclohexanediol (**5**) or undergo cleavage to adipic aldehyde in the manner of periodate oxidation of 1,2-glycols.[13] The aldehyde is oxidized in turn to adipic acid. This rationalization suggested the possible presence of some *cis*-1,2-cyclohexanediol (**5**) in the reaction products. The diol **5** is not formed as a major product but we were able to establish its presence through gas chromatographic studies by enrichment of the crude reaction product with authentic *cis*-diol **5**. The diols **5** and **6** are present in the crude reaction product in the ratio of 1:15. The presence of the *trans*-diol **6** was established readily through gas chromatographic studies and direct isolation from the reaction products. Distillation and recrystallization afforded a pure sample of the diol **6** which shows no depression in melting point on admixture with authentic *trans*-1,2-cyclohexanediol (**6**). The proposed routes permit accumulation of *trans*-diol **6** with simultaneous formation of adipic acid.

Milas[14] reported that the HP–VP oxidation of cyclohexene in *t*-butyl alcohol gives a small amount of *cis*-1,2-cyclohexanediol (**5**), an unidentified aldehyde, and considerable quantities of adipic acid. This suggests that it may be possible to control selectively direct attack on the double bond over allylic attack by altering the reaction conditions.

An interesting parallel to the HP–VP oxidation of cyclohexene is provided by the work of Farmer and Moore.[15] These investigators demonstrated that both 2-cyclohexen-1-ol (**2**) and 2-cyclohexen-1-one (**3**) are formed (ratio 6:1) when cyclohexene (**1**) is oxidized with *t*-butyl hydroperoxide at 140°. These authors also demonstrated that oxidation of 1-methyl-1-cyclohexene (**7**) with *t*-butyl hydroperoxide yielded both ketones and alcohols among the products and that all possible allylic positions except on the methyl group were attacked. This is to be expected for a nonselective oxidation process and was rationalized through a free radical mechanism with a hydroperoxide and an olefin radical as intermediates.

The effect of change in concentration of hydrogen peroxide on the composition of the products from the oxidation of cyclohexene was studied with gas chromatography. We found an increase of hydrogen peroxide

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[3] H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953).

[4] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

[5] R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).

[6] F. C. Whitmore and G. W. Pedlow, Jr., *ibid.*, **63**, 758 (1941).

[7] For a reference list of other preparations of 2-cyclohexen-1-one, see K. I. Williamson, R. T. Keller, G. S. Fonken, J. Szmuszkovicz, and W. S Johnson, *J. Org. Chem.*, **27**, 1612 (1962).

[8] R. Criegee, H. Pilz, and H. Flygare, *Ber.*, **72**, 1799 (1939).

[9] E. H. Farmer and A. Sundralingam, *J. Chem. Soc.*, 121 (1942).

[10] N. V. Sidgwick, "Chemical Elements and Their Compounds," Vol. 1, Oxford University Press, New York, N. Y., 1950, p. 810.

[11] R. Criegee, *Ann.*, **522**, 75 (1936).

[12] N. A. Milas and S. Sussmann, *J. Am. Chem. Soc.*, **58**, 1302 (1936).

[13] E. L. Jackson, "Organic Reactions," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 341.

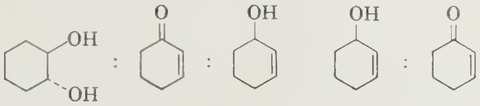
[14] N. A. Milas, *J. Am. Chem. Soc.*, **59**, 2342 (1937).

[15] E. H. Farmer and C. G. Moore, *J. Chem. Soc.*, 149 (1951).

concentration from 1/6 to 1/3 and 1/2 mole caused an increase in yield of **2** and **3**. However, additional increase of hydrogen peroxide failed to increase the yield, and not all the peroxide was consumed during the reaction. The results of these studies on 1/6, 1/3, and 1/2 mole of hydrogen peroxide per mole of cyclohexene are presented in Table I. Thus, the maximum yields of the mixture of **2** and **3** may be obtained with the 1/2 mole ratio.

TABLE I[a]

SUMMARY OF CYCLOHEXENE OXIDATIONS WITH HYDROGEN PEROXIDE



Moles of hydrogen peroxide per mole cyclohexene	Ratio of peak areas			Ratio
1/6	1	1.9	3.2	1.7
1/3	1	2.8	5.0	1.8
1/2	1	3.0	4.1	1.3

[a] These data are the average of two analyses.

To account for formation of a borate ester Treibs,[2] *et al.*, stated that 2-cyclohexen-1-one (**3**) exists in part as the enol **4**. In our hands, pure 2-cyclohexen-1-one (**3**) failed to give significant yields of borate ester since major portions of unchanged boric acid and 2-cyclohexen-1-one (**3**) were recovered (84 and 67%, respectively). We were, however, able to isolate a low yield (3.2%) of 2-cyclohexen-1-one (**3**) by steam distilling the pot residue after unchanged **3** had been distilled at 25–35° (0.05 mm.). To isolate **3** from the pot residue suggests that some **3** may have reacted with boric acid through the enol **4**. However, under identical conditions, 2-cyclohexene-1-ol reacted completely with boric acid, and a 78% yield of borate ester was isolated.

The HP–VP oxidations of each of the methylcyclohexenes (**7**, **13**, and **17**) in acetone were studied to determine whether the methyl substituent has any steric effect or directive influence on the site of the oxidation and, hence, the isomer composition. The gas chromatogram of the reaction products from 1-methyl-1-cyclohexene (**7**) showed seven *major* components of which five have been identified by successive enrichment with authentic products. The identified products from the oxidation of 1-methyl-1-cyclohexene (**7**) are **8**–**12** (see Table II).

