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

By Alfred R. Bader

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

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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.

The author wishes to thank Professor and Mrs. L. F. Fieser for helpful advice during the course of this investigation.

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

Compound oxidized	Crude product Wt. g.	M. p., °C.	Wt., g.	Pure product 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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(2) McKay and Bader, *J. Org. Chem.*, **13**, 75 (1948).
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(5) Swern, *ibid.*, **70**, 1239 (1948).
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THE PREPARATION AND PROPERTIES OF THE EIGHT DIASTEREOISOMERS OF 9,10,12,13-TETRAHYDROXYSTEARIC ACID

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[Contribution from the Department of Chemistry, Queen's University]

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

A. F. McKAY AND A. R. BADER

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
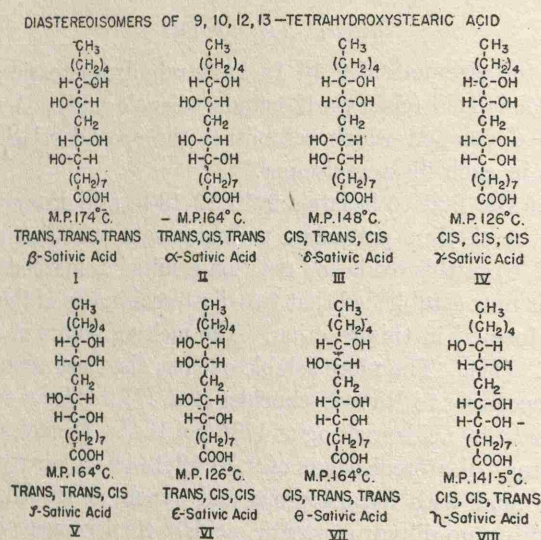
Scheme A

Scheme B
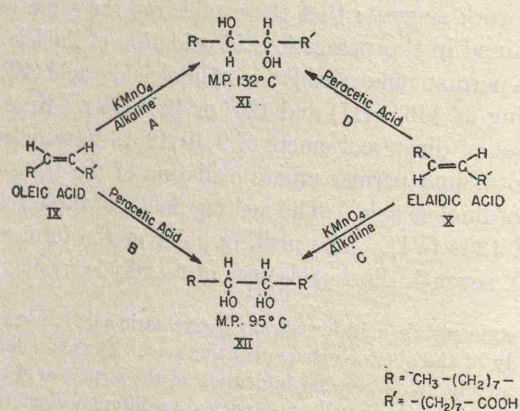
form as elaidic acid (X). The two 9,10-dihydroxystearic acids melting at 132° (XI) and 95° (XII) are formed respectively by the alkaline potassium permanganate oxidation (A) and the peracetic acid oxidation (B) of oleic acid. In antithesis to this, the alkaline potassium permanganate (C) and peracetic 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

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 prep-

Scheme C

$R = CH_3(CH_2)_7—$
$R' = (CH_2)_7COOH$
$R'' = CH_3(CH_2)_4—$
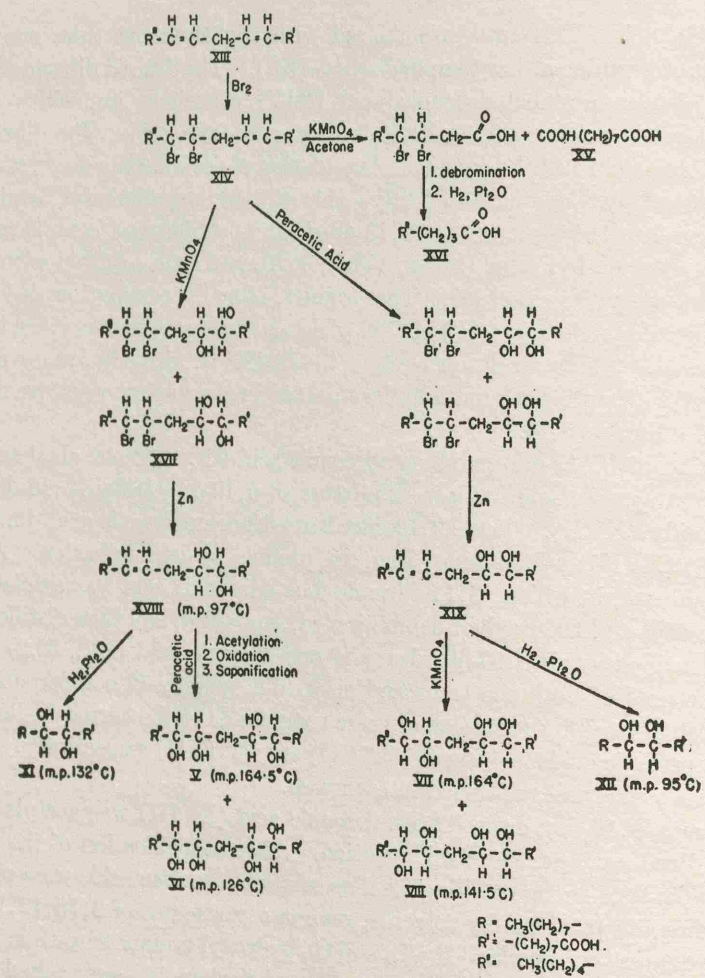
aration. If cis-9,10-dihydroxy-12-octadecenoic acid is acetylated and then oxidized with peracetic acid solution, the product on saponification gives the two diastereoisomers of 9,10,12,13-tetrahydroxystearic acid melting at 148° (III) and 126° (IV). These are identical with the two diastereoisomers 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.

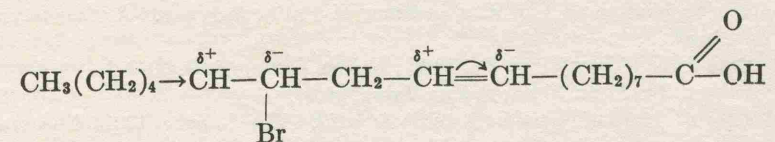Riemenschneider *et al.* (7) concluded that bromination of cis-9-cis-12-octade-

cadienoic 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:

$$CH_3(CH_2)_4 {\rightarrow} CH\underset{\delta^-}{=}CH—CH_2—CH\underset{\delta^+}{=}CH{\rightarrow}(CH_2)_7{\rightarrow}\overset{O}{\overset{\|}{C}}—OH$$
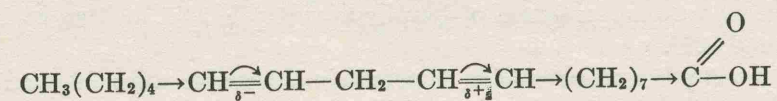
The electron attractive carboxyl group will have a greater effect on reducing the electron density of the 9-double bond than of the 12-double bond while the electron repulsive alkyl group will have a greater effect in increasing the electron density of the 12-double bond than of the 9-double bond. Both 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.*, $CH_3 \rightarrow CH\overset{\delta^+ \frown \delta^-}{=}CH_2$. Thus the attack of the electrophilic reagent $:\overset{..}{Br}:^+$ will be preferentially directed towards the 12-double bond. Once addition of this electrophilic reagent has occurred then the intermediate may be represented as:

$$CH_3(CH_2)_4{\rightarrow}\overset{\delta^+}{CH}—\overset{\delta^-}{\underset{Br}{CH}}—CH_2—\overset{\delta^+}{CH}\underset{\delta^-}{=}CH—(CH_2)_7—\overset{O}{\overset{\|}{C}}—OH$$

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 $: \ddot{Br}:^-$ 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-

[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 Rie-menschneider *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-12,13-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 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 no 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 amorphous 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.

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 Molybdate-catalyzed Hydrogen Peroxide Oxidation of beta-Naphthol

By Alfred R. Bader

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

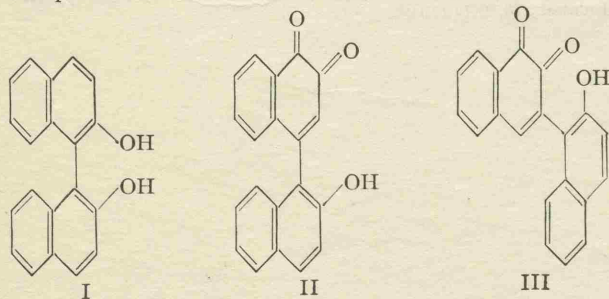# The Molybdate-catalyzed Hydrogen Peroxid e Oxidation of β-Naphthol

By Alfred R. Bader

The red compound, m.p. 148°, isolated by Raacke-Fels, *et al.*,[1] in the molyb date-catalyzed hydrogen peroxide oxidation of β-naphthol has been shown to be 4-(2'-hydroxy-1'-naphthyl)-1,2-naphthoqui none.

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]

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

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

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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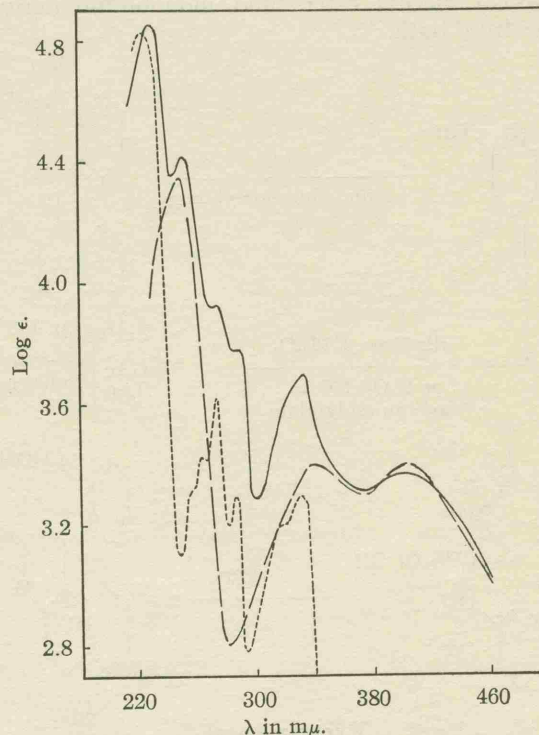(4) H. H. Hodgson and D. E. Hathway, *Trans. Faraday Soc.*, **41**, 115 (1945).

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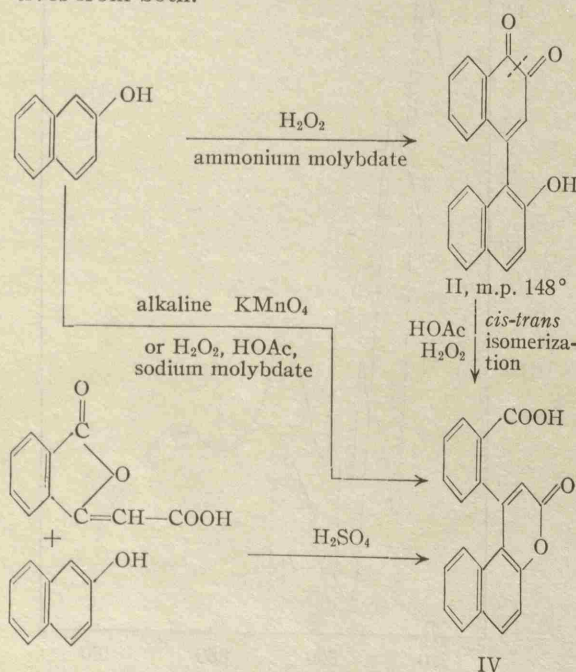(7) O. Dischendorfer and W. Danziger, *Monatsh.*, **48**, 315 (1927).

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Compound	Absorption maxima, wave lengths in $m\mu$, 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.

II, m.p. 148°

alkaline KMnO₄

or H₂O₂, HOAc, sodium molybdate

HOAc | cis-trans
H₂O₂ | isomerization

H₂SO₄

IV

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.

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4

Rearrangement and Reduction of Hindered 2-Hydroxy-3-alkyl-1,4-naphthoquinones
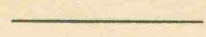
By Louis F. Fieser and Alfred R. Bader

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Rearrangement and Reduction of Hindered 2-Hydroxy-3-alkyl-1,4-naphthoquinones

BY LOUIS F. FIESER AND ALFRED R. BADER[1]

When a solution of 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone[2] (I) in 5% aqueous alkali is heated on the steam-bath with exclusion of air, the initially deep red solution becomes pure yellow in about 27 hours and acidification then precipitates a yellow, non-quinonoid isomer of I for which the structure of 2-cyclohexylindenone-3-carboxylic acid (III) has been tentatively suggested.[3] Further investigation has substantiated this assignment of structure. The yellow isomer has the ultraviolet absorption characteristics expected for III, it forms ester, amide and semicarbazone derivatives, and it is reduced by zinc dust and either acetic acid or alkali to a colorless dihydride of properties consistent with the indanone formula IX. Thus IX has an ultraviolet absorption spectrum similar to that of acetophenone and is reducible by the Clemmensen method to 2-cyclohexylindane-3-carboxylic acid. The indenone III also reacts with excess diazomethane to give a pyrazoline ester of the probable structure X.

Dr. Martin G. Ettlinger of this Laboratory observed in 1947 that 2-hydroxy-3-t-butyl-1,4-naphthoquinone (Ia) is rapidly converted by alkali into a similar yellow non-quinone and that a colorless intermediate is formed at about the same rate when the rearrangement is conducted in a buffer of pH 9.2. We isolated these products and found the properties in accordance with the indenone structure IIIa for the yellow compound and the 3-hydroxyindanone-3-carboxylic acid structure II for the intermediate. Colorless II, of acetophenone-like spectrum, is converted rapidly by alkali into IIIa. Cooke and Somers[4] have reported the independent isolation of the t-butyl compound IIIa and the isolation and synthesis of the corresponding isopropyl derivative[5]; these authors comment on the analogy, considered also by Dr.

Ettlinger, to the rearrangement of dunnione to allodunnione.[6]

According to our observations isomerization of 2-hydroxy-3-t-butyl-1,4-naphthoquinone by 5% alkali at 90° is complete in 1 hour. 2-Hydroxy-3-cyclohexyl-1,4-naphthoquinone is isomerized by 5% alkali in some 27 to 30 hours, and a trace of the indanone IX was isolated from the reaction mixture. When the rearrangement was conducted in 2% alkali, no by-product was observed and pure III was isolated in 88% yield. When the compound I was heated in a buffer at pH 9.2, the sole product was the indenone III (91% yield). In this instance the hydroxyindanonecarboxylic acid is probably the initial product but undergoes dehydration at a rate exceeding the rate of formation. Whereas the dehydration is base catalyzed, the rate of rearrangement is independent of the concentration of hydroxide ion, provided this is sufficient to maintain the quinone largely in the form of the anion.

The mechanism suggested in the formulation is that the hydroxyquinone anion present in the red solution affords a hydrate that undergoes aldol cleavage and recondensation to II; the reaction can be regarded alternately as a benzilic acid rearrangement of the trione anion. The mechanism evidently is the same as that of the alkaline cleavage of 2- and 3-hydroxy-1,4-phenanthrenequinone observed by one of us.[7] In the case of the 2-hydroxy-3-alkyl-1,4-naphthoquinones, a possible explanation of the fact that a bulky alkyl group favors rearrangement is that hindrance in the planar anion is relieved by formation of the nonplanar hydrate.
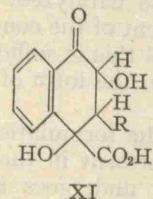
The intermediates in the Hooker oxidation[8] of 2-hydroxy-3-alkyl-1,4-naphthoquinones, obtained in high yield by the action of alkaline hydrogen peroxide, have been shown to be 2,3-dihydroxy-2-alkylindanone-3-carboxylic acids,[9] but

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(1) Abbott Laboratories Fellow, 1948–1950.
(2) Fieser, THIS JOURNAL, **70**, 3165 (1948).
(3) Fieser, ibid., **70**, 3237 (1948).
(4) Cooke and Somers, Nature, **165**, 314 (1950).
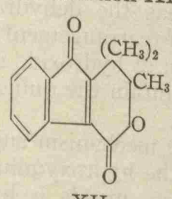(5) See also Cooke, ibid., **162**, 178 (1948); Shchukina, Kondrat'eva and Shemyakin, J. Gen. Chem., **18**, 2121 (1948).

(6) Price and Robinson, J. Chem. Soc., 1522 (1939).
(7) Fieser, THIS JOURNAL, **51**, 940, 1896 (1929).
(8) Hooker, ibid., **58**, 1164, 1174, 1179 1(936).
(9) Fieser and Fieser, ibid., **70**, 3215 (1948).
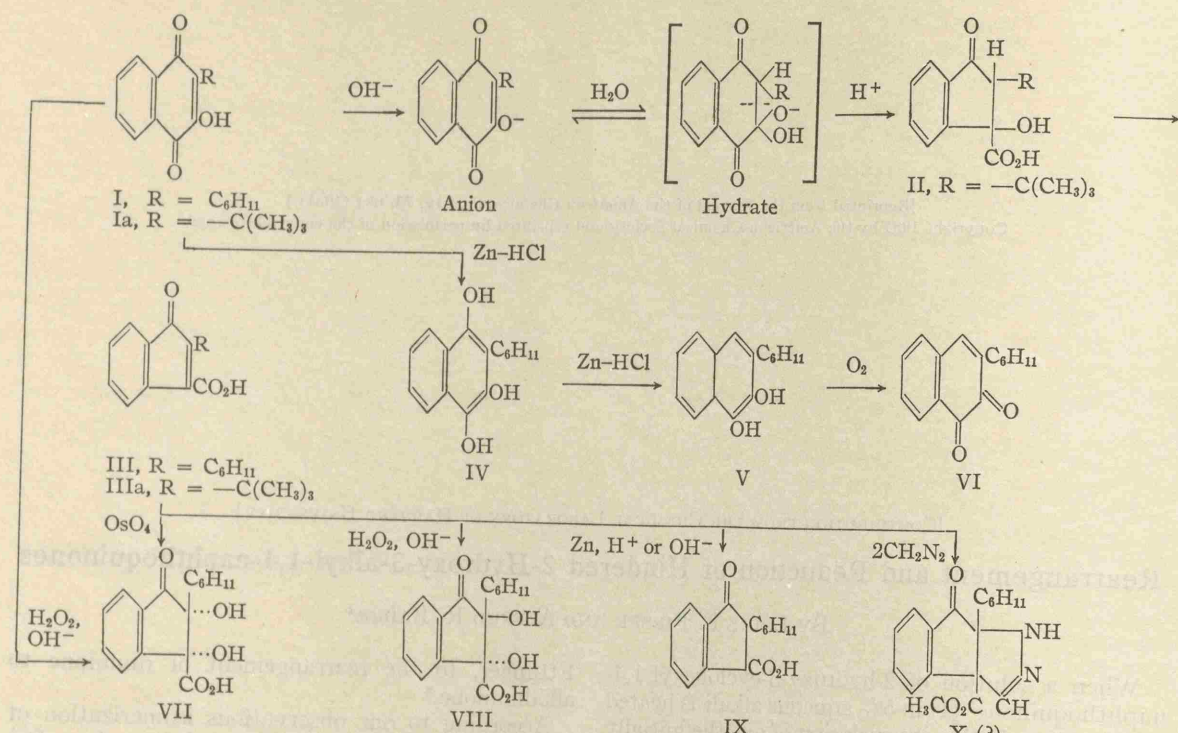
the configuration has not been established. We converted 2-cyclohexylindenone-3-carboxylic acid (III) with osmium tetroxide into the *cis*-diol VII (formulation of one of the two enantiomers) and with alkaline peroxide into the *trans*-diol VIII, and found the former diol (VII) to be identical with the previously described[9] Hooker intermediate. On titration with periodic acid, both the *cis*- and the *trans*-diol consumed two moles of reagent rapidly and a third mole more slowly; this behavior confirms the structures assigned and definitely excludes an open-chain formulation or the possible, if improbable, alternate cyclic formulation XI.


Allodunnione[6] corresponds to the 2-alkylindenone-3-carboxylic acids both in mode of formation and in ultraviolet absorption spectrum,[10] and hence the original formulation XII of Price and Robinson is substantiated. Our oxidation of III with alkaline hydrogen peroxide to the *trans*-diol VII was conducted by the procedure by which Price and Robinson converted allodunnione into a substance which they regarded as a lactone acid, $C_{12}H_{12}O_4$. The acid was not shown to be lactonic and the present results cast doubt on the formulation advanced.

A novel reaction was discovered as the result of an attempted Clemmensen reduction of a sample of III later found to have been contaminated with the starting hydroxyalkylnaphthoquinone (I). Clemmensen reduction of pure I, followed by air oxida-

(10) Cooke and Macbeth and Winzor, *J. Chem. Soc.*, 878 (1939).

tion, was found to afford 3-cyclohexyl-1,2-naphthoquinone (VI), characterized by its bright orange-red color, by formation of a phenazine derivative, and by reconversion to I by Thiele reaction, hydrolysis and oxidation. 3-Isopropyl-, 3-phenyl- and 3-*p*-bromophenyl-1,2-naphthoquinones were obtained similarly from the 2-hydroxyl-3-alkyl- or aryl-1,4-naphthoquinones, but the reaction failed in the case of 2-hydroxy-1,4-naphthoquinone, its 3-methyl, 3-isoamyl and 3-triphenylmethyl derivatives, as well as with 2-cyclohexyl-1,4-naphthoquinone. In the case of I, the reaction proceeded equally well when applied to the hydroquinone, IV. Since the 2-hydroxyl group seems essential and since reduction was observed only with bulky 3-substituents, it seems possible that the reaction involves the 1,3-diketone XIII, whose formation is favored by hindrance between the 2-substituent and the coplanar hydroxyl groups at C_1 and C_2.
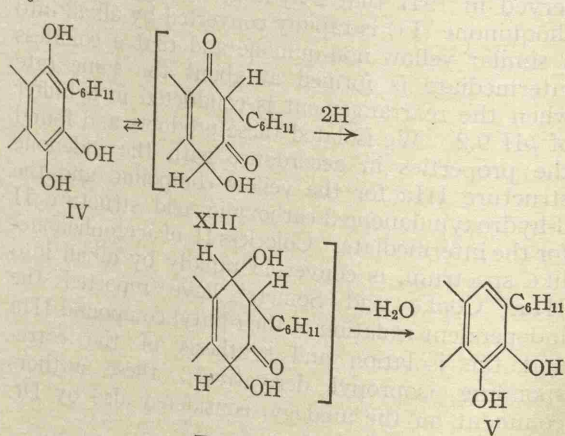
Experimental

2-Cyclohexylindenone-3-carboxylic Acid (III).—In a repetition of the previous experiment,[3] 1 g. of 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone[2] (I) was heated with 100

cc. of 5% sodium hydroxide on the steam-bath in the absence of air for 30 hours (pure yellow solution). The cooled solution was extracted with ether to remove the blue pigment, acidified and the yellow product crystallized from acetic acid to give 0.6 g. of III, m.p. 168–169°. Fractionation of the mother liquor afforded 35 mg. of fine white needles of 2-cyclohexylindanone-3-carboxylic acid (IX, below), m.p. and mixed m.p. 149°.

When 2% alkali was used for the isomerization, the reaction took longer but the yield of III was improved and no blue pigment was produced. Thus 8.6 g. of I was heated with 1 l. of 2% sodium hydroxide solution under nitrogen until dissolved and the flask was stoppered and heated at 90° for 48 hours. Acidification of the cooled yellow solution precipitated 8.6 g. of crude product, m.p. 162–165°, and crystallization from ligroin (60–90°)–acetone (10:1) gave 7.6 g. (88%) of yellow needles of III, m.p. 169–170°, and a second crop of 0.6 g., m.p. 167–169°.

Isomerization at about *p*H 9.2, conducted as above with 10 g. of I, 100 cc. of 1 *N* NaOH, and 2 l. of 0.2 *M* disodium hydrogen phosphate appeared complete in two weeks and the yield of once-crystallized product, m.p. 169–170°, was 9.1 g. (91%).

The following constants were found for pure 2-cyclohexylindenone-3-carboxylic acid (m.p. 171–172°): $\lambda_{max}^{C_2H_5OH}$ 245, 329 mμ (log ϵ 4.45, 3.15); λ_{max}^{Chf} 5.81, 5.88 μ. The maxima given for allodunnione were $\lambda_{max}^{C_2H_5OH}$ 244, 334 mμ (log ϵ 4.49, 3.34).[10]

The ethyl ester (Fischer method) crystallized from ethanol in yellow needles, m.p. 69°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.91; H, 7.09.

The amide, prepared through the acid chloride (oxalyl chloride) and crystallized from aqueous ethanol, formed yellow needles, m.p. 178° (yield 86%).

Anal. Calcd. for $C_{16}H_{17}O_2N$: N, 5.49. Found: N, 5.73.

The semicarbazone was crystallized from ethanol, m.p. 246° dec.

Anal. Calcd. for $C_{17}H_{19}O_3N_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.24; H, 6.51; N, 13.45.

A pyrazolo derivative, of probable structure X, was obtained from III in dry ether with excess diazomethane. One crystallization from ligroin gave white plates, m.p. 111° (72% yield). Recrystallized material melted at 112°.

Anal. Calcd. for $C_{18}H_{20}O_2N_2$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.39, 69.34; H, 6.52, 6.48; N, 9.26.

2-Cyclohexylindanone-3-carboxylic Acid (IX).—To an ice-cold solution of 2 g. of 2-cyclohexylindenone-3-carboxylic acid (III) in 50 cc. of 10% sodium hydroxide 5 g. of zinc dust was added in small portions. The yellow color was discharged almost at once and the solution was then treated with 50 g. of ice and 30 cc. of acetic acid and extracted with ether. Evaporation of the solvent left a white residue and one crystallization from aqueous ethanol gave 1.92 g. (96%) of fine white needles, m.p. 149°; $\lambda_{max}^{C_2H_5OH}$ 246, 292 mμ (log ϵ 4.06, 3.30).[11]

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.56; H, 7.25.

An identical product was obtained by warming 1 g. of III in 50 cc. of acetic acid with 3 g. of zinc dust for a few minutes until the solution became colorless. Dilution of the filtered solution gave a white solid that on crystallization afforded 0.8 g. of IX, m.p. 148–149°.

The methyl ester (diazomethane) formed fibrous needles from methanol, m.p. 88°.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.03; H, 7.45.

2-Cyclohexylindane-3-carboxylic Acid.—Clemmensen reduction of 1 g. of IX, with added toluene and acetic acid, afforded, after two crystallizations from aqueous alcohol, 0.84 g. (89%) of stout, colorless needles, m.p. 115°.

Anal. Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.71; H, 8.37.

The methyl ester (diazomethane) formed white needles, m.p. 60°, from ether.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.59. Found: C, 79.23; H, 8.72.

(11) Compare acetophenone, Ley and Winchen, *Ber.*, **67**, 501 (1934).

cis-**2,3-Dihydroxy-2-cyclohexylindanone-3-carboxylic Acid (VII).**—A solution of 0.95 g. of III and 1 g. of osmium tetroxide in 20 cc. of dry ether began to deposit a dark solid after standing for a few hours at room temperature. After 3 days the ether was removed in vacuum and a solution of the solid in 30 cc. of ethanol was refluxed with 5 g. of sodium sulfite in 25 cc. of water for 90 minutes. The filtered solution was acidified with hydrochloric acid, evaporated in vacuum to a small volume and extracted with ether. Evaporation of the ether left a colorless oil; this was dissolved in 1 l. of benzene and the solvent was largely distilled to effect dehydration. After extensive dilution with ligroin and cooling and scratching an amorphous solid was obtained, m.p. 180–183° (0.8 g.). Two recrystallizations from ethyl acetate–ligroin raised the m.p. to 190–191°; the sample did not depress the m.p. of the Hooker intermediate[9] and the infrared and ultraviolet spectra were identical.

The methyl and ethyl esters, prepared with use of the appropriate diazoalkane,[12] melted at 160° and at 96–100°, respectively, and were identical in melting point and infrared spectra with samples prepared from the Hooker intermediate.

Anal. Calcd. for $C_{17}H_{20}O_5$ and $C_{18}H_{22}O_5$ (respectively): C, 67.09, 67.91; H, 6.62, 6.97. Found: C, 67.35, 67.81; H, 6.81, 7.03.

The *cis*-diol consumed two moles of periodic acid in aqueous solution at room temperature in about 2 hours and a third mole after a further 10 hours.

trans-**2,3-Dihydroxy-2-cyclohexylindanone-3-carboxylic acid (VIII).**—A solution of 1 g. of III in 8 cc. of 10% sodium hydroxide and 50 cc. of water was heated on the steam-bath and treated in the course of 15 minutes with 5 cc. of 3% hydrogen peroxide. The resulting yellowish solution was cooled, acidified and extracted with ether to give a light yellow oil that on crystallization from 50% aqueous acetone gave 0.48 g. (43%) of shiny white platelets, m.p. 219–220°. The diol crystallized slowly and was accompanied by a few fine yellow needles of starting material that could be separated mechanically. Processing of the mother liquor afforded 30 mg. of phthalic acid. Recrystallized from ligroin–acetone, the diol melted at 223°; $\lambda_{max}^{C_2H_5OH}$ 243.5, 287 mμ (log ϵ 4.12, 3.18); behavior toward periodic acid like that of the *cis*-diol.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.29, 66.19; H, 5.93, 6.34.

The methyl ester (diazomethane) formed stout needles, m.p. 157–158°, from methanol.

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.11; H, 6.71.

2-*t*-Butyl-3-hydroxyindanone-3-carboxylic Acid (II).—A red solution of 150 mg. of 2-hydroxy-3-*t*-butyl-1,4-naphthoquinone[13] (m.p. 92–93°) in 7.5 cc. of 0.1 *N* NaOH and 75 cc. of 0.01 *M* disodium hydrogen phosphate was heated on the steam-bath for 90 minutes, when it had become colorless. The solution was cooled in ice, acidified with 12 cc. of 1:1 hydrochloric acid, filtered and extracted with ether until a drop of the aqueous solution no longer turned yellow when heated with alkali. Evaporation of the ether and processing with benzene and then ligroin afforded 110 mg. (68%) of needles, m.p. 135–136°, and recrystallization from ligroin–ethyl acetate gave colorless needles, m.p. 137–138°; $\lambda_{max}^{C_2H_5OH}$ 242.5, 288 mμ (log ϵ 4.08, 3.24).[11]

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.87, 67.87; H, 6.73, 6.32.

2-*t*-Butylindenone-3-carboxylic Acid (IIIa).—A solution of 50 mg. of 2-hydroxy-3-*t*-butyl-1,4-naphthoquinone in 10 cc. of 5% sodium hydroxide was heated on the steam-bath for 1 hour, when the color had changed from red to pure yellow. Acidification precipitated 48 mg. of bright yellow solid, m.p. 158–160°, which on crystallization from ligroin gave 40 mg. of fine yellow needles, m.p. 166°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.14. Found: C, 73.39; 73.20; H, 6.20, 6.05.

An identical product was obtained quantitatively by heating the colorless hydrate II in 5% sodium hydroxide for 1 hour at 90°.

2-Isopropylindenone-3-carboxylic acid[4] resulted from isomerization of 2-hydroxy-3-isopropyl-1,4-naphthoquin-

(12) McKay, THIS JOURNAL, **70**, 1974 (1948).

(13) Fieser, Leffler and co-workers, *ibid.*, **70**, 3175 (1948).

one[14] with alkali. On crystallization from ligroin–acetone, the substance formed yellow needles, m.p. 145–146°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.20; H, 5.60. Found: C, 72.03; H, 5.63.

Methyl 2,3-*cis*-Diacetoxy-2-β-isopentenyl-3-carboxylate.—This diacetate methyl ester of the ketol derived from lapachol[9] was obtained consistently by the following procedure. A solution of 1 g. of the anhydrous ketol (m.p. 157°) in 4 cc. of pyridine and 1 cc. of acetic anhydride was let stand at 25° for 4 days, diluted with water, acidified with hydrochloric acid and extracted with ether. The washed and dried solution was treated with excess diazomethane and evaporated to a small volume, when the product crystallized in stout needles; m.p. 136–137°, yield 0.9 g. Recrystallization from aqueous methanol raised the m.p. to 139°.

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 63.88; H, 5.90.

3-Cyclohexyl-1,2-naphthoquinone (VI).—A mixture of 1 g. of 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone, 3 g. of amalgamated zinc, 2 cc. of water, 1 cc. of acetic acid, 4 cc. of 36% hydrochloric acid and 3 cc. of toluene was refluxed for 24 hours, cooled and extracted with ether. Ten extractions with 10% carbonate solution (red extract) removed a total of 0.32 g. of starting material (m.p. 130–132°) and turned the initially colorless ethereal solution yellow (the naphthohydroquinone is not converted into the hydroxynaphthoquinone under these conditions). Evaporation of the dried ethereal solution and trituration with ligroin to effect separation from a red tar afforded shiny, micaceous orange-red leaflets, m.p. 159–160°; yield 0.31 g. (49%, allowing for recovery of starting material). Recrystallization from ethanol raised the m.p. to 161°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.12; H, 6.75.

In another experiment an ethereal solution of 2-hydroxy-3-cyclohexyl-1,4-naphthohydroquinone was added dropwise through an air condenser to a refluxing mixture of the reducing components and after the ether had been evaporated the mixture was refluxed for 36 hours and then processed as before. The yields of starting material and product were the same as in the experiment with the quinone cited.

The phenazine derivative, prepared by condensation of the *o*-quinone with *o*-phenylenediamine in acetic acid, formed fibrous yellow needles from ethanol, m.p. 189°.

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.70; H, 6.40; N, 9.01.

Reductive acetylation gave **1,2-diacetoxy-3-cyclohexylnaphthalene,** which formed shiny white plates from ethanol, m.p. 180°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.80. Found: C, 73.68; H, 6.82.

Conversion to 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone was effected by the Thiele reaction without isolation of intermediates. An ice-cold suspension of 100 mg. of 3-cyclohexyl-1,2-naphthoquinone in 2 cc. of acetic anhydride was treated with 0.3 cc. of 96% sulfuric acid and eventually warmed to 60°. The resulting nearly colorless solution was cooled, treated with ice-water and the flocculent white precipitate of the hydroquinone triacetate was collected, washed well and dissolved in 6 cc. of ethanol and 6 cc. of 10% sodium hydroxide. The solution rapidly turned cherry red and acidification precipitated 75 mg. of yellow solid, m.p. 125–128°. One crystallization from ethanol raised the m.p. to 133–134° and identity with hydroxycyclohexyl-

(14) Fieser, Hartwell and Seligman, THIS JOURNAL, **58**, 1223 (1936).

naphthoquinone was established by mixed m.p. and infrared comparisons.

3-Isopropyl-1,2-naphthoquinone, obtained by Clemmensen reduction of 2-hydroxy-3-isopropyl-1,4-naphthoquinone[14] formed red plates from ethanol, m.p. 118°.

Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.82; H, 5.89.

The phenazine formed needles from ethanol, m.p. 150°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29. Found: C, 83.87; H, 6.00; N, 10.36.

3-Phenyl-1,2-naphthoquinone, obtained similarly, crystallized from ethanol in red plates, m.p. 156°.

Anal. Calcd. for $C_{16}H_{10}O_2$: C, 82.04; H, 4.30. Found: C, 82.16; H, 4.39.

The phenazine derivative melted at 205°.

Anal. Calcd. for $C_{22}H_{14}N_2$: C, 86.25; H, 4.61; N, 9.15. Found: C, 86.13; H, 4.65; N, 9.24.

The required **2-hydroxy-3-phenyl-1,4-naphthoquinone,**[15] m.p. 143–144°, was obtained in 92% yield by the procedure described for preparation of the corresponding 3-cyclohexyl derivative[2] through **2-bromo-3-phenyl-1,4-naphthoquinone,** m.p. 84°, that resulted in 72% yield by bromination of 2-phenyl-1,4-naphthoquinone in acetic acid–sodium acetate.

Anal. Calcd. for $C_{16}H_9O_2Br$: C, 61.36; H, 2.90. Found: C, 61.53; H, 2.86.

3-*p*-Bromophenyl-1,2-naphthoquinone, obtained from the hydroxy-*p*-quinone,[16] melted at 203°.

Anal. Calcd. for $C_{16}H_9O_2Br$: C, 61.36; H, 2.90. Found: C, 61.26; H, 2.83.

The phenazine melted at 224°.

Anal. Calcd. for $C_{22}H_{13}N_2Br$: C, 68.58; H, 3.40; N, 7.27. Found: C, 68.45; H, 3.61; N, 7.41.

Attempts to produce 1,2-naphthoquinones by Clemmensen reduction were negative in the case of 2-hydroxy-1,4-naphthoquinone, phthiocol, hydrolapachol, 2-hydroxy-3-triphenylmethyl-1,4-naphthoquinone and 2-cyclohexyl-1,4-naphthoquinone.

Summary

Rearrangement of 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone and of the 3-*t*-butyl derivative by alkali affords 2-alkylindenone-3-carboxylic acids in nearly quantitative yield; in the second instance an intermediate hydroxy acid can be isolated.

Hydroxylation of the cyclohexylindenonecarboxylic acid with osmium tetroxide afforded a *cis*-diol identical with the Hooker oxidation intermediate of Fieser and Fieser.

Clemmensen reduction of 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone affords 3-cyclohexyl-1,2-naphthohydroquinone in 49% yield. This novel reduction was found applicable to the corresponding isopropyl, phenyl and *p*-bromophenyl derivatives, but not to the methyl, isoamyl or triphenylmethyl derivatives or to 2-hydroxy- or 2-cyclohexyl-1,4-naphthoquinone.

(15) Volhard, *Ann.*, **296**, 14 (1897).

(16) Fieser, Leffler and co-workers, THIS JOURNAL, **70**, 3203 (1948).

Transesterification.   I.   Beta-Keto Esters

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

Transesterification.   I.   β-Keto Esters

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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[5] and do not, as may some benzylic alcohols,[5] C-alkylate the β-keto ester. Tertiary alcohols react more sluggishly, and we have ob-

(1) T. Peters, *Ber.*, **20**, 3318 (1887); *Ann.*, **257**, 353 (1890).