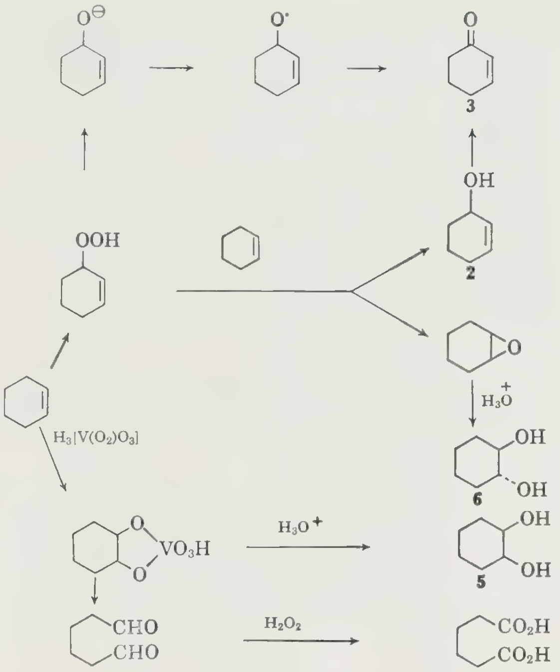
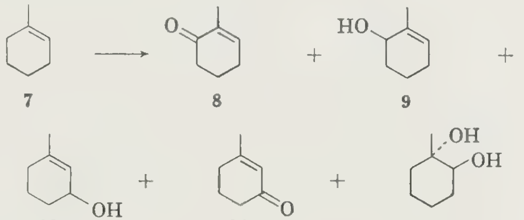


Figure 1



Reduction of the reaction mixture containing **8**, **9**, **10**, **11**, and **12** with lithium aluminum hydride caused

TABLE II

GAS CHROMATOGRAPHIC ANALYSES OF HP–VP–METHYLCYCLOHEXENE OXIDATION PRODUCTS

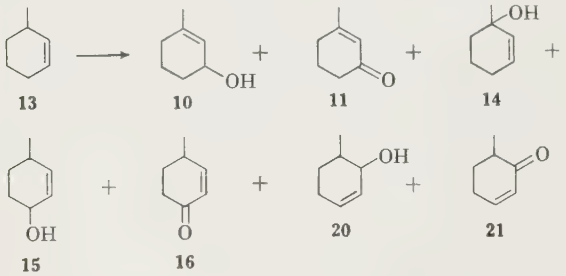
Starting material	Moles of hydrogen peroxide per mole of methylcyclohexene	Column	Oxidation products (time of emergence in min.; relative area)							
7	1/6	Carbowax[a]	Unknown alc.	Unknown ketone (2.8; 1.6)	**8** (5.9; 1)	**9** (8; 3.2)	**10** (8.8; shoulder)	**11** (12; 1.6)	**12** (22.2; 6.6)	
7	1/6	PDEAS[b]	Unknown (2.1; 1.2)	**10** (3.2; 1)	**9** (4.5; 3.3)	**8** (5.4; 1.2)	**11** (12.2; 1.4)	**12** (24.8; 10.7)		
13	1/6	PDEAS[c]	Unknown alc. (1.0; 1.3)	**14** (2.1; 3.3)	**20** (3.2; 5.7)	**15** (5.0; 3.2)	**10** (6.2; 6.3)	**21** (6.5; shoulder)	**16** (8.0; 1.0)	**11** (15; 2.1)
17	1/6	PDEAS[d]	Unknown (5.5; 1.4)	**20** (6.1; 5.3)	Unknown (6.7; shoulder)	**18** (7.0; 2.9)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 2.8)		
17	1/3	PDEAS[d]	Unknown (5.5; 0.7)	**20** (6.1; 2.8)	Unknown (6.7; shoulder)	**18** (7.0; 1.2)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 4.0)		
17	1/2	PDEAS[d]	Unknown (5.5; 0.5)	**20** (6.1; 3.6)	Unknown (6.7; shoulder)	**18** (7.0; 1.5)	**10** and **21**[e] (8.5; 1)	**19** (10.0; 4.2)		

[a] 10% Carbowax 20M on alkaline firebrick; 1/4 in. × 5 ft.; temperature programmed from 130–200°; helium flow, 80 ml./min. [b] 15% PDEAS on acid-washed firebrick; 1/4 in. × 5 ft.; 140°; [c] Same as *b*, except 135°. [d] 15% PDEAS on acid-washed firebrick; 1/4 in. × 4 m.; 160°; helium flow, 65 ml./min. [e] From PDEAS the alcohol **10** emerges with the ketone **21**; these can, however, be separated on Carbowax at 115°. A quantitative estimation is, however, difficult because **21** polymerizes on the alkaline support.

disappearance of **8** and **11**, and an increase of **9** and **10**; this latter compound is present as a minor component in the crude oxidation product. Oxidation of the mixture containing **8**, **9**, **10**, and **11** with Jones' reagent in acetone solution[4] caused disappearance of **9** and **10** with simultaneous increase of **8** and **11**.

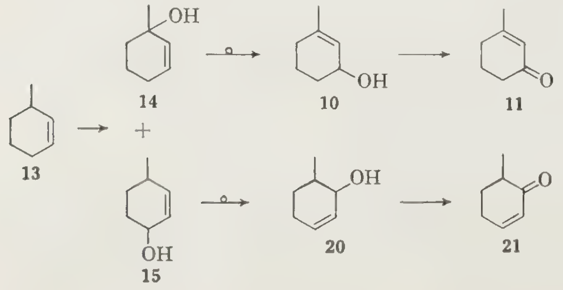
1-Methyl-1-cyclohexene (**7**) was oxidized with chromium trioxide in acetic acid, according to the method of Whitmore and Pedlow,[6] to determine whether this closely related reaction gives the reported mixture of 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexen-1-one (**11**) in the ratio of 1:9.6. We obtained a ratio of 1:7.8. Gas chromatographic analyses also showed the presence of five additional, minor products.

3-Methyl-1-cyclohexene (**13**) was oxidized with the HP–VP oxidant, and the crude product steam distilled to minimize high boiling products (presumed to be diols). These were observed as six minor peaks appearing late in the gas chromatogram. The gas chromatogram of the steam-distilled mixture showed eight peaks, of which seven have been identified (see Table II). The presence of the expected oxidation products **14**, **15**, and **16** from **13** was established by gas chromatographic studies of samples successively enriched with authentic materials.

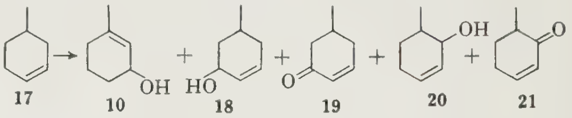


The identities of the remaining peaks were established in a circuitous manner. The total mixture was oxidized with Jones' reagent to a mixture of three ketones with gas chromatography peaks in the ratio 1.0:1.7:3.0. These peaks were shown to be due to ketones **21**, **16**, and **11** in this order, by collecting the ketones in a 2,4-dinitrophenylhydrazine solution as they emerged from the column. The 2,4-dinitrophenylhydrazones were recrystallized and melted at 147–151°, 164–165°, and 176–178°, respectively. An admixture with authentic 2,4-dinitrophenylhydrazones showed no depression in melting point. The presence of the alcohols **10** and **20** was then shown in the HP–VP oxidation mixture by enrichment with authentic materials.

The presence of the abnormal oxidation products **10**, **11**, **20**, and **21** among the expected allylic oxidation products suggested that allylic rearrangement takes place during the HP–VP oxidation of 3-methyl-1-cyclohexene (**13**). The products **10**, **11**, **20**, and **21** are presumed to form as shown (bottom, col. 1).



4-Methyl-1-cyclohexene (**17**) was oxidized similarly and five of the seven major steam-volatile products were identified by enrichment of the product mixture with authentic materials (see Table II). The presence of the unexpected alcohol **10** was confirmed by oxidizing the mixture with Jones' reagent, and showing the presence of **11** in the product by enrichment with authentic **11** in gas chromatographic studies, and by isolating the 2,4-dinitrophenylhydrazone of **11** as it emerged from the column.



While **13** yields both the normal oxidation products, **15** and **16**, and the products of the allylic shift, **20** and **21**, we were unable to detect **15** and **16**, the corresponding products produced by allylic shift accompanying **18** and **19** in the oxidation of **17**.

Experimental

Starting Materials.—The cyclohexene (**1**) used for the HP–VP oxidation was homogenous by gas chromatography (Ucon Polar column at 40°). 1-Methyl-1-cyclohexene (**7**), b.p. 110.3°, showed a single gas chromatographic peak (Ucon Polar column at 50°). 3-Methyl-1-cyclohexene (**13**), b.p. 102.5°, was obtained by fractional distillation from a mixture of 1-methyl-1-cyclohexene (**7**) and 3-methyl-1-cyclohexene (**13**). The gas chromatographic curve (200-ft. squalane capillary column at 26°, hydrogen flame detector) of the fractionated 3-methyl-1-cyclohexene showed 3-methyl-1-cyclohexene (**13**) to be 99% pure. Under these conditions 3-methyl-1-cyclohexene (**13**) and 4-methyl-1-cyclohexene (**17**) showed separation. 4-Methyl-1-cyclohexene (**17**), b.p. 102.7°, was shown to be 99% pure through the same gas chromatographic procedure as described for 3-methyl-1-cyclohexene.

Oxidations with HP–VP.[2] (a) **Cyclohexene, $^1/_6$ Mole Hydrogen Peroxide.**—To an 8-l. vessel equipped with stirrer, condenser, and dropping funnel were added 500 g. (6.1 moles) of cyclohexene (**1**) and 5.0 l. of acetone. To the well stirred mixture was added the catalyst prepared by mixing 20 ml. of 30% hydrogen peroxide and 2.0 g. of vanadium pentoxide at 5–10° and diluting with 200 ml. of precooled (−10°) acetone. The catalyst mixture was filtered as rapidly as possible so that the temperature did not rise above −2° during preparation. The flask was cooled in a water bath and 100 ml. (*ca.* 1 mole total) of 30% hydrogen peroxide was added to the agitated mixture over about 30 min. The reaction was maintained at 30°. After about 10 ml. of hydrogen peroxide was added, the color changed from orange to green. If the color change did not take place, an additional 5.0 ml. of hydrogen peroxide was added. The mixture was stirred an additional hour and then allowed to stand overnight. The reaction mixture was then held at reflux for 1 hr. with stirring and checked for hydrogen peroxide with titanium sulfate solution (if hydrogen peroxide was present, more cyclohexene was added and the reaction held at reflux for an additional hour). If peroxide was absent, acetone and excess cyclohexene were distilled (4 to 4.5 l.), the distillate diluted with water, and about 100 g. of cyclohexene was recovered from the water-insoluble layer. The residue was dried over anhydrous sodium sulfate, filtered, and distilled at 61–63° (14 mm.) to give 42–45 g. of a mixture of 2-cyclohexen-ol (**2**) and 2-cyclohexen-1-one (**3**). Gas chromatographic studies on 15% phenyldiethanolamine succinate (PDEAS) substrate supported on a column of 60–80-mesh acid-washed firebrick ($^1/_4$ in. × 5 ft.) showed the presence of two sharply defined, completely separated peaks (2 min. at 140°; 80 ml. helium/min.; Wilkens Model A-90P, thermal conductivity detector). A cleaner product containing less impurities in the gas chromatogram was obtained if the crude product was steam distilled before final distillation. The distilled product gave $\lambda_{\max}^{\mathrm{EtOH}}$ 225 mμ (ϵ 3905)[16]; $\lambda_{\max}^{\mathrm{CS_2}}$ 3.0 and 5.95 μ.

(b) **Cyclohexene, $^1/_3$ Mole Hydrogen Peroxide and** (c) **Cyclohexene, $^1/_2$ Mole Hydrogen Peroxide.**—These oxidations were carried out essentially as described for part a. The yield of product boiling at 61–64° (14 mm.) was 63–65 g. for $^1/_3$ mole and 78–80 g. for $^1/_2$ mole. Gas chromatographic data on parts a, b, and c are summarized in Table I and described as part of the Jones' oxidation procedure.

(d) **1-Methyl-1-cyclohexene** (**7**).—The oxidation of **7** was similar to part a and was carried out in a 2-l., three-necked flask containing 1 l. of acetone and 96 g. (1 mole) of **7**. The catalyst was prepared from 0.4 g. of vanadium pentoxide and 2 ml. of cold 30% hydrogen peroxide and diluted with 30 ml. of acetone after 2–3 min.; see Table II for gas chromatographic data of the steam-distilled product mixture. 1-Methyl-*trans*-1,2-cyclohexanediol (**12**) crystallized directly from the reaction mixture and was also isolated as a high boiling fraction, b.p. 100° (12 mm.), m.p. 84–86°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.53; H, 10.83. Found: C, 64.51; H, 10.59.

(e) **3-Methyl-1-cyclohexene** (**13**) **and** (f) **4-Methyl-1-cyclohexene** (**17**).—These olefins were oxidized in the same manner as described in part d, and the results are tabulated in Table II.

Oxidation of 1-Methyl-1-cyclohexene (**7**) **with Chromic Acid.** 1-Methyl-1-cyclohexene (**7**) (96 g. 1.0 mole), was oxidized according to the precedure of Whitmore and Pedlow[6] except that the reaction mixture was steam distilled rather than extracted. The steam distillate was saturated with salt, extracted with ether, the ether dried over anhydrous magnesium sulfate, filtered, and distilled. The distillation residue was directly injected onto a $^1/_4$ in. × 5 ft. gas chromatographic column containing 15% PDEAS on 60–80-mesh acid-washed firebrick. Flow rate was 80 ml. helium/min. and column temperature was 140°. Two major peaks in the ratio of 1:7.8 were observed. These were established as 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexene-1-one (**11**) by successively enriching the reaction product with authentic ketones **8** and **11** and analyzing by gas chromatography.