(2) P. Cohn, *Monatsh.*, **21**, 200 (1900); A. Lapworth and A. C. O. Hann, *J. Chem. Soc.*, **81**, 1499 (1902); A. McKenzie, *ibid.*, **89**, 365 (1906); H. Rupe and E. Lenzinger, *Ann.*, **395**, 87 (1913); H. Rupe and H. Kägi, *ibid.*, **420**, 33 (1920); G. Bruni, *Atti del Reale Istituto Veneto di Scienze*, **70**, II, 921 (1911); *Chem. Zentr.*, **83**, I, 1763 (1912).

(3) M. F. Carroll, *J. Chem. Soc.*, 704, 1266 (1940); 507 (1941); W. Kimel and A. C. Cope, This Journal, **65**, 1992 (1943).

(4) R. Alpern and C. Weizmann, *J. Chem. Soc.*, **99**, 84 (1911).

(5) R. Fosse, *Compt. rend.*, **145**, 1290 (1907); *Bull. soc. chim.*, [4] **3**, 1075 (1908).

TABLE I
ACETOACETATES

Parent alcohol	Formula	M.p. or b.p., °C.	Solvent of recryst.	n^{20}D	$[\alpha]^{25}$D,[a] CHCl₃	Found Carbon	Found Hydrogen	Calcd. Carbon	Calcd. Hydrogen
Cholesterol	C₃₁H₅₀O₃	96	Ethanol–water		−33	78.61, 78.50	10.46, 10.51	79.09	10.71
Cholestanol	C₃₁H₅₂O₃	97	Methanol		+12	78.68, 78.72	11.13, 11.07	79.46	10.91
β-Sitosterol	C₃₃H₅₆O₃	99–100	IPE[c]–methanol		−24	79.20, 79.44	10.88, 10.94	79.79	10.55
Stigmasterol	C₃₃H₅₄O₃	113–114	IPE–methanol		−44	79.42, 79.60	10.60, 10.70		
Dehydroepiandrosterone	C₂₃H₃₄O₄	163	Methanol		+1	74.13, 74.15	8.76, 8.66	74.16	8.66
1-Octanol	C₁₂H₂₄O₃	140–141 (16 mm.)		1.4372		66.85, 66.83	10.37, 10.32	67.25	10.35
1-Dodecanol	C₁₆H₃₂O₃	8–10	Methanol	1.4436		70.78, 70.80	11.32, 11.33	71.06	11.18
1-Octadecanol	C₂₂H₄₂O₃	40–41	Methanol			74.55, 74.45	11.96, 12.13	74.52	11.94
Cyclohexanol	C₁₀H₁₆O₃	130–131 (16 mm.)		1.4576		64.94, 64.96	8.92, 8.78	65.19	8.76
Menthol[?]	C₁₄H₂₄O₃	30–32	Ether			58.04	8.90	58.51	9.01
Butyl carbitol	C₁₂H₂₂O₅	168–170 (10 mm.)		1.4415		62.55	8.85	63.13	8.83
Decamethylene glycol	C₁₈H₃₀O₆	33–34	Methanol						

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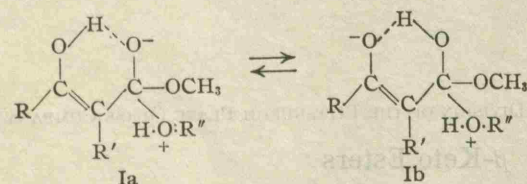
No transesterification takes place when disubstituted β keto esters such as ethyl diethylacetoacetate[6] are employed, and we are not yet certain whether this is due solely to steric hindrance of esters of tertiary acids or whether an active hydrogen atom is a prerequisite for reaction.

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

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

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°, $\lambda_{max}^{CHCl_3}$ 5.75, 5.83 μ,[7] $\lambda_{max}^{isooctane}$ 242.5 mμ (log ε 3.4)[8] melts at 189–190°, $[\alpha]^{25}$D −25° (chloroform).

Anal. Calcd. for C₃₂H₅₃O₃N₃: 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 C₂₂H₄₃O₂N: 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 C₃₆H₅₂O₃: 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 C₂₇H₄₄O₃: 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 C₃₉H₆₄O₅: C, 80.22; H, 10.73. Found: C, 80.57, 80.51; H, 10.71, 10.70.

(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 C₄₁H₈₀O₅: 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 re-distillation; 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 C₁₀H₁₆O₄: C, 59.98; H, 8.06. Found: C, 60.22, 60.14; H, 8.19, 8.31.

The Reaction of Diketene with Ketones

———

by Michael F. Carroll and Alfred R. Bader

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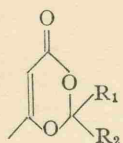
Ia, $R_1 = R_2 = CH_3$
Ib, $R_1 = CH_3$, $R_2 = C_6H_5$

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, $\lambda^{EtOH}_{max.}$ 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°, $\lambda^{EtOH}_{max.}$ 247.5 mμ, log ϵ 3.86, $\lambda^{isooctane}_{max.}$ 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 $\begin{smallmatrix} CH_2 \\ R_1 \end{smallmatrix}$
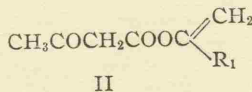
II
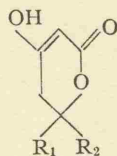
III

RESEARCH LABORATORIES
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LONDON, E. 15, ENGLAND ALFRED R. BADER[1]
RECEIVED NOVEMBER 20, 1952

(1) The Research Laboratories, The Pittsburgh Plate Glass Co., Milwaukee, Wisconsin.

Transesterification. II. Esters of Strong Organic Acids

By Alfred R. Bader and Henry A. Vogel

[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

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

$$R-COOR_2 + R_1OH$$
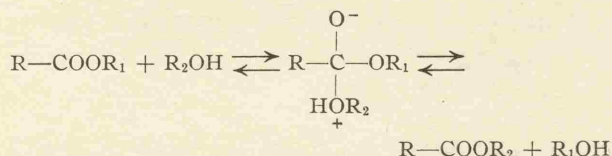
the equilibrium constants of which are probably not greatly different from 1^2 and the reason for the ease of transesterification of acetoacetates at first considered most likely was the inductive effect of the acetyl group which removes electrons from the ester carbonyl, increases its electrophilic 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

(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).

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-

(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

$$X-CH_2C\begin{smallmatrix}OR\\O\end{smallmatrix} \rightleftarrows X-\bar{C}H-\overset{+}{C}\begin{smallmatrix}OR\\OH\end{smallmatrix}$$

$$R^1OH + X-\bar{C}H-\overset{+}{C}\begin{smallmatrix}OR\\OH\end{smallmatrix} \rightleftarrows$$

$$X-CH_2-C\begin{smallmatrix}OR\\OR^1\\OH\end{smallmatrix} \underset{\longleftarrow}{\overset{slow}{\rightleftarrows}} X-\bar{C}H-\overset{+}{C}\begin{smallmatrix}OR^1\\OH\end{smallmatrix} + ROH$$

Mechanism B

$$X-CH_2-C\begin{smallmatrix}OR\\O\end{smallmatrix} + R^1OH \rightleftarrows$$

$$X-\bar{C}H-C\begin{smallmatrix}OR\\O\end{smallmatrix} + R^1OH_2{}^+$$

$$X-CH_2-C\begin{smallmatrix}OR\\O\end{smallmatrix} + R^1OH_2{}^+ \underset{\longleftarrow}{\overset{slow}{\rightleftarrows}}$$

$$X-CH_2C\begin{smallmatrix}OR^1\\O\end{smallmatrix} + ROH_2{}^+$$

$$X-\bar{C}H-C\begin{smallmatrix}OR\\O\end{smallmatrix} + ROH_2{}^+ \rightleftarrows$$

$$X-CH_2C\begin{smallmatrix}OR\\O\end{smallmatrix} + ROH$$

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

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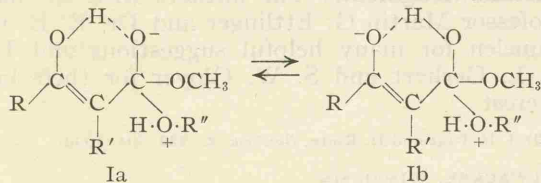
Although these intermediates suffer from the loss of conjugate carbonyl resonance of the acetoacetate enol, they offer the distinct advantage of possessing stronger than normal hydrogen bonds because these involve the electrostatic attraction of the proton to a *real* negative charge.

An alternate mechanism considered was A → B. The presumed rate determining step (*viz.*, the

A

B
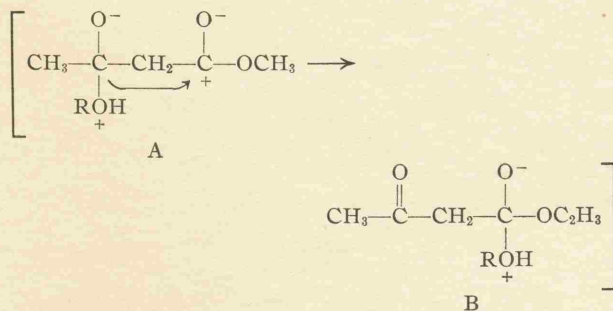
addition of the alcohol to the ester) should be facilitated by participation of the more electrophilic keto carbonyl, and is followed by a rapid intramolecular shift of the alcohol to the ester carbonyl. Shifts such as A → B are familiar from rearrangements of

the pinacol–pinacolone type, and this mechanism is analogous to one proposed to account for the increased SN2 reactivity of positive halogens.[4]

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_{max}^{EtOH}

(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); α^{25}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*-butyl-acetoacetate[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*-butyl-acetoacetate, b.p. 108–111° (0.3 mm.), n^{25}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°, α^{25}D −31° (chloroform), and 0.7 g. of the much less soluble **dicholesteryl malonate** which after crystallization from isopropyl ether melts at 178°, α^{25}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 $C_{32}H_{54}O_4$: 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°, α^{25}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.

(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).

MILWAUKEE, WISCONSIN

Cyclopentenylphenols

———

By Alfred R. Bader

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

Cyclopentenylphenols

BY ALFRED R. BADER

RECEIVED JUNE 26, 1953

The reaction of phenol with cyclopentadiene at 25° in the presence of phosphoric acid yields mainly *p*-2-cyclopentenyl-phenol IV, while *o*-2-cyclopentenylphenol VII is the major phenolic product at higher temperatures.

Cyclopentyl- and cyclopentenylphenols have hitherto been accessible only *via* cyclopentenyl chloride,[1] the Friedel–Crafts alkylation of phenol[2] and anisole[3] with cyclopentanol and cyclopentanone, and the decomposition of *p*-cyclopentylidenedi-phenol (I).[4]

The only recorded attempt to alkylate phenol with cyclopentadiene appears to have been that of v. Braun and Kühn[1] who obtained viscous oils in the reaction catalyzed by hydrochloric acid.

The availability of cyclopentadiene and the hope of preparing unsaturated, non-conjugated phenols for isomerization studies prompted the reinvestigation of its reactions with phenol. At room temperature and with substantial quantities of phosphoric acid, *p*-2-cyclopentenylphenol IV is formed in *ca.* 70% yield. This is a crystalline solid, m.p. 64–65°, characterized by a *p*-nitrophenylurethan, m.p. 174°. The phenol IV can be isomerized by palladium-on-charcoal or by sulfur to the known[4] *p*-1-

(1) J. v. Braun and M. Kühn, *Ber.*, **60**, 2551 (1927). Professor Martin G. Ettlinger has kindly pointed out that v. Braun and Kühn's *o*-2-cyclopentenylphenol probably was the product of C-alkylation rather than of Claisen rearrangement of phenyl cyclopentenyl ether as these authors believed. The ether, which these authors never had in hand, could not undergo normal rearrangement with inversion, for the transition state would be sterically improbable and would virtually violate Bredt's rule. The analogous 2-cyclohexenyl phenyl ether (J. W. Cornforth, G. K. Hughes and F. Lions, *J. Proc. Royal Soc. N. S. Wales*, **71**, 323 (1938); *C. A.*, **33**, 148 (1939), yields as the major products, phenol and cyclohexadiene. Furthermore, the cyclopentenyl ether of *o*-2-cyclopentenylphenol which v. Braun and Kühn apparently did have gave no 2,6-dicyclopentenylphenol on distillation, but cleaved to cyclopentadiene and *o*-2-cyclopentenylphenol. A direct C-alkylation under conditions similar to those of v. Braun and Kühn is described by L. Claisen and E. Tietze, *Ber.*, **59**, 2344 (1926).

(2) German Patent 615,448.

(3) C. Mentzer, D. Molho and D. Xuong, *Bull. soc. chim.*, 263 (1948).

(4) J. v. Braun, E. Anton, W. Haensel and G. Werner, *Ann.*, **472**, 1 (1929).

cyclopentenylphenol (II), melting at 149–150°, and hydrogenation of IV yields *p*-cyclopentylphenol (III), which had been reported to melt at 56°[2] and at 63–65°[4] and which, when pure, melts at 69°.

When dicyclopentadiene and phenol are refluxed with a catalytic amount of phosphoric acid, the dimer reacts in part to yield the known[5] solid phenoxydihydro-exo-dicyclopentadiene, V or VI, and a liquid isomer thereof, and in part decomposes to cyclopentadiene which then alkylates phenol in the ortho position. The identity of the crystalline ether with that prepared by Bruson and Riener by the sulfuric acid-catalyzed reaction of dicyclopentadiene with phenol at 30° was established by direct comparison, and by the preparation of identical di-

(5) H. A. Bruson and T. W. Riener, THIS JOURNAL, **68**, 8 (1946).

hydro and dihydro dibromo derivatives from both. In the high temperature reaction this solid ether is accompanied by about an equal quantity of a liquid isomer having similar infrared and ultraviolet spectra, perhaps of alternate structure V or VI.
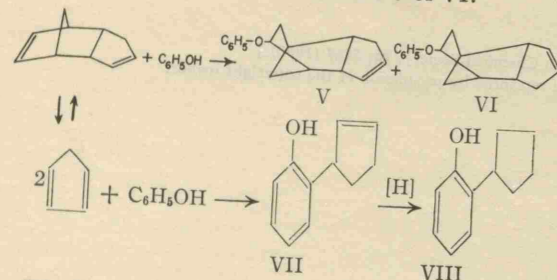
The known[1] o-2-cyclopentenylphenol (VII) which is the main phenolic product in the high temperature reaction, is a colorless oil, m.p. 3–5°, characterized by a p-nitrophenylurethan, m.p. 164°. That little or none of IV is formed under these conditions is indicated by the ease of purification of the derivative and by the quantitative hydrogenation of VII to o-cyclopentylphenol (VIII), m.p. 40°, characterized by a p-nitrophenylurethan melting at 155–156°.

The ultraviolet spectra of the phenols prepared at 25° and at 150–170° show the absence of conjugated isomers. The phenols IV and VII, like allyl phenol,[6] show two maxima of moderate intensity at ca. 225 and 275 mμ, while the higher intensity maximum of conjugated phenols such as II and propenylphenol[7] is shifted to ca. 260 mμ.

A consideration of the mechanism of formation of these cyclopentenylphenols suggests structures IV and VII rather than the alternate structures IX and X. Addition of a proton to cyclopentadiene can lead to the resonant carbonium ion XIa XIb and thence to IV and VII; the alternate carbonium ion XII is not stabilized by resonance.
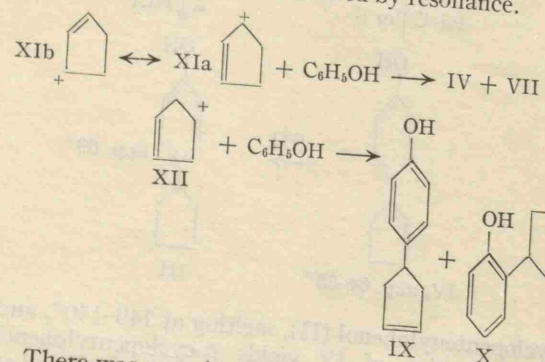
There was no evidence of a third para-substituted isomer in the high temperature palladium-on-charcoal catalyzed isomerization of IV, and this indirectly confirms the structure assigned.

Recently Pines and Vesely[8] have investigated the reactions of dienes, specifically isoprene, with phenol, and have concluded that "if both double bonds of the diene are tertiary or non-tertiary, each pos-

(6) T. J. Webb, L. I. Smith, W. A. Bastedo, Jr., H. E. Ungnade, W. W. Prichard, H. H. Hoehn, S. Wawzonek, J. W. Opie and F. L. Austin, *J. Org. Chem.*, **4**, 389 (1939).

(7) E. A. Braude, *J. Chem. Soc.*, 1902 (1949); M. Grumez, *Ann. chim.*, **10**, 378 (1938).

(8) H. Pines and J. A. Vesely, U. S. Patents 2,553,470 and 2,578,206 (May and December, 1951).

sesses the same order of reactivity, and it is difficult to react one double bond and not the other." The work here reported, and the reactions of butadiene with phenol,[9] trimethylhydroquinone,[10] and thiophene[11] suggest that such a generalization can apply only to the specific catalyst systems studied.

Experimental

p-2-Cyclopentenylphenol (IV).—To a stirred mixture of 940 g. (10 moles) of phenol in 1000 cc. of toluene and 300 g. of 85% sirupy phosphoric acid at 25°, there was added slowly a cooled solution of 330 g. (5 moles) of freshly distilled cyclopentadiene in 500 cc. of toluene. The reaction was slightly exothermic. The mixture became deep purple and was cooled and stirred at room temperature for 18 hours. Anhydrous sodium carbonate (180 g.) was then added, the mixture was filtered and the red filtrate was fractionated. After removal of solvent, some water, dicyclopentadiene, and phenol, there was obtained a colorless oil (45 g.), b.p. 80–110° (1.2 mm.), largely o-2-cyclopentenylphenol, and a main fraction (480 g., 67%) b.p. 110–135° (1.2 mm.), of p- and 2-cyclopentenylphenol which crystallized in the receiver, and after two low temperature crystallizations from ligroin, formed white needles, m.p. 64–65°, b.p. 114–117° at 1.5 mm.

In this preparation, the amount of catalyst, the reaction temperature, the solvent and the amount of diene added can be varied appreciably without materially affecting the yield. However, with small amounts of catalyst, or with larger quantities of cyclopentadiene, more higher phenols are formed. Slight cooling is sufficient to keep the reaction temperature below 40°; if the temperature is kept below 25°, the mixture does not become purple but the improvement in yield is insignificant. Mixtures of ligroin and benzene or toluene can serve as solvent; with ligroin alone the phenol–phosphoric acid complex becomes very viscous.

The product of m.p. 64–65° possessed these properties: λ$_{max}^{EtOH-0.1\% HOAc}$ 225 mμ (log e 3.99); 279 mμ (log e 3.30). The infrared spectrum in CS₂ showed a hydroxyl band at 2.82 μ and a strong band at 12.11 μ, indicative of para-substitution.

Anal. Calcd. for C₁₁H₁₂O: C, 82.46; H, 7.55. Found: C, 82.20, 82.42; H, 7.62, 7.76.

The phenol IV was characterized by a p-nitrophenylurethan which formed brittle, white needles from aqueous methanol, melting at 174–175° and strongly depressing the m.p. of the p-nitrophenylurethan of o-2-cyclopentenylphenol, but not that of the corresponding derivative of p-cyclopentylphenol.

Anal. Calcd. for C₁₈H₁₆N₂O₄: C, 66.65; H, 4.97; N, 8.64. Found: C, 67.15; H, 5.20; N, 8.85.

o-2-Cyclopentenyl-p-cresol.—The similar reaction of p-cresol, cyclopentadiene and phosphoric acid in toluene at 25–50° yields a viscous oil with a pleasant, earthy odor, b.p. 105–108° (1.3 mm.), n^{25}D 1.5595, d$^{25}_{25}$ 1.0570, M$_R$ (caled.) 52.87, M$_R$ (found) 53.24. λ$_{max}^{EtOH-0.1\% HOAc}$ 221.0 mμ (log e 3.82); 281.0 mμ (log e 3.39); λ$_{min}^{EtOH 0.1\% HOAc}$ 217.5 mμ (log e 3.81); 247.5 mμ (log e 2.16).

Anal. Calcd. for C₁₂H₁₄O: C, 82.72; H, 8.10. Found: C, 82.76; H, 8.03.

Isomerization of IV.—Sixty-three grams of IV was distilled from 2 g. of 5% palladium on charcoal.[12] The residue (18 g.) was a viscous, dark resin. The distillate (46.5 g.) was separated by solubility in ligroin into the less soluble p-1-cyclopentenylphenol (II) (5 g.) and unreacted starting material (36 g.), melting at 55–58° and not depressing the m.p. of pure IV.

The conjugated phenol II forms shiny platelets from aqueous ethanol, m.p. 149–150°, λ$_{max}^{EtOH-0.1\% HOAc}$ 262.5 mμ (log e 4.27); 290.0 mμ (inflection, log e 3.43); λ$_{min}^{EtOH-0.1\% HOAc}$ 227.5 mμ (log e 3.36).

The infrared spectrum in CS₂ showed a hydroxyl band at

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

(10) L. I. Smith and J. A. King, This Journal, **63**, 1887 (1944).

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

(12) Baker and Co., lot #785, activity 985.

2.79 μ and strong bands at 12.03 and 12.50 μ, indicative of para-substitution.

The acetate[4] of II, crystallized from aqueous ethanol, melts at 74°.

The phenol IV can be similarly conjugated by distillation from sulfur. No hydrogen sulfide and more resinous material is formed in this reaction. Surprisingly, IV could not be isomerized by alkali. Studies of the isomerization of this and other unsaturated phenols will be reported in a later paper. Hydrogenation of IV in methanol with Adams platinum catalyst at 90° quantitatively yielded p-cyclopentylphenol (III), which formed soft needles from ligroin melting sharply at 69° and not depressing the m.p. of IV.

Anal. Calcd. for C₁₁H₁₄O: C, 81.44; H, 8.70. Found: C, 81.27; H, 9.06.

The saturated phenol III was characterized by a p-nitrophenylurethan which crystallized from methanol in fine needles, m.p. 198–199°.

Anal. Calcd. for C₁₈H₁₈N₂O₄: C, 66.24; H, 5.56. Found: C, 66.09; H, 5.45.

Reaction of Dicyclopentadiene with Phenol.—A mixture of phenol (2256 g., 24 moles), dicyclopentadiene (660 g., 2.5 moles) and 85% sirupy phosphoric acid (5 g.) was refluxed under inert gas for 22 hours. Unreacted dicyclopentadiene and phenol (1700 g.) were then removed by distillation *in vacuo* and the dark residue (1130 g.) was washed, dried and distilled. The light yellow distillate (895 g.), b.p. 75–190° (0.4 mm.), was separated by solubility in 10% aqueous potassium hydroxide into 330 g. of a phenolic fraction A, and 560 g. of a fraction B, consisting of ethers and cryptophenols.

Fractionation of A yielded as main fraction a colorless oil (260 g.) o-2-cyclopentenylphenol (VII), which crystallized in the ice-box, m.p. 3–5°, b.p. 89–91° (0.7 mm.), n^{25}D 1.5652; n^{20}D 1.5666; d$^{25}_{25}$ 1.0755; M$_R$ (calcd.) 48.26; M$_R$ (found) 48.50.

The infrared spectrum in CS₂ showed hydroxyl bands at 2.83 and 2.90 μ, and a strong band at 13.3 μ indicative of ortho-substitution. This band is absent in the spectrum of IV. λ$_{max}^{EtOH}$ 220 mμ (log e 3.84); 275 mμ (log e 3.38).

Anal. Calcd. for C₁₁H₁₂O: C, 82.46; H, 7.56. Found: C, 81.87; H, 7.55.

Its p-nitrophenylurethan forms needles from methanol, m.p. 164°.

Anal. Calcd. for C₁₈H₁₆N₂O₄: C, 66.65; H, 4.97; N, 8.64. Found: C, 66.87; H, 5.33; N, 8.76.

The next fraction was a colorless oil, b.p. 140–145° (0.5 mm.), largely 2,4-di-(2-cyclopentenyl)-phenol, n^{25}D 1.5795. λ$_{max}^{EtOH}$ 222 mμ (log e 3.8); 278 mμ (log e 3.4).

Anal. Calcd. for C₁₆H₁₈O: C, 84.91; H, 8.02. Found: C, 84.70, 84.85; H, 7.93, 8.13.

Fractionation of alkali-insoluble B yielded a first fraction (20 g.) of **the coumaran XIII**, b.p. 85–89° (1.5 mm.), n^{25}D 1.5535, unchanged by prolonged refluxing at 242°[13]; λ$_{max}^{EtOH}$ 220 mμ (log e 3.67); 282.5 mμ (log e 3.44); 289 mμ (log e 3.33).[14]

Anal. Calcd. for C₁₁H₁₂O: C, 82.46; H, 7.55. Found: C, 82.65; H, 7.95.

When a mixture of 20 g. of VII, 80 cc. of glacial acetic

(13) Phenyl cyclopentenyl ether would decompose to phenol and cyclopentadiene under these conditions.

(14) The higher wave length maximum of 2-methylcoumaran is similarly resolved. *Cf.* ref. 6.

acid and 40 cc. of 48% hydrobromic acid was refluxed for 30 minutes, the coumaran XIII was obtained in 70% yield.
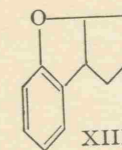
The exothermic reaction of bromine with XIII in carbon tetrachloride is accompanied by the evolution of hydrogen bromide. The product, 5(or 7)-bromo-2,3-cyclopentano-2,3-dihydrobenzofuran is an oil, b.p. 124–127° (0.7 mm.), n^{25}D 1.594.

Anal. Calcd. for C₁₁H₁₁BrO: C, 55.25; H, 4.64. Found: C, 55.02; H, 4.87.

The second fraction (455 g.), a colorless oil, b.p. 145–150° (1.5 mm.), n^{25}D 1.5624, was separated by solubility in methanol into approximately equal parts of a more soluble, colorless oil, n^{25}D 1.564, and a crystalline solid which formed white needles from methanol, m.p. 69–70°. Their ultraviolet and infrared spectra were indistinguishable. The m.p. of the solid isomer was not depressed by admixture with an authentic sample of the solid phenoxydihydro-exo-dicyclopentadiene,[5] λ$_{max}^{EtOH}$ 222.5 mμ (log e 3.8[15]); 273 mμ (log e 3.25), 279 mμ (log e 3.18).

Anal. Calcd. for C₁₆H₁₈O: C, 84.91; H, 8.02. Found: (solid isomer): C, 84.57; H, 8.11. (liquid isomer): C, 84.54; H, 8.13.

Hydrogenation of the solid isomer and of the ether prepared after Bruson and Riener[5] (methanol, Adams platinum catalyst, 100°) yielded identical colorless oils, m.p. 23–25°, the **phenoxytetrahydro-exo-dicyclopentadiene.**

Anal. Calcd. for C₁₆H₁₈O: C, 84.16; H, 8.83. Found: C, 84.77; H, 9.03.

Bromination of both in glacial acetic acid yielded identical samples of the **2,4-dibromophenoxytetrahydro-exo-dicyclopentadiene** which forms white shiny needles from methanol, m.p. 68–69°.

Anal. Calcd. for C₁₆H₁₈Br₂: C, 49.76; H, 4.70. Found: C, 49.70; H, 4.89.

The third fraction (37 g.), a colorless oil, b.p. 155–160° (0.8 mm.), n^{25}D 1.5790, is probably a mixture of higher ethers and cryptophenols, as its infrared spectrum shows a strong hydroxyl band at 2.83 μ.

Hydrogenation of VII in methanol with Adams catalyst at 100° quantitatively yielded o-cyclopentylphenol (VIII), which formed white needles from ligroin, m.p. 40°.[16]

Anal. Calcd. for C₁₁H₁₄O: C, 81.44; H, 8.70. Found: C, 81.69; H, 8.95.

Its p-nitrophenylurethan formed white needles from methanol, m.p. 155–156°.

Anal. Calcd. for C₁₈H₁₈N₂O₄: C, 66.24; H, 5.56. Found: C, 66.53; H, 5.42.

(15) The intensity of this band changes quite rapidly; the spectrum above 255 mμ is not affected.

(16) Reference 2 gives its m.p. as 34–35°.

Phenyl Esters

By Alfred R. Bader and Anthony D. Kontowicz

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The preparations of phenyl esters have hitherto been rather tedious as they have involved the use of acid chlorides, acid anhydrides or $POCl_3$, or in the case of phenyl esters of reactive acids such as acrylic[1] or methacrylic acid,[2] somewhat circuitous synthetic routes. Phenyl esters even of reactive acids have recently been prepared with trifluoro-

phenyl esters crystallized beautifully, and we are tempted to suggest them as derivatives for the characterization of acids.

Experimental

Table I lists the esters prepared.

In a representative experiment, 50 g. of salicylic acid, 150 g. of phenol and 100 g. of polyphosphoric acid (Victor Chemical Co.) were stirred and heated on the steam-bath for 24 hours. The cooled mixture was diluted with water, extracted with toluene; and the toluene solution was extracted with aqueous sodium bicarbonate solution from which 14 g. of unreacted salicylic acid was recovered on acidification.

Table I
Phenyl Esters

Acid	Formula	M.p., °C.	Solvent of cryst.	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found
Benzoic	$C_{13}H_{10}O_2$	70–71		67.12	67.45	4.93	4.91
Diglycolic	$C_{16}H_{14}O_5$	73–75	Heptane–toluene	68.73	68.92	6.30	6.46
Levulinic	$C_{11}H_{12}O_3$	32	Methanol–water	71.63	72.01	4.51	4.72
Maleic[a]	$C_{16}H_{12}O_4$	71–72	Heptane–toluene				
Methacrylic[b]	$C_9H_{10}O_2$	17					
Phthalic[a,c]	$C_{20}H_{14}O_4$	73–74	Toluene–acetone				
Salicylic	$C_{13}H_{10}O_3$	42–43	Methanol				
Stearic[d]	$C_{24}H_{40}O_2$	51–52	Toluene				

[a] The anhydride was used as the starting material. [b] This agreed in b.p. and n_D with the lit. values,[2] and crystallized easily in the ice-box. [c] E. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 291. [d] Ibid., p. 287.

acetic anhydride[3] which is not, however, readily accessible.

Phenyl esters of most carboxylic acids can be prepared easily and in good yields simply by heating the free acids with phenol in the presence of polyphosphoric acid on the steam-bath. In all cases tried the phenyl esters were easily separated from unreacted starting materials through their insolubility in dilute aqueous alkali. All solid

The toluene solution was washed, stripped *in vacuo* and the residue distilled to yield unreacted phenol and 53 g. (95% based on unrecovered salicylic acid) of phenyl salicylate, b.p. 108–110° at 0.4 mm., which crystallized in the receiver. There was no flask residue. One crystallization from methanol yielded 49 g. of pure product melting at 42–43°.

Substantial quantities of polyphosphoric acid are desirable. In the preparation of diphenyl phthalate, phenolphthalein also was formed, and during the separations of phenyl levulinate and phenyl methacrylate, the aqueous alkali extracted products other than only starting materials. The yields (based on unrecovered organic acid) of phenyl levulinate and phenyl methacrylate were 35 and 55%, respectively, and in the other preparations yields ranged from 85 to 98%.

(1) E. M. Filachione, J. H. Lengel and C. H. Fisher, This Journal, **66**, 494 (1944).

(2) E. M. Filachione, J. H. Lengel and W. P. Ratchford, *ibid.*, **72**, 839 (1950).

(3) (a) E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949); (b) A. H. Ahlbrecht and D. W. Codding, This Journal, **75**, 984 (1953).

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Pyrolysis of the Addition Product of Diphenyldiazomethane and 1,4-Naphthoquinone

To Alfred, in lasting testimony of prized friendship,

Martin

By Alfred R. Bader and Martin G. Ettlinger

Pyrolysis of the Addition Product of Diphenyldiazomethane and 1,4-Naphthoquinone

BY ALFRED R. BADER AND MARTIN G. ETTLINGER

RECEIVED JULY 7, 1952

The pyrolysis product of 2,3-(3',3'-diphenylisopyrazolo)-1,4-naphthohydroquinone previously formulated as a derivative of methylenecyclopropane consists of 4-hydroxy-1-phenyl-2,3-benzofluorenone, the major component, and 4-hydroxy-9-phenyl-2,3-benzo-1-isofluorenone.

During the study of the addition of diazo compounds to quinones, Fieser and Peters[1] pyrolyzed the azo compound I, the adduct of diphenyldiazomethane and 1,4-naphthoquinone, and isolated besides II and III a small portion of nitrogen-free fiery red needles, m.p. 274°. To the red substance, which dissolved in aqueous carbonate, formed a monoacetate, m.p. 245°, and was believed to be reducible to 2-benzhydryl-1,4-naphthohydroquinone, characterized as its diacetate and the quinone III, the unusual structure IV was tentatively assigned. The present investigation began with the idea that structure V, analogous to the known enols of 1,2-naphthoquinones,[2,3] might fit the properties of the red substance. The molecule V would form in base the resonant anion VI, which would be obtained also by removal of a proton from III. However, it was found that although both the red pyrolysis product and III formed purple solutions in hot alcoholic alkali, the pyrolysis product was recovered on acidification, whereas III furnished an unknown mixture. Furthermore, III did not yield well-defined products on treatment with sulfuric acid or with acetic anhydride and catalysts and thus gave no indication of the existence of a stable enol V.[2]

The red pyrolysate, m.p. 274°, was eventually found to be a mixture of two compounds which could not be separated by crystallization. The

(1) L. F. Fieser and M. A. Peters, THIS JOURNAL, **53**, 4080 (1931).

(2) L. F. Fieser and J. L. Hartwell, *ibid.*, **57**, 1484 (1935).

(3) L. F. Fieser and M. Fieser, *ibid.*, **61**, 596 (1939); *cf.* F. Sachs and L. Oholm, *Ber.*, **47**, 955 (1914).
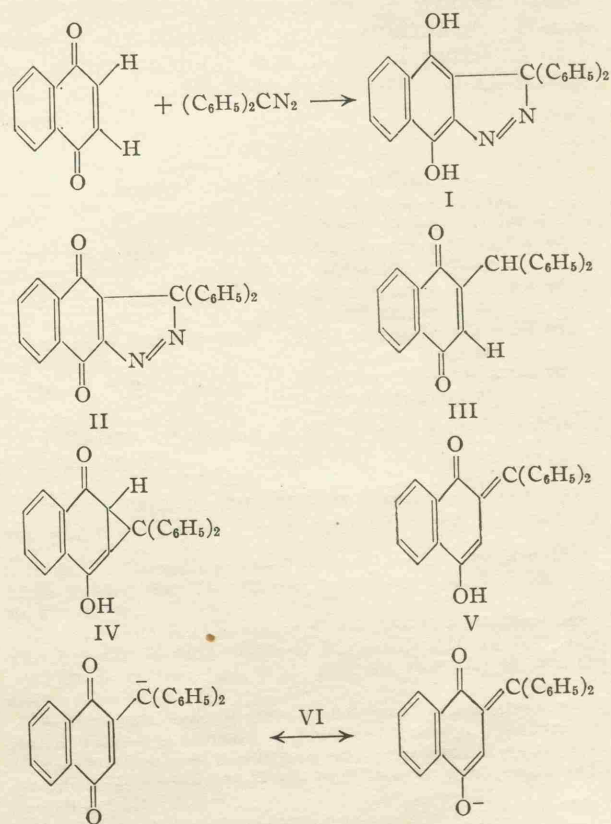
previously described acetate, m.p. 245°, was difficultly purifiable and furnished on hydrolysis an

orange compound, m.p. 297°. The pyrolysis product could be resolved directly by chromatography on alumina into the orange substance, which constituted some two thirds of the mixture, and a *deep* red substance, m.p. 227°. The orange compound, which could be reconverted to the monoacetate, m.p. 245°, and methylated to a yellow monoether, m.p. 180°, formed in alkali a purple solution unaltered by cold dithionite but decolorized by hot hydrogen peroxide. The red substance, m.p. 227°, gave a monoacetate, m.p. 223°, and a methyl ether, m.p. 153°, and dissolved in alkali to a dark blue solution. Analyses of the two pyrolysis products and derivatives failed to provide clear distinction between the parent molecular formulas $C_{23}H_{14}O_2$ and $C_{23}H_{18}O_2$. Determination of structures proved that the parent substances each contained fourteen hydrogen atoms, two less than formula IV. Neither pure pyrolysis product could be reduced by zinc in acetic acid and acetic anhydride to 2-benzhydryl-1,4-naphthohydroquinone diacetate. The previous contrary report stemmed perhaps from misapprehension of the reduction product or contamination of the benzene-insoluble pyrolysate with the quinone III.