Jones' Oxidations[4] of the Reaction Products from HP–VP Oxidations. (a) **Crude Mixture of 2-Cyclohexen-1-ol** (**2**) **and 3-Cyclohexen-1-one** (**3**).—The crude reaction product from the oxidation of cyclohexene with HP–VP[2] was steam distilled, the steam distillate saturated with salt, extracted with ether, the ether layer dried over anhydrous magnesium sulfate, filtered, and the ether distilled slowly under water aspirator vacuum. The concentrate (424 g.) was dissolved in 5 l. of redistilled acetone and oxidized by dropwise addition of Jones' reagent[4] to the well stirred solution. The reagent is a mixture of 267 g. of chromium trioxide and 230 ml. of sulfuric acid (Spectro Grade 1.84) made up to 1.0 l. with distilled water.[4] The temperature of the reaction was maintained at 20–30° by cooling in a water bath. Progress of the oxidation (2 hr.) was followed by occasionally withdrawing a 1-ml. sample to which was added about 25 mg. of sodium bicarbonate and the pH checked to ensure neutrality. The sample was shaken; the solution decanted and dried over anhydrous magnesium sulfate. The supernatent liquid was directly injected onto the PDEAS column at 140°. Two peaks were observed before oxidation was begun. As the oxidation proceeded, the second peak grew at the expense of the first peak until at termination only the second peak remained. The orange-yellow end point was maintained for about 10 min. This end point is demonstrated easily with a drop of Jones' reagent in a few mililiters of acetone. A few drops of isopropyl alcohol will consume the excess reagent. The reaction product was decanted and the suspension of green salts rinsed with a few milliliters of acetone. Sodium bicarbonate (50 g.) was added to reaction mixture, suspension filtered, anhydrous magnesium sulfate (500 g.) added, the suspension filtered once more, and the acetone distilled through a Vigreux column. On occasion it was necessary once more to dry the product with anhydrous magnesium sulfate before final distillation. Distillation at 61° (14 mm.) gave 371 g. of 2-cyclohexen-1-one (**3**); $\lambda_{\max}^{\mathrm{EtOH}}$ 224 mμ (ϵ 11,716) and $\lambda_{\max}^{\mathrm{CS_2}}$ 5.95 μ.[16] The red 2,4-dinitrophenylhydrazone was recrystallized from isopropyl alcohol and melts at 166–167°.[3,6]

(b) **Products from 1-Methyl-1-cyclohexene** (**7**).—The crude reaction product obtained from the HP–VP oxidation of 1-methyl-1-cyclohexene (**7**) was steam distilled, the steam distillate saturated with salt, extracted with ether, the ether separated and concentrated by distillation. The concentrate was oxidized with Jones' reagent in a manner similar to part a but on a smaller scale. The oxidation product was isolated by steam distillation, extracted with ether, and the dried ether concentrate injected onto an alkaline Carbowax 20M gas chromatographic column, temperature programmed from 30–200°.

The peaks represented by 2-methyl-2-cyclohexen-1-one (**8**) and 3-methyl-2-cyclohexen-1-one (**11**) were identified by enriching the reaction product sample with authentic materials. The peaks due to the alcohols **9** and **10** were not present in the gas chromatogram.

(c) **Products from 3-Methyl-1-cyclohexene** (**13**).—The Jones' oxidation of the products from HP–VP oxidation of **13** was conducted in the same manner as for part b. The gas chromatogram (PDEAS column at 135°) showed three peaks in the ratio of 1.0: 1.7:3.0. The ketones were collected from the PDEAS column in a 2,4-dinitrophenylhydrazine solution. The resulting red 2,4-dinitrophenylhydrazone derivatives were collected, recrystallized, and found to melt at 147–151°, 164–165°, and 176–178°. Admixtures of these red 2,4-dinitrophenylhydrazones with 2,4-dinitrophenylhydrazones derivatives of authentic 6-methyl-2-cyclohexen-1-one (**21**), 4-methyl-2-cyclohexen-1-one (**16**), and 3-methyl-2-cyclohexene-1-one (**11**), respectively, show no depression in melting point. The ketones from the individual peaks were collected in ether as they emerged from the column and used to identify peaks in the chromatogram of the crude reaction product and as a source for lithium aluminum hydride reduction to obtain the respective alcohols.

(d) **Products from 4-Methyl-1-cyclohexene** (**17**).—The Jones' oxidation of **17** was carried out as in part b. The presence of **11**, which emerged last on the PDEAS column, was shown by enrichment with authentic **11** and by the isolation of its red 2,4-dinitrophenylhydrazone derivative, m.p. 176–178°, which does not depress the melting point of the 2,4-dinitrophenylhydrazone of authentic 3-methyl-2-cyclohexen-1-one (**11**).

Lithium Aluminum Hydride Reductions. (a) **Mixture of 2-Cyclohexen-1-ol** (**2**) **and 2-Cyclohexen-1-one** (**3**).—To a 5-l., three-necked flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel with pressure equalizing side arm, containing 42 g. lithium aluminum hydride dissolved in 3 l. of anhydrous ether, was added a 300-g. sample of a mixture comprised of 37% 2-cyclohexen-1-one (**3**) and 63% 2-cyclohexen-1-ol (**2**) at a rate to maintain gentle reflux. Two hours were required for addition. The reaction mixture was stirred an additional 4 hr. at reflux temperature and water was added dropwise until evolution of gases ceased. The suspension was allowed to settle; the ether solution was decanted and tested with water to ensure complete destruction of lithium aluminum hydride. The suspended salts were rinsed twice with 200-ml. portions of ether and the combined ether solution dried over anhydrous magnesium sulfate, filtered, and ether distilled. The concentrate was distilled at 64–65° (10.5 mm.) to give 240 g. of 2-cyclohexen-1-ol (**2**) whose infrared spectrum showed $\lambda_{\max}^{\mathrm{CS_2}}$ 3.0 and 6.08 μ. The gas chromatogram (PDEAS at 115°) showed a single major peak and no peak corresponding to 2-cyclohexen-1-one (**3**). The phenyl urethane melts at 107–109°.[6]

(b) **Crude Products from 1-Methyl-1-cyclohexene** (**7**).—The crude HP–VP products of 1-methyl-1-cyclohexene (**7**) were reduced with lithium aluminum hydride as described under part a. The products were isolated by steam distillation. The steam distillate was saturated with salt and extracted with ether; the ether layer was separated and washed with small portions of water, dried over anhydrous magnesium sulfate, filtered, and distilled. The concentrate was analyzed with gas chromatography (PDEAS column at 130°). The peaks corresponding to the ketones **8** and **11** were completely absent. The peaks corresponding to the alcohols **9** and **10** were found to have increased.