The types of structures containing an acidic hydroxyl group that could be formed from I by loss of nitrogen and potential rearrangement of the residue by 1,2-migrations were VII, VIII (R = H), IX (R = H), X and XI. Of these formulas, VII
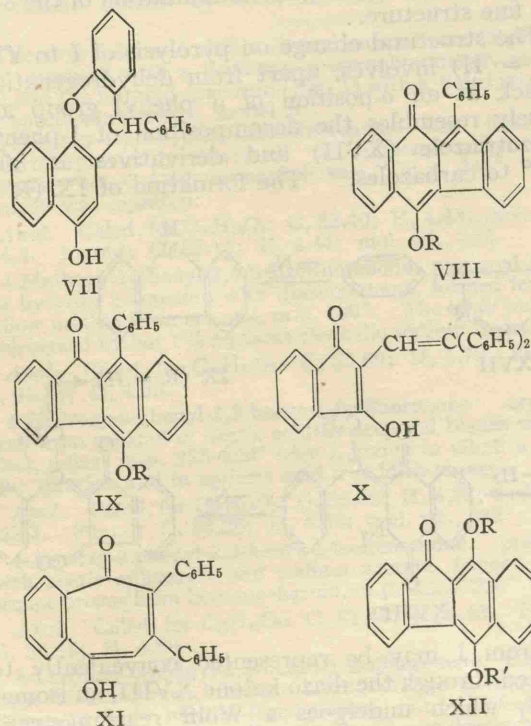
did not imply intense color[4] and was discarded. The choice for the orange compound was delimited by the infrared absorption spectra of the substance (Fig. 1) and its methyl ether, which exhibited carbonyl maxima at 5.85–5.92 μ. A carbonyl group conjugated, as in VIII–XI, to unsaturation on both sides would absorb in a strainless system at 5.97 μ

(4) *Cf.* E. Mayer-Pitsch, *Z. Elektrochem.*, **49**, 368 (1943).
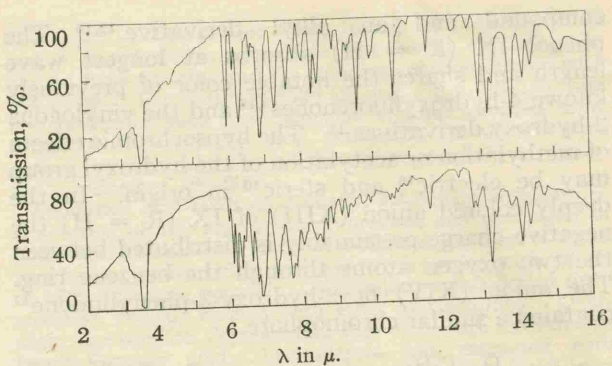
Fig. 1.—Infrared absorption spectra of the orange pyrolysis product (upper), 4-hydroxy-1-phenyl-2,3-benzofluorenone (IX, R = H), and the red pyrolysis product (lower), 4-hydroxy-9-phenyl-2,3-benzo-1-isofluorenone (VIII, R = H), as crystalline mulls in mineral oil.

or more,[5] but inclusion of the carbonyl in a five-membered ring decreases the peak wave length.[6] The model substance fluorenone was found to absorb in chloroform solution at 5.83 μ,[7,8] 0.17 μ less than benzophenone. Hence the orange substance might be IX (R = H) or X. Oxidation by alkaline peroxide furnished *o*-benzoylbenzoic acid, which could arise only from IX. Furthermore, the ultraviolet absorption spectra (Table I) of the acetate of the orange substance and the known 1,4-diacetoxy-2,3-benzofluorenone[9] (XII, R = R' = COCH₃) were remarkably similar. As 1-substituents on the 2,3-benzofluorenone nucleus both the phenyl group, which is non-coplanar,[10] and acetoxyl[11] would be expected to be weakly bathochromic and spectrally nearly equivalent. Hence the orange product, m.p. 297°, of pyrolysis of I was IX (R = H), 4-hydroxy-1-phenyl-2,3-benzofluorenone.

TABLE I

ULTRAVIOLET AND VISIBLE SPECTRA

Compound	Absorption maxima: wave lengths in $m\mu$ (log ϵ)
IX (R = H)[b]	260(4.67), 293(4.55), 320(4.14), 350[a](3.66), 455(3.45)
IX (R = CH₃)[c]	260(4.57), 289(4.75), 315(4.07), 335[a](3.65), 425(3.28)
IX (R = COCH₃)[c]	263(4.56), 288(4.81), 312(4.05), 330[a](3.65), 412(3.20)
XII (R = R' = COCH₃)[c]	255(4.53), 285(4.86), 310(4.00), 330[a](3.62), 413(3.24)

[a] Inflection.   [b] Solvent, 0.1% acetic acid in ethanol.   [c] In ethanol.

The spectra of substituted 2,3-benzofluorenones reported in Table I resemble those of the parent

(5) H. W. Thompson and P. Torkington, *J. Chem. Soc.*, 640 (1945); M. St. C. Flett, *ibid.*, 1441 (1948); R. N. Jones, *et al.*, THIS JOURNAL, **72**, 956 (1950).

(6) J. Lecomte, *J. phys. radium*, **6**, 257 (1945); R. N. Jones, *et al.*, THIS JOURNAL, **70**, 2024 (1948); C. D. Gutsche, *ibid.*, **73**, 786 (1951).

(7) *Cf.* E. D. Bergmann, *et al.*, *Bull. soc. chim.*, [5] **18**, 661, 669 (1951).

(8) The cyclic carbonyl group of fluorenone-1-carboxylic acid, reported to absorb at 6.00μ (M. L. Josien and N. Fuson, THIS JOURNAL, **73**, 478 (1951)), may be bonded internally to the acidic hydrogen atom. 1,4-Dihydroxy-2,3-benzofluorenone (XII, R = R' = H) absorbs in an oil mull at 6.01μ.

(9) C. F. Koelsch, *ibid.*, **67**, 159 (1945).

(10) R. N. Jones, *ibid.*, **67**, 2127 (1945).

(11) J. W. H. Lugg, A. K. Macbeth and F. L. Winzor, *J. Chem. Soc.*, 1597 (1937).

VII

VIII

IX

X

XI

XII

compound and an alkyl derivative.[12,13] The phenol IX (R = H) absorbs at longest wave length and shares the notable color of previously known 4-hydroxyfluorenones[9,14] and the vinylogous 2-hydroxy derivatives.[15] The hypsochromic effects of methylation or acetylation of the hydroxyl group may be electric[16] and steric[10] in origin. In the deeply colored anion (XIII) of IX (R = H) the negative charge presumably is distributed between the two oxygen atoms through the benzene ring. The anion (XIV) of 2-hydroxy-3-phenylindone[17] contains a similar chromophore.

XIII

XIV

The red pyrolysis product, m.p. 227°, absorbed in the infrared (Fig. 1) at 5.99 (weakly) and 6.07 μ, consistently with structures VIII (R = H) or XI. Oxidation with alkaline peroxide gave much neutral material and no identifiable fragment save phthalic acid. An unambiguous synthesis of VIII (R = H) was eventually accomplished by reaction of phenyllithium and 1,4-dihydroxy-2,3-benzofluorenone[9] (XII, R = R' = H). The phenolic ketone initially formed only a salt,[18] but prolonged treatment with excess phenyllithium in boiling ether effected addition to the carbonyl group to furnish in good yield 1,4,9-trihydroxy-9-phenyl-2,3-benzofluorene (XV, R, R', R'' = H). The diacetoxybenzofluorenone XII (R = R' = COCH₃) was phenylated much more rapidly than the dihydroxy compound, evidently because reaction at the 9-position preceded cleavage of the ester groups, but the final yield was less. The intermediate XV (R, R', R'' =

XV

XVI

H), which was never purified but was characterized by conversion to the 1,4-diacetate XV (R = R' = COCH₃, R'' = H) and the quinone XVI, was smoothly dehydrated by hot acetic acid to the o-fuchsone VIII (R = H).[19] The resultant authentic 4 - hydroxy - 9 - phenyl - 2,3 - benzo - 1 - isofluorenone, judged by melting points and comparisons of the spectra and monoacetates, proved to be identical with the deep red compound, m.p. 227°, from I.

In parallel experiments, 1-acetoxy-4-methoxy-2,3-benzofluorenone[9] (XII, R = COCH₃, R' = CH₃) reacted with phenyllithium to afford 1,9-dihydroxy-4-methoxy-9-phenyl-2,3-benzofluorene (XV, R = R'' = H, R' = CH₃), isolated in pure crystalline condition. The carbinol was dehydrated to 4-methoxy-9-phenyl-2,3-benzo-1-isofluorenone (VIII, R = CH₃) by fusion or treatment with acids, and notably also by hot aqueous base, which precipitated the neutral product. The methoxyisofluorenone was also obtained from VIII (R = H) and diazomethane. A reverse transformation from the isofluorenone to the fluorene series was achieved by reaction of VIII (R = H) with acetic anhydride and sulfuric acid in a Thiele-type addition to produce 1,4,9-triacetoxy-9-phenyl-2,3-benzofluorene (XV, R, R', R'' = COCH₃). The two acetates XV (R = R' = COCH₃, R'' = H or COCH₃) resembled 2,3-benzofluorene[13] in ultraviolet absorption, with a small bathochromic shift of the 260-mμ maxima and marked diminution of the 340-mμ fine structure.

The structural change on pyrolysis of I to VIII (R = H) involves, apart from dehydrogenation, attack at an o-position of a phenyl group and closely resembles the decomposition of 1-phenylbenzotriazole (XVII) and derivatives at 300–380° to carbazoles.[20] The formation of IX (R =

XVII   IX (R = H)

I   −H₂   −N₂

XVIII

H) from I may be represented conveniently to proceed through the diazo ketone XVIII, an isomer of II, which undergoes a Wolff rearrangement similar to that of azibenzil to diphenylketene[21]

(12) L. F. Fieser and M. D. Gates, Jr., This Journal, 62, 2335 (1940).

(13) M. Orchin and R. A. Friedel, ibid., 71, 3002 (1949); R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, spectra 427–429.

(14) C. Graebe and P. Schestakow, Ann., 284, 306 (1895); H. Richtzenhain and P. Nippus, Ber., 77, 566 (1944).

(15) O. Diels, ibid., 34, 1758 (1901); E. R. Wasserman, Ph.D. Thesis, Radcliffe College, 1948; W. Borsche, Ann., 526, 1 (1936).

(16) M. G. Ettlinger, This Journal, 72, 3085 (1950).

(17) C. F. Koelsch, ibid., 58, 1321 (1936).

(18) Compare C. F. Koelsch and E. J. Prill, ibid., 67, 1299 (1945). Analogs with acyclic carbonyl groups add organometallic reagents more readily.

(19) Cf. H. Kauffmann and M. Egner, Ber., 46, 3779 (1913); F. Preissecker, Monatsh., 35, 889 (1914); M. Gomberg and W. J. McGill, This Journal, 47, 2392 (1925).

(20) C. Graebe and F. Ullmann, Ann., 291, 16 (1896); F. Ullmann, ibid., 332, 82 (1904); F. Ullmann and E. Ilgen, Ber., 47, 380 (1914); H. Lindemann and F. Werther, ibid., 57, 1316 (1924); R. W. G. Preston, S. H. Tucker and J. M. L. Cameron, J. Chem. Soc., 500 (1942).

(21) G. Schroeter, Ber., 42, 2336 (1909).

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or 2-diazo-1-naphthone to 1-indylketene dimer,[22] followed by cyclization.[23]

The authors thank Dr. L. F. Fieser for kind interest.

Experimental

2,3-(3',3'-Diphenylisopyrazolo)-1,4-naphthohydroquinone (I) was prepared and pyrolyzed at 210° as previously described.[1] The combined products of eight pyrolyses of 1-g. portions were extracted several times with warm benzene to remove the bulk of the major constituents, 2,3-(3',3'-diphenylisopyrazolo)-1,4-naphthoquinone and 2-benzhydryl-1,4-naphthoquinone, and chromatographed on alumina (Fisher, 80–200 mesh). The benzene eluate contained a little quinonoid material. The orange benzene–ether and ether–methanol eluates furnished 0.50 g. of 4-hydroxy-1-phenyl-2,3-benzofluorenone, pure after one crystallization. The red methanol–water eluate (from acid-washed adsorbent) afforded 0.29 g. of 4-hydroxy-9-phenyl-2,3-benzo-1-isofluorenone. Chromatography of 150 mg. of the previously reported red material,[1] m.p. 273°, obtained by crystallization of the pyrolysate, gave 100 mg. of the fluorenone and 38 mg. of the isofluorenone. Since the fluorenone and benzhydrylnaphthoquinone mixtures were only sparingly soluble in hexane and benzene, it was advantageous to acylate with acetic anhydride and sodium acetate and chromatograph the more soluble acetates on ordinary alumina containing free alkali. The esters were hydrolyzed by the adsorbent and the fluorenone was obtained as before. The isofluorenone was eluted by aqueous methanol as the blue salt and precipitated by acetic acid.

4-Hydroxy-1-phenyl-2,3-benzofluorenone crystallized from ethanol as orange needles, m.p. 296.5–298°, giving a purple solution in alkali and in concentrated sulfuric acid an olive coloration.

Anal. Calcd. for C₂₃H₁₄O₂: C, 85.69; H, 4.38; mol. wt., 322.3. Found: C, 85.51; H, 4.45; mol. wt. (Rast), 323.

The ultraviolet and visible absorption spectrum (Table I) was measured with a Beckman spectrophotometer, model DU and the infrared spectrum (Fig. 1) with a Baird recording spectrophotometer, model B.

4-Acetoxy-1-phenyl-2,3-benzofluorenone was identical with the previously described[1] "2,3-diphenylmethylene-1-acetoxy-4-keto-3,4-dihydronaphthalene," m.p. 245°. The analysis was repeated.

Anal. Calcd. for C₂₅H₁₆O₃: C, 82.40; H, 4.43; mol. wt., 364.4. Found: C, 82.11; H, 4.44; mol. wt., 352.

4-Methoxy-1-phenyl-2,3-benzofluorenone, prepared from the hydroxy compound with diazomethane, formed lemon-yellow needles from ethanol, m.p. 180°. The ether was not hydrolyzed by hot 1% aqueous alcoholic sodium hydroxide.

Anal. Calcd. for C₂₄H₁₆O₂: C, 85.69; H, 4.79. Found: C, 85.73; H, 4.95.

4-Hydroxy-9-phenyl-2,3-benzo-1-isofluorenone crystallized from ethanol or acetic acid as deep red blades with a black reflex, m.p. 225–229° (dec.), giving in alkali a dark blue solution and in sulfuric acid a reddish-orange.

Anal. Calcd. for C₂₃H₁₄O₂: C, 85.69; H, 4.38; mol. wt., 322.3. Found: C, 85.26; H, 4.42; mol. wt., 332.

4-Acetoxy-9-phenyl-2,3-benzo-1-isofluorenone, prepared with acetic anhydride and sodium acetate, formed small orange prisms from benzene–ligroin, m.p. 222.5–224°.

Anal. Calcd. for C₂₅H₁₆O₃: C, 82.40; H, 4.43. Found: C, 82.18; H, 4.69.

4-Methoxy-9-phenyl-2,3-benzo-1-isofluorenone, prepared with diazomethane, formed orange prisms from ligroin or fluffy needles from alcohol, m.p. 152.5–153.5°, gave a red solution in sulfuric acid and was decolorized by hot concentrated alcoholic potassium hydroxide. The "carbonyl" infrared absorption band in chloroform solution lay at 6.1 μ.

Anal. Calcd. for C₂₄H₁₆O₂: C, 85.69; H, 4.79. Found: C, 85.32; H, 4.90.

Reduction of 4-Hydroxy-1-phenyl-2,3-benzofluorenone.—A mixture of 30 mg. of 4-hydroxy-1-phenyl-2,3-benzo-

fluorenone, 0.5 g. of zinc dust, 10 mg. of sodium acetate and 5 cc. of acetic anhydride was boiled two minutes, filtered from the zinc and the colorless solution diluted with 12 cc. of hot water. The resultant solid (21 mg., m.p. 98–110°) on two crystallizations from aqueous ethanol afforded some 5 mg. of white crystals, m.p. 209–210°. A mixture with authentic 2-benzhydryl-1,4-diacetoxynaphthalene (m.p. 215°) melted at 180–205°.

Oxidation of 4-Hydroxy-1-phenyl-2,3-benzofluorenone.—A solution of 100 mg. of the fluorenone and one pellet of potassium hydroxide in 15 cc. of methanol and 5 cc. of water was heated under reflux and treated dropwise with 12 cc. of 17% hydrogen peroxide. The mixture was boiled until colorless, cooled, washed with ether and acidified. Overnight the solution deposited 11 mg. of impure hydrated o-benzoylbenzoic acid. The filtrate was extracted with ether, the ether distilled and the residue crystallized from aqueous acetone by gradual evaporation. There formed first 11 mg. of stout needles of o-benzoylbenzoic acid, which after prolonged desiccation in high vacuum melted at 118–126°, undepressed by mixture with the authentic substance (m.p. 124.5–127.5°). The identity of the keto acid was confirmed by examination of the infrared spectrum and by cyclization in hot sulfuric acid to anthraquinone, crystallized and characterized by a pink vat. Further crops of oxidation products were 11 mg. of mixed crystals and finally 61 mg. of small hemispheres of impure phthalic acid, m.p. 185–190°, identified as phthalic anhydride, m.p. 129°.

Preparation of Benzofluorenones.—Benzalphthalide[24] was isomerized to 2-phenyl-1,3-indanedione by the theoretical quantity of a hot 2% solution of sodium in methanol and the dissolved sodium salt alkylated by methyl bromoacetate to methyl 2-phenyl-1,3-indanedione-2-acetate[25] in 88% yield. The vigorous isomerization of the ester by a 10% solution of sodium in methanol furnished in 83% yield 2-carbomethoxy-3-phenyl-1,4-naphthohydroquinone, which formed pale yellow prisms from methanol, m.p. 121.5–122.5°.

Anal. Calcd. for C₁₈H₁₄O₄: C, 73.46; H, 4.80. Found: C, 73.58; H, 5.14.

Cyclization with hot sulfuric acid produced 1,4-dihydroxy-2,3-benzofluorenone as orange-bronze blades from acetic acid, m.p. 264–266°. The purple alkaline solution faded irreversibly in air. From the dihydroxy compound were prepared the diacetate and 1-acetoxy-4-methoxy-2,3-benzofluorenone, m.p. 187–189°.[26] The ether acetate in hot alcoholic alkali formed a bright yellow solution with green fluorescence.

Syntheses of Isofluorenones.—A mixture of 1.9 g. of lithium chips, 14.2 cc. of bromobenzene and 100 cc. of ether was boiled under reflux four hours, freed of unreacted ether (0.3 g.) and treated with 8.9 g. of solid 1,4-dihydroxy-2,3-benzofluorenone and 100 cc. of ether. The suspension was boiled six hours and decomposed cautiously with 100 cc. of 10% acetic acid and 100 cc. of ether. The dark aqueous layer was separated and filtered to give 1.65 g. of recovered dihydroxybenzofluorenone, m.p. 253–259°. The washed ether solution was run slowly into 350 cc. of acetic acid maintained at 90–102° and the acid was heated five minutes longer, cooled and filtered to furnish 5.5 g. (62% of unrecovered starting material) of shiny, dark red blades of 4-hydroxy-9-phenyl-2,3-benzo-1-isofluorenone, m.p. 230–240° (dec.). Experiments on phenylation in ether–benzene or ether–dioxane afforded no product.

When a solution of phenyllithium from 0.75 g. of lithium, 5.5 cc. of bromobenzene and 25 cc. of ether was treated with 2.5 g. of solid 1,4-diacetoxy-2,3-benzofluorenone and 25 cc. of ether, a vigorous reaction ensued. The mixture was boiled under reflux half an hour, decomposed and the ether boiled down to 100 cc. of hot acetic acid. From the cold phase added to 100 cc. of water there crystallized 1 g. (43%) of dark red needles of 4-hydroxy-9-phenyl-2,3-benzo-1-isofluorenone, m.p. 222–230°.