Borate Ester Preparation. (a) **From 2-Cyclohexen-1-ol** (**2**).—A mixture of 49.0 g. (0.5 mole) of 2-cyclohexene-1-ol (**2**), 8.4 g. (0.136 mole) boric acid, and 100 ml. of dry benzene was heated at reflux temperature for approximately 2 hr. until water–benzene azeotrope (7.0 ml. total) no longer collected in the Dean–Stark separator. The boric acid completely dissolved within a few minutes after reflux was attained. Most of the benzene (75 ml.) was distilled at atmospheric pressure and the product distilled through a short-path Vigreux column at 30–115° (0.04 mm.). The benzene forerun was discarded and the product fractionated

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[16] D. Dusterhoft of Lakeside Laboratories kindly carried out these determinations.

through a spiral column to give 15.8 g. recovered **2** and 32.0 g. (0.133 mole, 78% yield based on boric acid) of colorless boric acid ester, b.p. 133–145° (0.2 mm.). A center cut, b.p. 142–145° (0.2 mm.), was used for analyses and infrared spectrum; $\lambda_{\max}^{\text{neat}}$ 2.95, 6.08, 7.05, 7.24, 7.60, 8.00, 9.60, 9.40, 9.56, 10.42, 10.76, 11.11, and 13.80 μ.

Anal. Calcd. for $C_{18}H_{27}BO_3$: B, 3.57. Found: B, 3.73.

A 14.9-g. (0.049 mole) sample of the borate ester of **2** was steam distilled, the distillate extracted with ether, the ether extract dried over anhydrous magnesium sulfate, filtered, and the ether distilled to give 12.3 g. (85% recovery) of regenerated 2-cyclohexen-1-ol (**2**). The infrared spectrum and gas chromatogram (PDEAS at 140°) were identical with those of original **2**. The contents of the steam distillation reaction flask were colorless.

(b) **From 2-Cyclohexen-1-one** (**3**).—Under conditions similar to part a, 2-cyclohexen-1-one (**3**) (0.5 mole) and boric acid (0.136 mole) in 100 ml. of benzene gave 2 ml. of water–benzene azeotrope. The dark-colored reaction product was filtered to yield 7.1 g. (84% recovery) of unchanged boric acid. The filtrate was distilled at 25–35° (0.05 mm.) to give 32.1 g. (66% recovery) of 2-cyclohexene-1-one whose gas chromatogram (PDEAS at 125°) and infrared spectrum were identical with those of original ketone **3**.

The dark-colored, viscous pot residue was steam distilled to give 1.6 g. (0.016 mole, 3.2%) of regenerated 2-cyclohexen-1-one (**3**) whose infrared spectrum, gas chromatogram (PDEAS at 125°) and gas chromatogram of an admixture with **3** were identical with 2-cyclohexene-1-one (**3**). A dark-colored tar remained in the steam distillation flask.

Preparation of Comparison Compounds. (a) *cis*-**1,2-Cyclohexanediol** (**5**).—A sample of a mixture of *cis*-1,2-cyclohexanediol (**5**) and *trans*-1,2-cyclohexanediol (**6**) was separated by gas chromatography on PDEAS at 162° and collected in ethyl acetate. The retention times were 11.5 and 12.4 min., respectively.

(b) **2-Methyl-2-cyclohexen-1-one** (**8**).—2-Methyl-2-cyclohexen-1-one (**8**) was obtained by dehydrohalogenation[17] of 2-chloro-2-methylcyclohexanone[18] with lithium bromide and lithium carbonate in dimethylformamide. The ketone **8**, $n^{23}\text{D}$ 1.4852, $\lambda_{\max}^{\text{neat}}$ 6.05 μ, gives a single peak on the PDEAS gas chromatographic column at 145°. Its red 2,4-dinitrophenylhydrazone crystallized from isopropyl alcohol melts at 207–209°.[19]

(c) **2-Methyl-2-cyclohexen-1-ol** (**9**).—The alcohol **9** was obtained from the ketone **8** *via* lithium aluminum hydride reduction in ether solution followed by steam distillation. The product shows a single gas chromatographic peak on the PDEAS column at 145°.

(d) **3-Methyl-2-cyclohexen-1-ol** (**10**).—A sample of 3-methyl-2-cyclohexen-1-one (**11**) was reduced with lithium aluminum hydride in ether to give 3-methyl-2-cyclohexen-1-ol (**10**), $n^{23}\text{D}$ 1.4835, b.p. 82–84° (15 mm.,) and $\lambda_{\max}^{\text{neat}}$ 3.07 and 6.08 μ. Gas chromatographic analysis on PDEAS at 140° shows a single peak.

(e) **3-Methyl-2-cyclohexen-1-one** (**11**).—A 182-g. (1.0 mole) sample of 4-carbethoxy-3-methyl-2-cyclohexen-1-one,[20] $n^{23}\text{D}$ 1.4842, was hydrolyzed by steam distilling from 1 l. of 15% sulfuric acid. The steam distillate was saturated with salt and extracted with ether; the ether layer was washed with water, dried over anhydrous magnesium sulfate, filtered, and distilled to give 87 g. (0.79 mole, 79% yield) of 3-methyl-2-cyclohexene-1-one (**11**), b.p. 80–95° (9 mm.,) $n^{25}\text{D}$ 1.4910, and $\lambda_{\max}^{\text{neat}}$ 6.05 and 6.2 μ. The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate melts at 176–178°.

(f) **1-Methyl-2-cyclohexen-1-ol** (**14**).—A 24-g. sample (0.25 mole) of 2-cyclohexen-1-one was added to 2 equivalents of methylmagnesium iodide contained in a 1-l., three-necked flask equipped with stirrer, condenser protected with a calcium chloride tube, and dropping funnel. The 2-cyclohexene-1-one was added to the chilled (−5°) reaction flask over a 2-hr. period. The reaction mixture was allowed to come to room temperature and then heated at reflux temperature for 0.5 hr. The reaction mixture was then poured onto 500 g. of ice, and the product was directly steam distilled without addition of ammonium chloride or acid. [It was intentional that acid was avoided to minimize isomerization of 1-methyl-2-cyclohexen-1-ol (**14**) to 3-methyl-2-cyclohexen-1-ol (**10**).] The steam distillate (1 l.) was saturated with salt, extracted with 200 cc. of ether, and washed with two small portions of water; the ether layer separated, dried over anhydrous magnesium sulfate, filtered, and the ether distilled. The concentrate was analyzed with gas chromatography (PDEAS column at 100°) and found to be a mixture of 36% 1-methyl-2-cyclohexen-1-ol (**14**),[6] 58% 3-methylcyclohexanone,[6] and 6% 3-methyl-2-cyclohexen-1-ol (**10**).[6] The 3-methylcyclohexanone and the alcohol **10** were identified by enriching the total reaction product with authentic materials and analyzing by gas chromatography. A pure sample of the alcohol **14** was obtained by collection from the PDEAS column at 125°.