A suspension of 0.35 g. of 1,4-dihydroxy-2,3-benzofluorenone with the phenyllithium from 0.08 g. of metal and 0.7 cc. of bromobenzene in 10 cc. of ether was boiled under

(22) L. Horner, E. Spietschka and A. Gross, Ann., 573, 17 (1951).

(23) L. I. Smith and H. H. Hoehn, This Journal, 63, 1181 (1941).

(24) R. Weiss, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 61.

(25) D. Radulescu and G. Gheorgiu, Ber., 60, 186 (1927).

(26) Previously reported as 163–164°.[9] Dr. Koelsch has courteously informed us that according to a recent redetermination the original sample melted at 183–185°.

reflux six hours and decomposed with 10 cc. of 5% acetic acid, and the ether solution was washed with aqueous sodium bicarbonate, dried and evaporated in nitrogen. The dark residue was taken up in 5 cc. of boiling benzene, cooled and filtered to give 0.35 g. of crude 1,4,9-trihydroxy-9-phenyl-2,3-benzofluorene as a brown solid, m.p. 222–226° (dec.) (other specimens melted as low as 185°), soluble in alkali. The substance was converted to 4-hydroxy-9-phenyl-2,3-benzo-1-isofluorenone in ten minutes by acetic acid at 100°.

9-Hydroxy-9-phenyl-2,3-benzofluorene-1,4-quinone, obtained by oxidation of the hydroquinone in ether with silver oxide, formed bright orange-yellow prisms from ether, m.p. 193–194°. The compound gave a pink solution in alcoholic alkali, a greenish-yellow vat and a dark olive solution in sulfuric acid. The ultraviolet and visible absorption maxima in ethanol solution lay at 258 mμ (log ϵ 4.34), 308 (3.86) and 417 (3.41).

Anal. Calcd. for $C_{23}H_{14}O_3$: C, 81.64; H, 4.17. Found: C, 81.37; H, 4.45.

A solution of 0.03 g. of the quinone in 3 cc. of acetic acid mixed with a solution of 0.1 g. of stannous chloride dihydrate and 0.1 cc. of 6 N hydrochloric acid in 1 cc. of water and heated ten minutes at 100° deposited when cold 0.02 g. of dark red needles of 4-hydroxy-9-phenyl-2,3-benzo-1-isofluorenone, m.p. 223–227°.

1,4-Diacetoxy-9-hydroxy-9-phenyl-2,3-benzofluorene, obtained from the trihydroxy compound, acetic anhydride and sodium acetate or the quinone by reductive acetylation, formed white prisms from dilute acetic acid or ether–petroleum ether, m.p. 187.5–189°. The substance tended to separate as a gel from non-aqueous solvents. The ultraviolet absorption maxima in chloroform lay at 256 mμ (log ϵ 4.66), 265 (4.56) (inflection), 276 (4.50), 290 (4.18), 303 (4.28), 316 (4.34), 330 (3.09) (inflection) and 348 (2.68).

Anal. Calcd. for $C_{27}H_{20}O_5$: C, 76.40; H, 4.75. Found: C, 76.46; H, 5.44.

A mixture of 0.1 g. of 4-hydroxy-9-phenyl-2,3-benzo-1-isofluorenone, 3 cc. of acetic anhydride and a drop of sulfuric acid was warmed five minutes at 60°, cooled and treated with 0.3 g. of sodium acetate, 1 cc. of acetic acid and 4 cc. of water, shaken vigorously to hydrolyze the anhydride and chilled. The product, 0.14 g. of yellow solid, m.p. 182–199° (dec.), afforded on recrystallization from ethyl acetate–ligroin pure **1,4,9-triacetoxy-9-phenyl-2,3-benzofluorene** as white prisms, m.p. 223–226° (dec., bath preheated to 210°). The decomposition point is sensitive to impurity: certain samples melted near 230°, whereas material precipitated from acetic acid by water sometimes melted below 160°. The ultraviolet absorption maxima in chloroform lay at 256 mμ (log ϵ 4.60), 265 (4.57), 275 (4.55), 291 (4.19), 303 (4.26) and 316 (4.32).

Anal. Calcd. for $C_{29}H_{22}O_6$: C, 74.67; H, 4.75. Found: C, 74.57; H, 5.05.

A solution of 0.4 g. of 1-acetoxy-4-methoxy-2,3-benzofluorenone in 10 cc. of benzene was added to a cold solution of phenyllithium from 0.8 cc. of bromobenzene and 0.1 g. of lithium in 5 cc. of ether, boiled half an hour under reflux and poured into 20 cc. of cold 10% sulfuric acid. The organic phase, washed, evaporated, taken up in 3 cc. of benzene and 3 cc. of petroleum ether and chilled, deposited 0.15 g. of **1,9-dihydroxy-4-methoxy-9-phenyl-2,3-benzofluorene**, which formed pale yellow prisms from benzene–ligroin, soluble without color in aqueous alcoholic alkali. The substance heated slowly turned orange at 140° and melted at 175–179° (dec.); the "instantaneous" decomposition point appeared to be near 193°.

Anal. Calcd. for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.17; H, 5.11.

4-Methoxy-9-phenyl-2,3-benzo-1-isofluorenone could be obtained from 1,9-dihydroxy-4-methoxy-9-phenyl-2,3-benzofluorene by fusion at 190° or by solution in acetic acid at 100° or sulfuric acid at room temperature. In addition, when 20 mg. of the phenol and 0.15 g. of potassium hydroxide were dissolved in 1 cc. of methanol and 3 cc. of water and boiled under reflux 20 minutes, the dark mixture on dilution with 10 cc. of water and filtration afforded 15 mg. of bright orange methoxyisofluorenone, m.p. 152–153.5°.

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The Reactions of Diketene with Ketones

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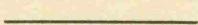
By Michael F. Carroll and Alfred R. Bader

The Reactions of Diketene with Ketones[1]

BY MICHAEL F. CARROLL AND ALFRED R. BADER[2]

RECEIVED JUNE 1, 1953

The acid-catalyzed reactions of diketene with ketones yield 2,2-disubstituted-4-methyl-6-keto-1,3-dioxenes (I), many reactions of which parallel those of diketene.

Although the preparation of ketene and diketene in acetone is a commercial process, the reaction of diketene has not been investigated in any detail.[3] When acetone and diketene are heated on the steam-bath with a catalytic amount of p-toluenesulfonic acid, a crystalline solid, $C_7H_{10}O_3$, melting at 12–13°, can be isolated in 91% yield. Reactions with other unhindered ketones proceed similarly, and pure adducts are obtained from methyl ethyl ketone, acetophenone and dibenzyl ketone. Ketones which are more hindered sterically react more sluggishly and diisobutyl ketone, benzophenone and also acetoacetates do not appear to react at all.

Three structures, I, II and III were considered.
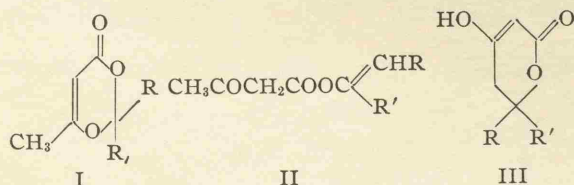
That of the enol acetoacetate II was rejected because of the adducts' non-reactivity with carbonyl reagents and because the adducts' ultraviolet spectra are inconsistent with II. Acetoacetates, even of complex alcohols, are known to react readily with carbonyl reagents[4] whereas the adducts do not. Intensities of absorption maxima of acetoacetates increase sharply on passage to non-polar solvents because chelated enols are favored by non-solvating media. The adducts' ultraviolet spectra show identical intensities in water, ethanol and isoöctane.[5] Furthermore the spectra of acetoacetates of the enols of acetophenone and dibenzyl ketone would be the composite of the spectra of substituted styrenes and acetoacetates. The spectra of the

(1) For a preliminary communication, *cf.* THIS JOURNAL, **74**, 6305 (1952).

(2) The Research Laboratories, The Pittsburgh Plate Glass Co., Milwaukee, Wisconsin.

(3) In the reaction of ketene with acetone, which is catalyzed by zinc chloride, R. F. Naylor (*J. Chem. Soc.*, 244 (1945)), observed the formation in low yield of a product, $C_7H_{10}O_3$, thought to be isopropenyl acetoacetate. This may have been the diketene–acetone adduct here described.

(4) M. F. Carroll, *J. Applied Chem.*, 443 (1951).

(5) The log ε's reported in ref. 3 were 3.93 in water and 4.0 in cyclohexane. Our values for the acetone adduct are 3.94 in water and 3.93 in isoöctane.

adducts of these ketones, however, are very similar to that of the acetone adduct.

The enol III can be considered as the lactone of an aldol condensation product of acetoacetic acid and ketones. Similar 4-hydroxy-5,6-dihydro-2-pyrones have been prepared as analogs of the enol lactone form of auxin b. The methyl analog[6] (III, R = –CH₃, R' = –H) reacts readily with dinitrophenylhydrazine and semicarbazide, and absorbs in the ultraviolet at somewhat lower wave lengths than do the diketene adducts. The phenyl analog[7] (III, R = –C₆H₅, R' = –H) also reacts with semicarbazide and in contrast to the spectra of the diketene adducts shows in the infrared a strong enolic hydroxyl band at *ca.* 4.0 μ and no carbonyl band below 6.1 μ.

2,2-Disubstituted-4-methyl-6-keto-1,3-dioxenes (I) should be unstable in aqueous acid and alkali, should not react with carbonyl reagents and should react as do diketene and acetoacetic acid with alcohols and amines. The adducts' ultraviolet and infrared spectra are in accord with structure I. Their ultraviolet maxima in ethanol at 247–252 mμ are at longer wave lengths than those of β-alkoxycrotonates,[8] an exaltation attributable to resonance contributions of structures Ia ↔ Ib ↔ Ic analogous to the exaltation of cyclohexadiene.[9]
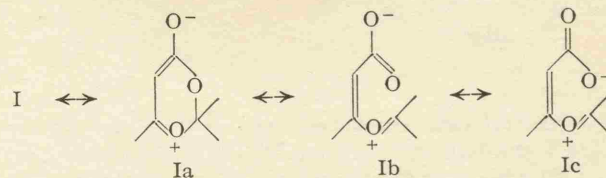
Figure 1 shows the infrared spectra of the acetone and acetophenone adducts. The pronounced associated hydroxyl band present in the spectra of cyclic 1,3-diketones such as dimedone at 3.4 μ, and in six-membered enol lactones such as III at *ca.* 4.0 μ is absent, and the carbonyl bands, at *ca.* 5.8 μ, are at significantly lower wave lengths than the carbonyl band of III. Thus we favor structure I for these diketene ketone adducts.

(6) E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1419 (1949).

(7) E. B. Reid and W. R. Ruby, THIS JOURNAL, **73**, 1054 (1951).

(8) K. Bowden, E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 948 (1946).

(9) R. S. Mulliken, *J. Chem. Phys.*, **7**, 339 (1939).

Fig. 1.—Infrared absorption spectra of the acetophenone–diketene adduct, 2,4-dimethyl-2-phenyl-6-keto-1,3-dioxene (upper) in chloroform solution, and of the acetone–diketene adduct, 2,2,4-trimethyl-6-keto-1,3-dioxene (lower) in carbon disulfide solution.

The mechanism of this acid-catalyzed reaction might be pictured as the attack on the carbonyl of the ketone by the resonant cation IV formed by addition of a proton to diketene, followed by cyclization of V to I.

Diketene, acetoacetates and I are all fairly stable to anhydrous acids[10]; with alkali all yield dehy-

dracetic acid and resins, the reaction rates being in the order diketene ≫ I > acetoacetates; and all

(10) I is considerably more stable to acids than are ordinary acetals. A proton probably adds to the carbonyl of I to give a salt stabilized by considerable resonance.

react with alcohols and aniline to yield acetoacetates and acetoacetanilide, respectively. The base-catalyzed formation of dehydracetic acid VIII from I can be rationalized by assuming initial ring opening of I by hydroxide ion followed by a nucleophilic attack of the resultant resonant anion VI on another molecule of I, and lactonization of the product VII.

Dehydracetic acid and resins are also formed by the prolonged action of acids on the adducts I and on diketene, and the latter also decomposes to ketene. Thus in the acid-catalyzed formation of I, it is accompanied by dehydracetic acid, ketene, and isopropenyl acetate from the reaction of ketene with acetone.

The adducts can be prepared easily and economically, and they are pleasant smelling, and quite stable in the absence of alkali. They may conveniently be used in place of diketene in many reactions.

Experimental

2,2,4-Trimethyl-6-keto-1,3-dioxene.—A mixture of dry acetone (100 cc.), diketene (100 cc., 109 g., 1.3 moles) and p-toluenesulfonic acid (0.5 g.) was refluxed for 3 hours, when the odor of diketene had disappeared. Excess acetone

was removed by distillation, and the product distilled to yield 168 g. (1.18 moles, 91% yield based on diketene) of the ketodioxene, b.p. 65–67° (2 mm.), m.p. 12–13°, $n^{20}D$ 1.4636, d^{20}_4 1.0879[11]; λ^{water}_{max} 252.5 mμ (log ε 3.94); λ^{EtOH}_{max} 247.5 mμ (log ε 3.92); $\lambda^{isoöctane}_{max}$ 239.0 mμ (log ε 3.93).

Anal.[12] Calcd. for $C_7H_{10}O_2$: C, 59.14; H, 7.09. Found: C, 59.20; H, 7.15.

No reaction took place when the acid catalyst was replaced by diethylamine. Careful fractionation of the product from a large scale experiment showed no fraction identifiable as isopropenyl acetoacetate. The forefractions, $n^{20}D$ 1.4590–1.4610, contained only traces of acetone, easily removed by water washing, and the later fractions, $n^{20}D$ 1.4650–1.4680, contained small amounts of dehydracetic acid. With larger amounts of catalysts, ketene and isopropenyl acetate are also formed. Thus in an experiment as above, but with three times as much catalyst, there was obtained only a 70% yield of the adduct, 2% of ketene and 10% of isopropenyl acetate

2,4-Dimethyl-2-ethyl-6-keto-1,3-dioxene.—Methyl ethyl ketone reacts similarly to yield a water-white liquid, b.p. 70–74° (5 mm.), $n^{20}D$ 1.4633, d^{20}_4 1.065.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.20; H, 7.50.

2,4-Dimethyl-2-phenyl-6-keto-1,3-dioxene.—A mixture of acetophenone (120 g.), diketene (84 g.) and *m*-xylenesulfonic acid (0.4 g.) was heated at 90° for 7 hours and then stripped *in vacuo*. Cooling yielded 100 g. of crude adduct, m.p. 75–80°, which crystallized from a mixture of benzene and cyclohexane in shiny white platelets melting at 93.5°. λ^{EtOH}_{max} 247.5 mμ (log ε 3.86); $\lambda^{isoöctane}_{max}$ 240.0 mμ (log ε 3.84).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.21; H, 5.80. Kuhn-Roth[13] C–CH₃ det.: Calcd. for 1 C–CH₃: 7.35. Found: 8.67, 8.92.

2,2-Dibenzyl-4-methyl-6-keto-1,3-dioxene prepared similarly from dibenzyl ketone and diketene with *p*-toluenesul-

fonic acid, and crystallized from benzene melts at 104–105°; λ^{EtOH}_{max} 252.5 mμ (log ε 3.77); $\lambda^{isoöctane}_{max}$ 246.0 mμ (log ε 3.77).

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 78.00; H, 6.25.

Dehydracetic Acid.—A mixture of the acetone adduct (10 g., 0.07 mole), toluene (200 cc.) and calcium acetate (0.1 g.) was heated with solvent take-off for 5 hours, when 4.0 g. (0.069 mole) of acetone had collected in the distillate. The residue was extracted with dilute aqueous sodium carbonate from which 3 g. (51%) of dehydracetic acid was obtained on acidification.

Higher Acetoacetates.—A mixture of the acetone adduct (20 g., 0.14 mole), 1-butanol (20 g., 0.27 mole) and a trace of *p*-toluenesulfonic acid was heated at 100° for 3 hours. Distillation of the product *in vacuo* yielded 21 g. (95%) of *n*-**butyl acetoacetate**, $n^{20}D$ 1.4280.

Similarly, a mixture of the acetophenone adduct (13 g.) and methanol (10 cc.) yielded 9 g. of a mixture of acetophenone and **methyl acetoacetate**.

A mixture of 4 g. of cholesterol, 8 g. of the acetone adduct, 10 cc. of toluene and a trace of *p*-toluenesulfonic acid was refluxed for 5 hours. Distillation *in vacuo* yielded 4 g. of unchanged acetone adduct, and crystallization of the residue from aqueous ethanol gave 4 g. of **cholesteryl acetoacetate**[14] identical with authentic material (mixed m.p. and I.R. spectra).

Acetoacetanilide.—A solution of 28.4 g. (0.2 mole) of the acetone adduct, 18.6 g. (0.2 mole) of aniline and 1 g. of diethanolamine in 100 cc. of xylene was heated until no more acetone could be detected in the distillate. The mixture was then cooled and acidified with concd. hydrochloric acid until acid to brom phenol blue. The solid which had precipitated and the xylene solution were combined and extracted with dilute aqueous sodium hydroxide from which 16 g. of acetoacetanilide, m.p. 84–85°, was obtained on acidification.

Acknowledgment.—We are deeply indebted to Professor Martin G. Ettlinger for valuable criticism and advice and to the Directors of Messrs. A. Boake, Roberts and Company (Manufacturing), Ltd., for permission to publish.

(11) Since the publication of our preliminary communication,[1] we have prepared some 5 kg. of the acetone adduct. The constants here reported are those of our purest product.

(12) Analyses by the Micro-Tech Laboratories, Skokie, Illinois.

(13) The experimental value of 1.2 C-methyls is as much as might be expected, as acetophenone gives only 0.1 C-methyl. Also, as acid hydrolysis may precede oxidation, this is not adduced as structural evidence.

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

LONDON, ENGLAND

Michael F. Carroll and Alfred R. Bader. The reactions of Diketene with Ketones.

Page 5401. Structure IVc should read CH_3-C-CH_2 with $\overset{|}{O}$ ^+CO

and the resonant hybrid of the ketone below it $\overset{R}{\underset{R}{>}}C-O.$ (with $^+$ and $^-$)

Structure VIa should read $CH_2-C=CH-COOH.$— with O^-

ALFRED R. BADER.

Gamma,gamma-Bis-(*p*-hydroxyphenyl)-valeric Acid
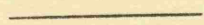
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By Alfred R. Bader and Anthony D. Kontowicz

γ,γ-Bis-(p-hydroxyphenyl)-valeric Acid

By Alfred R. Bader and Anthony D. Kontowicz
Received April 21, 1954

A study of the reaction of phenol with levulinic acid has shown that the condensation to yield the bisphenol I proceeds easily in the presence of acids such as sulfuric, hydrochloric and phosphoric;
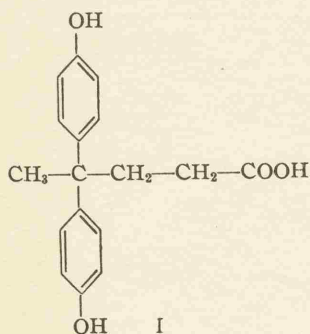
with polyphosphoric acid a mixture of condensation products and phenyl levulinate[1] results.

The bisphenol I is dimorphic; an amorphous modification forms crystalline solvates with aromatic hydrocarbons, and a crystalline, solvent-free modification melts at 171–172°.

Experimental

γ,γ-Bis-(p-hydroxyphenyl)-valeric Acid (I).—A cooled mixture of 94 g. (1 mole) of phenol, 58 g. (0.5 mole) of levulinic acid, 45 g. of water and 180 g. of concd. sulfuric acid was stirred at 25° for 20 hours. The reaction is slightly exothermic. The mixture was diluted with water and extracted with ethyl acetate. The organic solution was in turn extracted exhaustively with aqueous sodium bicarbonate, stripped and distilled to yield 20 g. of unreacted phenol. The almost colorless bicarbonate extract was acidified, extracted with ether and the washed ether extract stripped *in vacuo* to yield 87 g. (0.30 mole, 77% yield based on un-

(1) A. R. Bader and A. D. Kontowicz, This Journal, **75**, 5416 (1953).

recovered phenol) of I, an almost colorless glass, m.p. *ca.* 90°, acid value found 192, calcd. 195.

A similar yield of I is obtainable with a catalyst mixture of 75 cc. of concd. hydrochloric acid and 37 cc. of water, and a reaction temperature of 90–95°. With 85% phosphoric acid at 90–95° the yield is smaller and the product darker.

The amorphous product forms crystalline solvates with aromatic hydrocarbons. From benzene it crystallizes in flat, white needles, m.p. 120–122°; from toluene in stout needles, m.p. 108–109°; from m-xylene in flat needles, m.p. 96–98°. Removal of the solvent of crystallization *in vacuo* at 90° leaves the glass, m.p. *ca.* 90°. Crystallization of the benzene solvate from m-xylene yielded the m-xylene solvate.

Anal.[2] Benzene solvate: Calcd. for $C_{17}H_{18}O_4 \cdot {}^{1}\!/_{2}C_6H_6$: C, 73.82; H, 6.51. Found: C, 73.48; H, 6.62. Toluene solvate: Calcd. for $C_{17}H_{18}O_4 \cdot {}^{1}\!/_{2}C_7H_8$: C, 74.07; H, 6.67. Found: C, 74.44; H, 7.02.

After many unsuccessful attempts to obtain I crystalline and solvent-free, a large batch crystallized solvent-free from a mixture of toluene and acetone, m.p. 168–170°. It formed hard, white rosettes from water containing a trace of acetic acid, m.p. 171–172°, and could also be crystallized well from mixtures of heptane and ethyl acetate, or benzene and acetone. Hot solutions of the amorphous modification in aromatic hydrocarbons when seeded with solvent-free crystals, yielded the crystals, m.p. 171–172°, on cooling.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 70.99, 70.94; H, 6.62, 6.46.

$\lambda^{\text{EtOH}-0.1\% \text{ HOAc}}_{\text{max}}$, mμ 225.0 (log E 4.20); 227.5 (infl., log E 4.18)
279.0 (log E 3.57); 282.5 (infl., log E 3.53)
λ_{min} 250.0 (log E 2.71)

The ultraviolet spectra of the solvates are very similar. The infrared spectrum of I in a nujol mull shows a strong band at 12.0 μ (indicative of *para* substitution), and no band at 13.2–13.4 μ.

Solvent-free, crystalline I forms a methyl ester which crystallizes from aqueous methanol with water of crystallization and melts at 87–89°.

Anal. Calcd. for $C_{18}H_{20}O_4 \cdot 3H_2O$: C, 61.00; H, 7.40. Found: C, 61.43; H, 7.60.

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

The Research Laboratories
The Paint Division
The Pittsburgh Plate Glass Company
Milwaukee, Wisconsin

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

By Alfred R. Bader

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

By Alfred R. Bader

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.

(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.

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The Proton Magnetic Resonance Spectrum
and Structure of Diketene

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By Alfred R. Bader, H. S. Gutowsky, G. A. Williams and P. E. Yankwich

[CONTRIBUTION FROM THE ALDRICH CHEMICAL CO. INC., AND THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Proton Magnetic Resonance Spectrum and Structure of Diketene[1]

BY ALFRED R. BADER, H. S. GUTOWSKY, G. A. WILLIAMS AND P. E. YANKWICH

RECEIVED DECEMBER 1, 1955

The proton magnetic resonance spectrum of diketene in the liquid state has been investigated under high resolution at temperatures between 25 and 170°. The results show that the liquid up to 120° is in the 3-buteno-β-lactone form, with no evidence of any other kind of molecule. At higher temperatures, irreversible changes occur in diketene.

Introduction

The definitive X-ray study by Katz and Lipscomb[2] has established that the structure of diketene in the solid state is the 3-buteno-β-lactone form, V. This has been confirmed by Ford and Richards[3] who observed the broad proton magnetic resonance absorption line shape in the solid. However, the vibrational spectra[4,5] of diketene in the liquid and vapor phases as well as in solution suggest that diketene may be an equilibrium mixture of V and the 2-buteno-β-lactone form, IV, or perhaps the 1,3-cyclobutadione form, III. The main spectroscopic argument favoring a mixture[4] is the appearance of five strong bands in the double bond stretching region (1500 to 2000 cm.$^{-1}$), while each of the postulated forms, I to V, would have at most two fundamentals in this region. In addition, Miller and Koch[5] found that the spectrum of diketene vapor changes at temperatures between 30 and 180° in a manner suggesting a reversible equilibrium of two (or more) forms.

$$CH_3-C-CH=C=O \qquad O=C-CH \qquad O=C-CH_2$$
$$\underset{O}{\overset{\|}{}} \qquad\qquad H_2C-C-OH \qquad H_2C-C=O$$
$$\text{I} \qquad\qquad \text{II} \qquad\qquad \text{III}$$

$$CH_3-C=CH \qquad CH_2=C-CH_2$$
$$O-C=O \qquad\qquad O-C=O$$
$$\text{IV} \qquad\qquad \text{V}$$
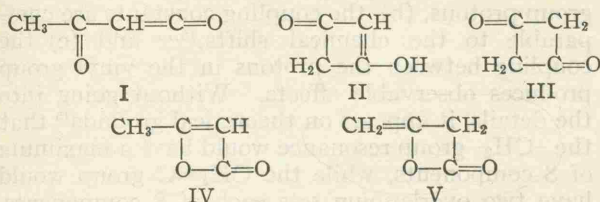
The kind of structural problem presented by liquid diketene lends itself very readily to investigation by high resolution nuclear magnetic resonance techniques,[6,7] and indeed our results for diketene serve as an excellent example of one of the main advantages in certain types of problems of the NMR techniques over more conventional methods. To a first approximation, the number and relative intensities of the components in the NMR spectrum of a liquid sample are given simply by the number of non-equivalent structural sites and by the fraction of the nuclei in each type of site. The different components result from the influence of the electronic environment of a given nuclear species on the position of its magnetic resonance; this

influence produces "chemical shifts" in the resonance position, which in general are different for different structural sites.[6] The absorption intensities, on the other hand, are directly proportional to the concentrations of the nuclei.

In this manner, the proton resonance of diketene is predicted to have two main components with relative intensities of 3:1, if the molecular structure is I; if II, 2:1:1; III, 4; IV, 3:1; and V, 2:2. A mixture would, of course, give a composite spectrum. This relative simplicity contrasts with the vibrational spectra, where some of the absorption in the double bond region could be overtones or combination bands. Accordingly, we undertook a high resolution proton magnetic resonance study to establish the structure of liquid diketene.

Experimental

The commercially available diketene was redistilled.[8] Three fractions were taken at a reduced pressure of 91.4 mm.: (1) b.p. 63–68.4°, (2) b.p. 68.4–69.4°, and (3) b.p. 69.4–69.5°. The proton spectra were recorded as a function of applied magnetic field at a fixed frequency of 17.735 Mc. using an improved version[9] of the high resolution spectrometer described earlier.[6,10] The volume of sample in the rf coil was about 0.02 ml. The spectra of all three fractions were observed. Representative spectra are reproduced in Figs. 1–3. The abscissa is in δ-units, defined as $10^5(H_r - H_c)/H_r$ where H_r is the magnetic field applied for resonance in a reference sample of H_2O and H_c that applied to the diketene.

The room temperature spectrum under moderate resolution of fraction (2) is given in Fig. 1; it is identical with that of fraction (3). The chemical shifts of the two resonance components found were measured as δ-values of -0.13 ± 0.02 and -0.06 ± 0.02. Under higher resolution each of the two components exhibits fine structure, as shown in Fig. 2. The b.p. of fraction (1) demonstrates that it is impure and in fact its proton spectrum has a weak impurity line at -0.33, a position characteristic[6] of CH_3 groups, which
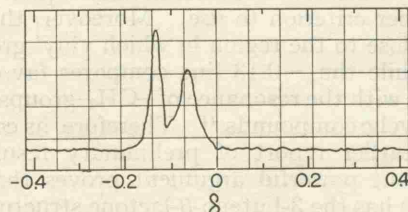
Fig. 1.—The proton magnetic resonance absorption spectrum of pure liquid diketene at room temperature. The absorption was plotted at a fixed frequency of 17.735 Mc. as a function of applied magnetic field. The total field sweep is 35 milligauss, sweep time, 12 sec.

(1) This research was supported in part by the U. S. Office of Naval Research and by a grant-in-aid from E. I. du Pont de Nemours and Co.

(2) L. Katz and W. N. Lipscomb, *Acta Cryst.*, **5**, 313 (1952).

(3) P. T. Ford and R. E. Richards, *Disc. Faraday Soc.*, **19**, 230 (1955).

(4) D. H. Whiffen and H. W. Thompson, *J. Chem. Soc.*, 1005 (1946).

(5) F. A. Miller and S. D. Koch, Jr., THIS JOURNAL, **70**, 1890 (1948).

(6) L. H. Meyer, A. Saika and H. S. Gutowsky, *ibid.*, **75**, 4567 (1953).

(7) H. S. Gutowsky, *Disc. Faraday Soc.*, **19**, 187, 248 (1955).

(8) We are indebted to Mr. H. E. Knipmeyer for the distillation.

(9) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **24**, in press (1956).

(10) H. S. Gutowsky, L. H. Meyer and R. E. McClure, *Rev. Sci. Instr.*, **24**, 644 (1953).

most likely is from either acetic acid originally added to stabilize the diketene or else from acetic anhydride, a common impurity.[4] On standing at room temperature the samples became somewhat discolored due to polymerization of the diketene, but the room temperature spectra of fractions (2) and (3) did not appear to change.
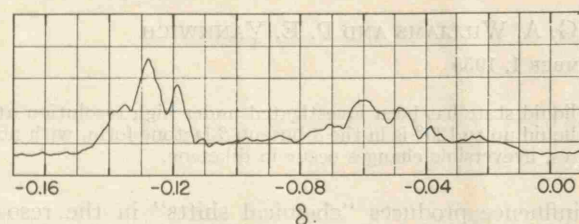

Fig. 2.—The proton magnetic resonance absorption spectrum of pure liquid diketene at room temperature under higher resolution than the spectrum in Fig. 1. The total sweep is 7.1 milligauss; sweep time, 18 sec.

The spectrum of a sample taken from fraction (2) was observed at temperatures up to 170°. A new line started to appear at 120° at a δ of -0.31 ± 0.02. This line increased in intensity and apparent complexity at higher temperatures, at the expense of the two original components, and a weak line developed at a δ of $+0.07$. However, the effects were irreversible and the new absorption remained in the spectrum when the sample was cooled to room temperature, as shown by the spectrum reproduced in Fig. 3. After the cycle, the sample was badly discolored suggesting extensive polymerization.
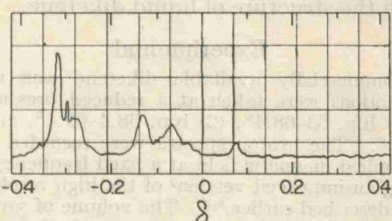
Fig. 3.—The proton magnetic resonance absorption spectrum at room temperature of a sample of liquid diketene which had been heated to 170°; otherwise same as Fig. 1.

Discussion

Structure V, the 3-buteno-β-lactone form, is the only one for which two main proton resonance components of equal intensity are predicted. The observed room temperature spectrum, in Fig. 1, has only two main components. They are of somewhat different peak intensity but the more intense line is sharper so the areas are essentially equal which is the proper criterion to use. Moreover, the -0.06 line is close to the region in which vinyl groups absorb[6] while the -0.13 line compares favorably in position with the resonance of $-CH_2-$groups in small heterocyclic compounds.[11] Therefore, as concluded in an earlier report of preliminary results,[7] this simple but powerful argument proves that liquid diketene has the 3-buteno-β-lactone structure, V.

There is still the question of whether any of the other forms is present to a small extent, perhaps with absorption overlapping that of V or else too weak to detect. Structures I and III contain a CH_3 group whose proton resonance would be in the region[6] -0.42 to -0.30, where no absorption was observed in pure diketene. This component would be the strongest one for either of the struc-

(11) H. S. Gutowsky, R. L. Rutledge, S. Searles and M. Tamres, This Journal, 76, 4242 (1954).

tures, and the sensitivity of our measurements is such that certainly no more than 3 to 5% of I or III could be present without our having detected it.

Forms II and III have $-CH_2-$ groups for which the proton resonance positions would be close to or overlap that of the $-CH_2-$ group in the 3-buteno-β-lactone. However, the spectrum in Fig. 2, under higher resolution than in Fig. 1, reveals no structure attributable to either II or III. Indeed, the fine structure observed supports the assignment of components and the structural conclusions already drawn. Most of this fine structure arises from the indirect coupling, via the bonding electrons, of the proton spins.[12] If the coupling of each proton in the $-CH_2-$ group was the same to each proton in the $CH_2=C$ group, and small compared to the chemical shift between the two groups, each of the two chemically shifted resonances would be a triplet.

The two $-CH_2-$ group protons are entirely equivalent since they are symmetrically disposed on either side of the plane which contains the rest of the molecule. And the resonance centered at -0.13, assigned to the $-CH_2-$ group, does appear to be a triplet. However, the resonance at -0.06 is more complex; but this is expected because the two protons in the vinyl group are not quite equivalent; they are in the plane of the "molecular skeleton" and one is cis and the other trans to the lactone ring. The resulting very small chemical shift spreads the vinyl group triplet into two overlapping triplets, more or less as observed. The actual situation is somewhat more complicated than just described because (a) the two vinyl group protons have different coupling constants with the $-CH_2-$ group protons, (b) the coupling constants are comparable to the chemical shifts,[13,14] and (c) the coupling between the protons in the vinyl group produces observable effects. Without going into the details, it appears on theoretical grounds[15] that the $-CH_2-$ group resonance would have a maximum of 8 components, while the $CH_2=C$ group would have two overlapping sets each of 8 components. Under higher resolution than given in Fig. 3, the $-CH_2-$ group resonance does appear to have 4 components, each a doublet. Structure III, if present, would have a single absorption line in this region; but all lines observed are accounted for. So unless the absorption from III is obscured by that from V, none of form III is present. This places an upper limit of about 5% on III.

One might argue that the observed spectrum has really three main chemically shifted components of relative intensities 2:1:1, and that the sample was therefore II. But this would require that the broad absorption at -0.06 be assigned to the $-CH=C$ and $C=C-OH$ groups and the absorption at -0.13 to the $-CH_2-$ group. However, $-CH=C$ groups are known[6] to absorb at $+0.05$ to $+0.15$ and the $C=C-OH$ group would be expected near phenols at about $+0.20$, so diketene cannot be II.

(12) H. S. Gutowsky, D. W. McCall and C. P. Slichter, J. Chem. Phys., 21, 279 (1953).
(13) E. L. Hahn and D. E. Maxwell, Phys. Rev., 88, 1070 (1952).
(14) M. K. Banerjee, T. P. Das and A. K. Saha, Proc. Roy. Soc. (London), A226, 490 (1954).
(15) H. M. McConnell, A. D. McLean and C. A. Reilly, J. Chem. Phys., 23, 1152 (1955).

The absence of any detectable absorption in these regions as well as in the vicinity of the $-CH_2-$ group resonance at -0.13 places an upper limit of 5 to 10% on the presence of form II.

As to the spectra at higher temperatures, we did not detect any reversible changes. There is, of course, the possibility that the large irreversible changes shown in Fig. 3 could have obscured a small reversible effect. Moreover, the temperature dependence of the infrared spectrum was observed[5] in the vapor phase where intermolecular reaction would be slower than for the liquid used in our experiments. So we cannot prove the absence of a small percentage of another form in equilibrium with V at temperatures above 120°. But this appears to us to be rather unlikely. For one thing, the arguments of Miller and Koch[5] supporting an equilibrium mixture imply comparable percentages of at least two forms at room temperature; and we have shown this definitely not to be the case. The changes with temperature reported[5] in the relative intensities of the infrared bands in the double bond region are comparable to those found at room temperature upon changing solvents.[4] Both observations can be ascribed to a dependency of the infrared transitions probabilities on molecular environment. A last point is that the new infrared bands found[5] at 180° could be spurious. New bands were also found at 100° upon heating the sample but disappeared or decreased in intensity upon further heating or upon heating to 180° and then cooling to 100° again. There is no assurance that the new bands found at 180° might not also have changed upon such treatment.

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The Proton Magnetic Resonance and Structure of the Diketene-Acetone Adduct

Alfred R. Bader, H. S. Gutowsky, and J. P. Heeschen

The Proton Magnetic Resonance and Structure of the Diketene-Acetone Adduct[1]

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In previous work there is some question regarding the molecular structure of the adduct obtained from the reaction of diketene with ketones.[2]

The infrared and ultraviolet spectra[2] and the chemical behavior[2,3] of the adduct with acetone have been interpreted as favoring structure I. On the other hand, similar evidence led to the suggestion[4] that the structure is II. We have observed the proton magnetic resonance spectrum[5] of the adduct, and obtained results which show con-

I II III
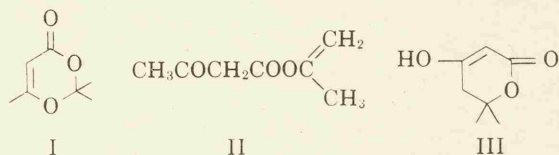
clusively that the structure is I, the 2,2-dimethyl-4-methyl-6-keto-1,3-dioxene.

The proton spectrum of the liquid adduct at room temperature under conditions of moderate resolution is given in Fig. 1A. Three absorption lines are present, with relative intensities of approximately 6:3:1 suggesting immediately that they arise respectively from the $C(CH_3)_2$, CH_3—C=C and C=CH—C groups of structure I. Structure II would be expected to have four lines with relative intensities of 3:3:2:2 and structure III, which has also been considered,[2] four lines, 6:2:1:1. The δ-values, referred to H_2O, of the three lines observed are -0.335, -0.305, and $+0.025$, which agree very well with the characteristic absorption regions of CH_3—C, CH_3—C=C, and C=CH—C groups in compounds of known structure.[5] The enolic form of II is eliminated by similar arguments.