(g) **4-Methyl-2-cyclohexen-1-ol** (**15**).—The ketone **16** was reduced with lithium aluminum hydride in ether to give 4-methyl-2-cyclohexen-1-ol (**15**) which shows essentially a single gas chromatographic peak; the yield of **15** was 71%.

(h) **4-Methyl-2-cyclohexen-1-one** (**16**).—A procedure similar to j was employed in the preparation of 4-methyl-2-cyclohexen-1-one (**16**) from 4-methylcyclohexanone. The ketone **16** gave a red 2,4-dinitrophenylhydrazone which melts at 168–169° on recrystallization from isopropyl alcohol.

(i) **5-Methyl-2-cyclohexen-1-ol** (**18**).—A sample of 5-methyl-2-cyclohexen-1-one (**19**) was purified by gas chromatography on PDEAS, reduced by lithium aluminum hydride, and the product isolated by steam distillation. The product, 5-methyl-2-cyclohexen-1-ol (**18**), shows a single peak on the PDEAS gas chromatographic column.

(j) **5-Methyl-2-cyclohexen-1-one** (**19**).—A 112-g. sample of *dl*-3-methylcyclohexanone was chlorinated with sulfuryl chloride in carbon tetrachloride solution.[19] The chlorocyclohexanone was distilled at 35–87° (0.1 mm.) and shown by gas chromatography on PDEAS at 170° to contain 3-methylcyclohexanone in the initial cut. Center cuts, b.p. 50–80° (0.1 mm.), were free of 3-methylcyclohexanone but appeared to be a mixture of 2-chloro-3-methylcyclohexanone and 2-chloro-5-methylcyclohexanone since double peaks were observed in the gas chromatogram on PDEAS at 170° column temperature.

Dehydrohalogenation[17] in the presence of lithium bromide and lithium carbonate in dimethylformamide solvent was carried out on a 50-g. sample of the mixture of chloro ketones. The product was isolated by steam distillation and extraction of the steam distillate with ether. Dimethylformamide was removed from the ether extract by washing with water. The product, b.p. 34–54° (0.1 mm.), was shown by gas chromatography on PDEAS at 170° to be a mixture containing the desired product, 5-methyl-2-cyclohexen-1-one (**19**) (3.5 min. retention time), as well as 3-methyl-2-cyclohexen-1-one (**11**) and 3-methylphenol (6.2 and 14 min., respectively). The latter compounds were identified by enriching the mixture with authentic materials. A pure sample of 5-methyl-2-cyclohexen-1-one (**19**) was obtained by collecting the ketone as it emerged from the column. An orange 2,4-dinitrophenylhydrazone was prepared from the collected sample and found to melt at 148–149°[21] after recrystallization from methanol.

(k) **6-Methyl-2-cyclohexen-1-ol** (**20**).—A sample of 6-methyl-2-cyclohexen-1-one (**21**) was purified through gas chromatography (PDEAS column at 150°) by collecting in ether solution. The ether solution was added dropwise to a stirred solution of lithium aluminum hydride in ether. The reaction was heated at reflux temperature for approximately 0.5 hr., cooled, and the excess lithium aluminum hydride cautiously destroyed by the dropwise addition of water. Additional water was added and the reaction product steam distilled. The alcohol **20** was isolated from the steam distillate by extraction with ether, the ether solution dried, concentrated, and analyzed by gas chromatography (PDEAS column at 120°) which showed essentially a single peak with a slight trailing shoulder. This shoulder was assumed to be due to the presence of *cis* isomer. The yield of **20** was 72%. The alcohol **20** was added to a sample of the HP–VP oxidation product of 4-methyl-1-cyclohexene (**17**) and this enrichment established the presence of **20** in the reaction mixture.

(l) **6-Methyl-2-cyclohexen-1-one** (**21**) was generously donated by D. R. Coulson and E. J. Warawa of Columbia University. Reduction with lithium aluminum hydride gave 6-methyl-2-cyclohexen-1-ol (**20**).

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[17] R. Joly, J. Warnaut, G. Nomine, and D. Bertin, *Bull. soc. chim. France*, 360 (1958).

[18] Generously donated by J. Levy and H. L. Goering of the University of Wisconsin.

[19] E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953).

[20] C. Th. L. Hagemann, *Ber.*, **26**, 876 (1893).

[21] H. L. Goering and J. P. Blanchard, *J. Am. Chem. Soc.*, **73**, 5863 (1951).

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6-Trimethylammoniopurinide

Rainer Klemm, Helmut Schulze, Martin G. Ettlinger, and Alfred R. Bader

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6-Trimethylammoniopurinide[1]

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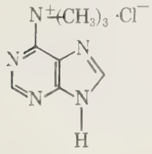
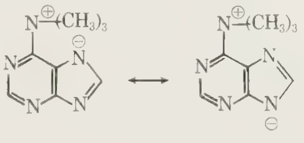
Current clinical interest[2] in the carcinostatic activity of the antimetabolite 6-purinyltrimethylammonium chloride[3] (I) led us to investigate methods for the purification of this salt. Precipitation of its aqueous solution by organic solvents consistently yielded products low in chlorine.[4] During further study, an aqueous solution of I was passed through an anion-exchange column in its hydroxide form, yielding on evaporation a new substance, mp 190–192°, which was chlorine free and had structure II (see Experimental Section).



I



II etc.

Experimental Section

Purin-6-yltrimethylammonium chloride (**I**) was prepared by the method of Horwitz and Vaitkevicius.[3] Small quantities of crude I were purified by solution in cold water and quick precipitation with acetone; pure I melts at 191–192°.

6-Trimethylammoniopurinide (**II**).—A solution of 170 g of I in 1 l. of water was passed through an ion-exchange column with 1.5 l. of Dowex 1-X8 (hydroxyl form), and the column was then washed thoroughly with water. The combined eluates were then evaporated to dryness *in vacuo* at 50°, and the product crystallized from water and was dried *in vacuo* (P_2O_5) to yield 112 g of II, mp 190–192°.

Anal. Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.30, 54.30; H, 6.03, 6.20; N, 39.18, 39.49.

Structure II is supported by the nmr spectrum[5] in D_2O which shows, besides two equal peaks at 221 and 212 cycles below the signal from solvent protons, only one, much more intense, peak at 59 cycles above solvent reference. The dipolar salt II has the same melting point as 6-dimethylamino-1-methylpurine[6] (III), and the melting points of the respective picrates are also similar. However, the mixture melting point of II and III is depressed, the maximum of the ultraviolet spectrum of II is at much lower wavelength than that of III, and the nmr spectrum of III shows two well-separated methyl group signals. Electrometric titration shows that II is a weak base and the pK_a of the conjugate acid I is 6.8. This value appears reasonable, for purine has $pK_a = 8.9$,[7] and the trimethylammonium group would lower the pK.[8]

Similarly, the ultraviolet spectrum of II appears reasonable [$\lambda_{max}^{H_2O}$ (pH 10) 274 mμ (log ε 3.86)] when compared with that of purine anion[9] [λ_{max} (pH 11) 271 mμ (log ε 3.88)]; the trimethylammonium group, being nonconjugating, would be expected to have little effect. The spectrum of II at pH 1 (that is, of I), with λ_{max} 265 mμ (log ε 3.94), is also close to that of neutral purine [λ_{max} 263 mμ (log ε 3.90)].

Saline solutions of I and II are indistinguishable.

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[1] Alpurine (Trademark applied for).

[2] V. K. Vaitkevicius and M. L. Reed, *Proc. Am. Assoc. Cancer Res.*, **7**, 72 (1966).

[3] J. P. Horwitz and V. K. Vaitkevicius, *Experientia*, **17**, 552 (1961).

[4] Similar material, which can now be construed as a solvated equimolar mixture of I and II, was obtained by E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3274 (1962).

[5] We wish to thank Dr. George Slomp for determining the nmr spectrum of II.

[6] (a) L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Am. Chem. Soc.*, **86**, 5320 (1964); (b) B. C. Pal and C. A. Horton, *J. Chem. Soc.*, 400 (1964); (c) we wish to thank Professor R. K. Robins for a sample of III.

[7] A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

[8] H. C. Brown, D. H. McDaniel, and O. Häfliger in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press Inc., New York, N. Y., 1955, p 592.

[9] S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

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Transesterification. II. Esters of Strong Organic Acids

By Alfred R. Bader and Henry A. Vogel

[Reprinted from the Journal of the American Chemical Society, **74**, 3992 (1952).]

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE PAINT DIVISION OF THE PITTSBURGH PLATE GLASS COMPANY]

Transesterification. II. Esters of Strong Organic Acids

BY ALFRED R. BADER AND HENRY A. VOGEL

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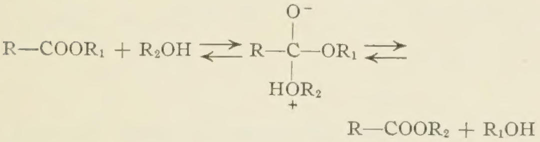
The transesterification of β-keto esters has been compared with that of esters of other strong organic acids. Malonates and oxalates, like acetoacetates, are transesterified under mild conditions, and it is suggested that the ease of transesterification of β-keto esters is due mainly to special structural features inherent in these esters, while that of oxalates is due to the inductive effect of the neighboring group.

In our first communication[1] we reported on the transesterification of β-keto esters which proceeds at steam-bath temperatures in the absence of catalysts. We have now completed a qualitative study of transesterifications of acids of strength similar and greater than that of acetoacetic acid to determine whether this facile transesterification is due to the inductive effect of the acetyl group, to intermolecular catalysis by active hydrogen or to structural features unique in β-keto esters. Table I lists the acids investigated, their ionization constants and the products obtained after heating representative primary and secondary alcohols with excess ester on the steam-bath without catalysts for 16 hours.

In any ester interchange one has the equilibria



$$R{-}COOR_1 + R_2OH \rightleftharpoons R{-}\underset{\underset{+}{HOR_2}}{\overset{O^-}{C}}{-}OR_1 \rightleftharpoons R{-}COOR_2 + R_1OH$$

the equilibrium constants of which are probably not greatly different from 1[2] and the reason for the ease of transesterification of acetoacetates at first considered most likely was the inductive effect of the acetyl group which removes electrons from the ester carbonyl, increases its electrophilic reactivity and thus the speed with which the equilibria are set up. A correlation is that acetoacetic acid is over ten times as strong an acid as acetic. Our qualitative data indicate, however, that the inductive effect can only be a mildly contributory factor in the ease of transesterification of β-keto esters because esters of some stronger acids do not react under our experimental conditions. Nor does it seem likely that the ease of transesterification of β-keto esters is due to an active hydrogen catalysis because we have found that when alcohols are heated in unreactive esters such as ethyl butyrate containing ethyl acetoacetate in a molar ratio of 10:1, the higher acetoacetate is the sole reaction product. Such experiments are, however, not entirely conclusive because one would expect the acetoacetate to be the more basic ester and its reaction might be the only one catalyzed.

TABLE I

Acid	$10^5 K_1$ at 25°	Products
Caprylic	1.44[a]	None
Butyric	1.50[b]	None
Crotonic	2.03[b]	None
Levulinic	......	None
Benzoic	6.27[b]	None
Lactic	13.9[c]	None
Acetoacetic	26[d]	Acetoacetates
Benzoylacetic	......	Benzoylacetates
Furoic	68[e]	None
Fumaric	95.7[f]	Small amt. fumarates
Tartaric	104[g]	None
Phthalic	112[h]	None
Malonic	177[f]	Mixed and symm. malonates
Ethyl-*n*-butylmalonic	......	None
Maleic	1200[f]	None
Oxalic	5900[i]	Mixed and symm. oxalates

[a] C. G. Derrick, THIS JOURNAL, **33**, 1152 (1911). [b] J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939). [c] A. W. Martin and H. V. Tartar, THIS JOURNAL, **59**, 2672 (1937). [d] K. J. Pedersen, *J. Phys. Chem.*, **38**, 993 (1934). [e] W. L. German, G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1604 (1937). [f] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 201. [g] I. Jones and F. G. Soper, *J. Chem. Soc.*, 1836 (1934). [h] W. J. Hamer, G. D. Pinching and S. F. Acree, *J. Research Natl. Bur. Standards*, **35**, 539 (1945); *C.A.*, **40**, 3044 (1946). [i] R. Gane and C. K. Ingold, *J. Chem. Soc.*, 2153 (1931).

After the completion of this work, our attention was drawn to a paper by Carroll[3] which independently describes the facile alcoholysis of acetoacetic and related esters. Carroll attempted to determine the rates of transesterification of acetoacetates by measuring the rates of distillation of lower alcohols evolved, and on the basis of these possibly inaccurate data concluded that the rate determining step is first order with respect to the ester when pri-

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(1) A. R. Bader, L. O. Cummings and H. A. Vogel, THIS JOURNAL, **73**, 4195 (1951).

(2) P. R. Fehlandt and H. Adkins, *ibid.*, **57**, 193 (1935).

(3) M. F. Carroll, *Proc. XIth. Intern. Congr. Pure and Applied Chem.*, **2**, 39 (1947); *C. A.*, **45**, 7015 (1951).

271.5 mμ (log ε 4.09), 281.5 mμ (log ε 4.10), 292.0 mμ (log ε 3.86); $\alpha^{25}\text{D}$ −79.3° (chloroform).

Anal. Calcd. for $C_{32}H_{48}O_3$: C, 79.95; H, 10.06. Found: C, 79.80, 79.60; H, 10.12, 10.10.

Twenty-five g. of *l*-menthol and 10 g. of ethyl *s*-butylacetoacetate[8] were heated at 145–150° for five hours; the unreacted starting materials were removed by distillation *in vacuo* and the almost water white flask residue (9.0 g.) was distilled to yield 7.5 g. of water-white **_l_-menthyl _s_-butylacetoacetate**, b.p. 108–111° (0.3 mm.), $n^{25}\text{D}$ 1.4582.

Anal. Calcd. for $C_{18}H_{32}O_3$: C, 72.92; H, 10.88. Found: C, 73.01, 72.96; H, 11.08, 11.02.

Malonates.—Ten grams of cholesterol and 100 cc. of ethyl malonate were heated on the steam-bath for 15 hours, the excess ethyl malonate was removed by distillation *in vacuo*, and the product chromatographed on Fisher adsorption alumina, 80–200 mesh. There were isolated from the hexane eluate 7.8 g. of white flakes, m.p. 60–63° which after crystallization from ethanol yielded 6.5 g. of pure **ethyl cholesteryl malonate** melting at 63.5–64.0°, $\alpha^{25}\text{D}$ −31° (chloroform), and 0.7 g. of the much less soluble **dicholesteryl malonate** which after crystallization from isopropyl ether melts at 178°, $\alpha^{25}\text{D}$ −33° (chloroform).

Anal. Calcd. for $C_{32}H_{52}O_4$: C, 76.75; H, 10.47. Found: C, 76.76; H, 10.71. Calcd. for $C_{57}H_{92}O_4$: C, 81.37; H, 11.02. Found: C, 81.30, 81.37; H, 10.90, 11.13.

Five grams of octadecyl alcohol and 50 cc. of ethyl malonate were heated on the steam-bath for 18 hours, the unreacted ethyl malonate was removed as above, and the residue dissolved in hot acetone. On cooling, white shiny platelets of **dioctadecyl malonate** (250 mg.) deposited which after recrystallization from acetone melt sharply at 64°. The combined mother liquors were evaporated to dryness, dissolved in hexane and chromatographed. The first eluates yielded 4.3 g. of a waxy solid, **ethyl octadecyl malonate**, m.p. 30–32°.

Anal. Calcd. for $C_{23}H_{44}O_4$: C, 71.82; H, 11.53. Found: C, 71.54; H, 11.76. Calcd. for $C_{39}H_{76}O_4$: C, 76.91; H, 12.58. Found: C, 77.28, 77.10; H, 12.74, 12.81.

Oxalates.—Ten grams of β-sitosterol, 75 cc. of ethyl oxalate and 25 cc. of toluene were heated on a steam-bath for 16 hours, the solvent and unreacted ethyl oxalate were removed by distillation *in vacuo*, and the residue was separated by solubility in a mixture of ethanol and acetone into the sparingly soluble **di-β-sitosteryl oxalate** (0.7 g.) and the more soluble **ethyl β-sitosteryl oxalate** (9.2 g.). The symmetrical ester crystallized from a mixture of toluene and ethanol in flat, shiny needles, m.p. 195–196°, while the mixed ester, crystallized from a mixture of ethanol and acetone, melts at 65–66°.

Anal. Calcd. for $C_{33}H_{54}O_4$: C, 77.00; H, 10.57. Found: C, 77.03; H, 10.70. Calcd. for $C_{60}H_{98}O_4$: C, 81.57; H, 11.18. Found: C, 81.87; H, 11.20.

Cholesterol treated similarly yielded corresponding amounts of **dicholesteryl oxalate**[9] which forms fine needles from a mixture of ethanol and toluene, m.p. 220–222°, and **ethyl cholesteryl oxalate** which after crystallization from a mixture of ethanol and acetone melts at 94.5–95.5°, $\alpha^{25}\text{D}$ −33° (chloroform).

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 77.00, 76.94; H, 10.70, 10.54.

Ethyl octadecyl oxalate prepared similarly and crystallized from ethanol melts at 36.5–37.0°.

Anal. Calcd. for $C_{22}H_{42}O_4$: C, 71.30; H, 11.43. Found: C, 71.18, 71.20; H, 11.51, 11.47.

Competitive Reactions.—Ergosterol (1.0 g.) dissolved in a mixture of 58 g. (0.5 mole) of redistilled ethyl butyrate and 6.5 g. (0.05 mole) of redistilled ethyl acetoacetate was heated on the steam-bath for three hours. The solvent mixture (42 g.) was then removed quickly by distillation *in vacuo*, and the residual water-white solution was diluted with 50 cc. of hot ethanol and 30 cc. of water. On cooling the solution deposited shiny white platelets (0.80 g., m.p. 122–124°) which after two crystallizations from aqueous ethanol yielded similar crystals (0.7 g.) which melted at 124–125° and did not depress the m.p. of authentic ergosteryl acetoacetate. Their infrared spectra in chloroform were identical.

Anal. Calcd. for $C_{32}H_{48}O_3$: C, 79.95; H, 10.06. Found: C, 79.79; H, 10.09.

Similar treatment of cholesterol and β-sitosterol with methyl acetoacetate in large molar excesses of methyl benzoate and methyl phthalate also yielded only the corresponding acetoacetates.

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(8) Prepared by the general procedure of "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 243.

(9) I. H. Page and H. Rudy, *Biochem. Z.*, **220**, 304 (1930).