Conclusive support of structure I is afforded by the multiplet structure,[6] shown in Fig. 1B and 1C, exhibited under higher resolution by the lines assigned to the CH_3—C=CH—C protons. The CH_3 group resonance is a doublet while that of the
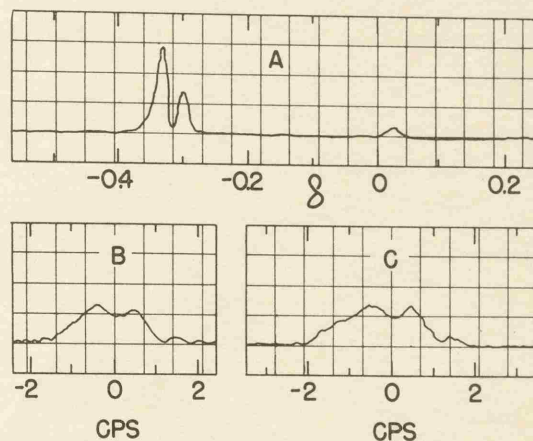
Fig. 1. The Proton Magnetic Resonance Absorption spectrum of the liquid diketene-acetone adduct at room temperature, using a spinning sample with an effective volume of 0.02 ml. A. The entire spectrum under conditions of moderate resolution; the total sweep in magnetic field is 34 milligauss; sweep time, 10 sec. B and C. The line at a δ of -0.305 and the line at a δ of $+0.025$, respectively, under higher resolution. The intensity scale for C is one-fourth that for B.

C=CH—C group is a 1:3:3:1 quartet, as expected for a 3-proton system coupled to a single proton with a chemically shifted resonance.[6] Structure I is the only one in which such an interaction can occur. Moreover, the protons in the CH_3—C=CH=C group are "insulated" by six chemical bonds from the $C(CH_3)_2$ protons so there should be no splitting of the latter, again agreeing with experiment.

EXPERIMENTAL

Sample. The commercially available diketone acetone adduct (Aldrich Chemical Company, Inc.) was carefully redistilled (b.p. 66.0–66.5°/2 mm.; n_D^{20} 1.464) a few days before the spectrum was observed. The spectra of samples several months old exhibited absorption in addition to that shown in Fig. 1, indicating a small amount of decomposition. There was no evidence in the spectrum of the newly distilled sample of other than the one component.

Procedure. The apparatus and experimental procedure were similar to those used earlier,[5] with some modifications described elsewhere.[7] The spectra were recorded at a fixed frequency of 17.735 Mc using the permanent magnet with a field of about 4165 gauss. The standard deviations of the measured δ-values are no more than ± 0.01.

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(1) This work was supported by the Office of Naval Research and by a grant-in-aid from E. I. du Pont de Nemours and Co.

(2) M. F. Carroll and A. R. Bader, *J. Am. Chem. Soc.*, **75**, 5400 (1953).

(3) N. G. Gaylord and D. J. Kay, *J. Am. Chem. Soc.*, **77**, 6641 (1955).

(4) Kh. V. Bal'yan and A. L. Shtangeev, *Zhur. Obshchei Khim.*, **24**, 238 (1954); *Chem. Abstr.*, **49**, 4525 (1955).

(5) L. H. Meyer, A. Saika, and H. S. Gutowsky, *J. Am. Chem. Soc.*, **75**, 4567 (1953).

(6) H. S. Gutowsky, D. W. McCall, and C. P. Slichter, *J. Chem. Phys.*, **21**, 279 (1953).

(7) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **24**, in press (1956).

Unsaturated Phenols.   III.   Alkali Isomerization

———

By Alfred R. Bader

Unsaturated Phenols. III.[1a,b] Alkali Isomerization

BY ALFRED R. BADER

The alkali isomerizations of the six β,γ-unsaturated phenols I–VI have been compared with that of o-allylphenol. All six are isomerized with greater difficulty than is o-allylphenol and, surprisingly, the *ortho* isomers are isomerized faster than the corresponding *para* isomers. The possible mechanisms of isomerization are considered.

The ease[2] of isomerization of allyl- to propenyl-phenol and of related systems, such as eugenol to isoeugenol, raises the question of whether that ease of isomerization is due largely to the products' conjugation with the benzene ring or to their hyperconjugation with the terminal methyl group. To answer this, the isomerizations of six β,γ-unsaturated phenols, I–VI, accessible through the acid-catalyzed reactions of dienes with phenol[3-5] have been studied.

o-Allylphenol is isomerized to o-propenylphenol by the action of methanolic potassium hydroxide at 110° in six to ten hours.[6] Under those conditions *none* of the phenols I–VI is isomerized to any measurable extent. After 100 hours, both cyclopentenylphenols, II and V, and p-3-methylcrotyl-phenol (VI) were recovered, essentially unchanged, while there was found to be *ca.* 80 and 60% isomerization in the o-substituted phenols I and III, respectively, and 30% isomerization in the p-crotyl-phenol (IV). Only when I–VI were heated with potassium hydroxide without solvents at 200° could the six conjugated phenols be isolated in good yields.

When the difficulty of isomerizing all γ-substituted β,γ-unsaturated phenols was realized, but before the surprisingly faster isomerization of *ortho* alkenylphenols in a given *ortho–para* pair was noted, an attempt was made to highlight the difference in reactivity of allylphenol and γ-substi-

(1) (a) For Paper II, see THIS JOURNAL, **77**, 4155 (1955); (b) presented in part before the XIV International Congress of Pure and Applied Chemistry, Zürich, July, 1955.

(2) D. S. Tarbell in R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 19.

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

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

(5) H. Pines and J. A. Vesely, U. S. Patents 2,553,470 and 2,578,206 (May and December, 1951).

(6) See p. 27 of ref. 2.
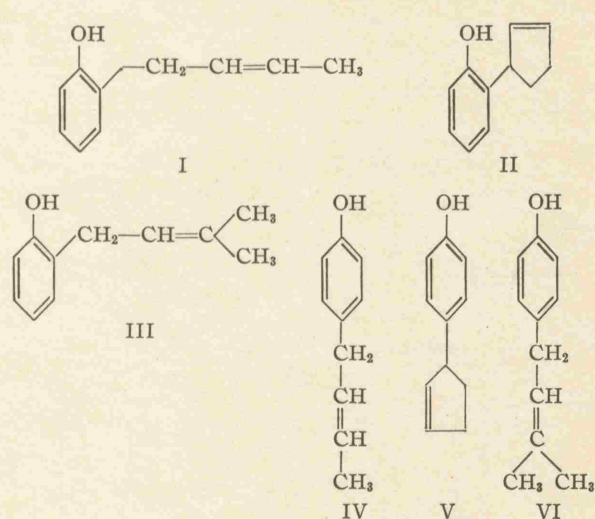
tuted β,γ-unsaturated phenols by isomerizing VII exclusively to VIII. The 2,6-diallyl-4-crotylphenol (VII) was synthesized via successive O-alkylations and Claisen rearrangements from IV, and the mild conditions sufficient to isomerize o-allylphenol to o-propenylphenol yielded only VIII, as shown by its ultraviolet spectrum which was very similar to that of IX.
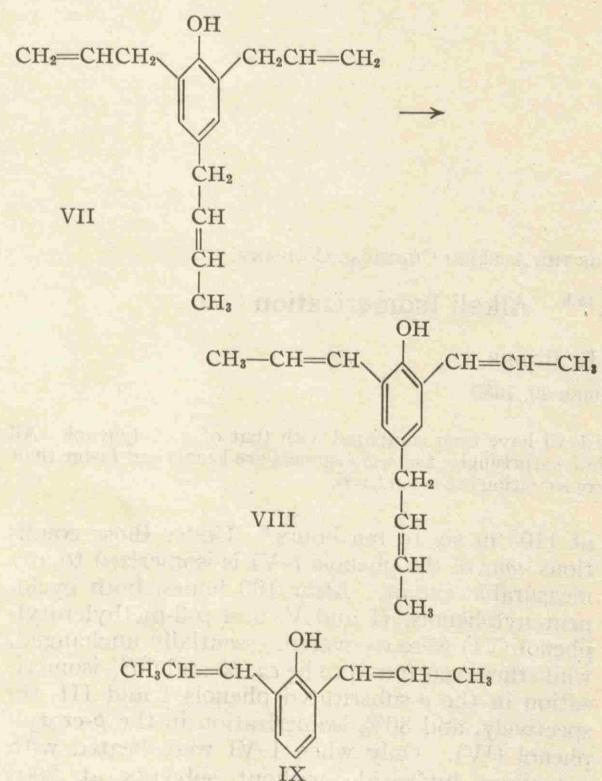
If the isomerizations of all β,γ-alkenylphenols proceed by removal of a proton from the phenolate ion, perhaps with simultaneous γ-addition of a proton, it seemed reasonable to suppose that both steric and electrostatic effects would, in any ortho-para pair, make the reaction ortho to the phenolate oxygen, even if concerted, the slower of the two. Thus, the faster isomerization of ortho alkenylphenols suggested that a different mechanism might be

(7) This is similar to the isomerization of eugenol to isoeugenol (S. K. Gokhale, J. S. Sudborough and H. E. Watson, J. Indian Inst. Sci., 6, 241 (1923)) which at 220° also requires at least two equivalents of potassium hydroxide and in which sodium hydroxide is ineffective. Mr. M. F. Carroll has kindly told me that in the industrial isomerization of eugenol a well-defined, crystalline dipotassium isoeugenol can be isolated. This may, however, be just a solid compound of the phenolate with potassium hydroxide.

operative with ortho isomers, and several were considered. One was a unimolecular reaction of the ion, XI, possibly with concerted γ-carbon proton attachment
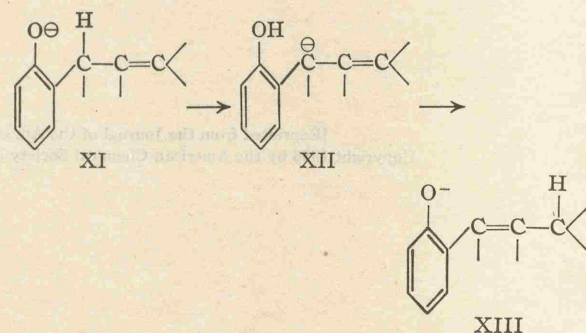
and perhaps involving a solvent bridge to explain the unreactivity of o-cyclopentenylphenol; the simple intramolecular mechanism would have a small steric factor. Alternately, a cyclic mechanism XIV → XV, with or without solvent bridge, was considered. This involves the abstraction of a
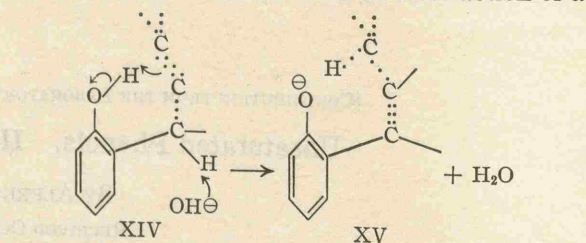
proton from the α-carbon atom of the un-ionized phenol with concerted proton transfer from the phenolic hydroxyl to the γ-carbon atom.

In the mechanism involving simply abstraction of a proton by hydroxide from the α-carbon atom of the phenolate ion, the rate must be dependent on alkali concentration. In the other mechanisms considered for ortho isomers, the rate would be roughly independent of the concentration of alkali in excess of that required to form the phenolate. Actually, the rate of isomerization of para and ortho alkenylphenols is very dependent on the concentration of alkali; there is no isomerization of I or IV with equivalent amounts of methanolic potassium hydroxide at 110° for 40 hours, and even in the reaction at 200° excess potassium hydroxide is required to effect the isomerization.[7]

The dependence of the rate of isomerization on the alkali concentration appeared to rule out the special mechanisms considered for ortho isomers, and it became necessary to reconsider the initial assumption that steric and electrostatic effects would make the abstraction of a proton ortho to the phenolate oxygen the slower. Sterically, this is certainly so.
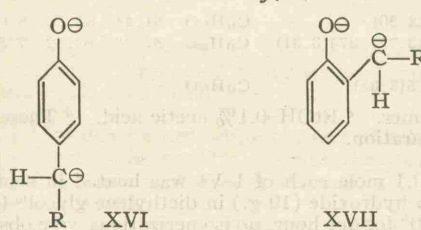
As to electrostatic effect, the initial assumption was based on the closer proximity of negative charges in XVII than XVI. It may be, however, that under the reaction conditions, there is a higher electron density at the para, rather than the ortho position of the phenolate, making abstraction of a proton next to it more difficult. Also XVII must be stabilized by resonance with XVIIa, having both
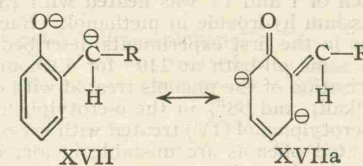
charges in the ring and para to each other. The para isomer XVI is stabilized less because the corresponding structure XVIa has adjacent negative charges. Thus, the stabilization of XVII by XVIIa may make the isomerizations of the ortho isomers the faster.
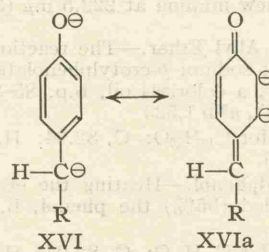
As allyl- and propenylphenol are about equally hyperconjugated (a benzyl group being roughly the equivalent of methyl), conjugation alone determines the equilibrium. The same applies to the isomerization of the cyclopentenylphenols. The crotylphenols are doubly and the 3-methylcrotylphenols triply hyperconjugated, while the corresponding conjugated phenols are singly hyperconjugated; here hyperconjugation opposes isomerization. Even the 3-methylcrotylphenols are isomerized, showing that conjugation is the more important driving force.

As the rates of isomerization are rates of ionization, one might try to correlate them with the acidities of the unconjugated olefins. The acidities of allyl-, crotyl- and 3-methylcrotyl-aromatics decrease in that order because one of the structures (e.g., Xb) contributing to the anion becomes progressively a primary, secondary and tertiary anionic structure and hence less stable. The rates of

isomerization decrease in the same order. The rates of the cyclopentenylphenols are unexpectedly the slowest. One might have expected an isomerization slower than that of allylphenol (because the two added methylene groups supply electrons), but faster than that of the crotylphenols, because the anions from cyclopentenylphenols are presumably

more favored relative to olefin than CH_3—CH=CH—CH=CH—Ar which has diminished hyperconjugation. This failure in the equilibrium–rate parallelism is reminiscent of the nitroalkyls,[8] where the acidities increase from nitromethane to nitroethane to 2-nitropropane, and the rates of ionization decrease. Presumably, there is steric hindrance to the approach of a hydroxide ion to the α-carbon atom of the cyclopentenyl phenolate. As judged by ultraviolet spectra, however, there is little steric inhibition of conjugation in the o- and p-1-cyclopentenylphenols.

At equilibrium, I–VI are almost completely isomerized. Bateman and Cunneen[9] have recently discussed the importance of hyperconjugation as well as conjugation in isomerizations of alkenylbenzenes and their data also show the great retardation of the reaction of crotyl- compared to allyl-aromatics. Table I lists the equilibrium concentrations of the conjugated isomers in the isomerizations of alkenylbenzenes, alkenylphenols and unsaturated acids. With the phenolate, presumably resonance contributions of structures such as XVIIIa shift the equilibria further toward conjugation than in alkenylbenzenes.
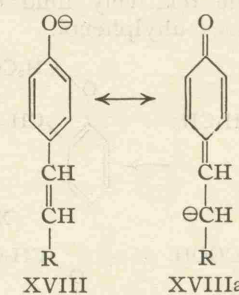
TABLE I
% CONJUGATE ISOMER

R	R—CO₂		
-CH₂—CH=CH₂	98[a]	100	95
-CH₂—CH=CH—CH₃	68[a]	82	95
-CH₂—CH=C(CH₃)₂	22[b]	57	90

a R. P. Linstead and E. G. Noble, J. Chem. Soc., 614 (1934). b R. P. Linstead, ibid., 1603 (1930).

It also seemed of interest to compare the isomerization of o-allylphenol with that of 2-allyl-3,5-dimethylphenol (XIX). The ultraviolet spectrum of the product XX has a long wave length maximum which is weaker and at shorter wave length than in other conjugated o-alkenylphenols and, as the nor-

(8) S. H. Maron and V. K. LaMer, THIS JOURNAL, 60, 2588 (1938). (9) L. Bateman and J. I. Cunneen, J. Chem. Soc., 2283 (1951).
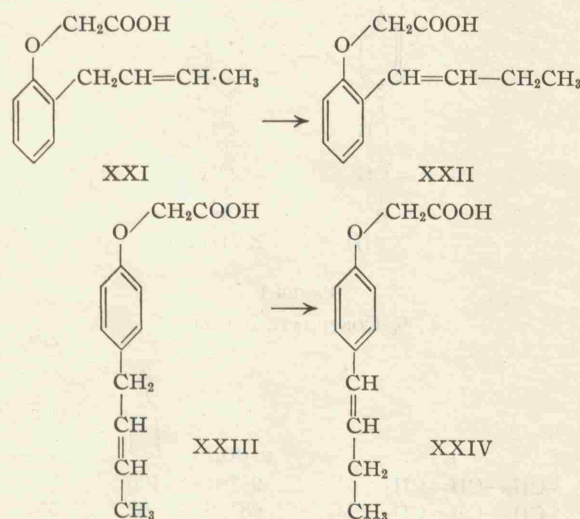
TABLE II
CONJUGATED PHENOLS

Phenols	M.p., °C.	Solvent of crys.	λ_{max},[c,d] mμ (log e)	λ_{min}, mμ (log e)	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
o-1-Butenyl-	−3 to −1	....	250(4.04); 303(3.62)	234(3.86); 273(3.20)	$C_{10}H_{12}O$	81.04	80.81	8.16	8.12
p-1-Butenyl-	85–86	Heptane	261(4.29); 285(infl. 3.47)	227.5(3.47)	$C_{10}H_{12}O$	81.04	80.63	8.16	8.10
o-3-Methyl-1-butenyl-	Liquid[b]	....	253(3.95); 285(infl. 3.45); 301(3.54)	235(3.75); 274(3.37)	$C_{11}H_{14}O$	81.44	81.24	8.69	8.75
p-3-Methyl-1-butenyl-	83–84	Heptane	261(4.27); 298(infl. 3.36)	228(3.50)	$C_{11}H_{14}O$	81.44	81.16	8.69	8.78
o-1-Cyclopentenyl-	48–49	Heptane	227.5(3.87); 253(3.88); 295(3.59); 304(infl. 3.50)	237(3.77); 274(3.31)	$C_{11}H_{12}O$	82.46	82.12	7.55	7.80
p-1-Cyclopentenyl-[e]	149	Aq. ethanol	262.5(4.27); 290(infl. 3.43)	227.5(3.36)	$C_{11}H_{12}O$				

[a] See ref. 4.   [b] This probably contained some of the unconjugated isomer.   [c] EtOH–0.1% acetic acid.   [d] These spectra will be discussed in detail in a paper with Prof. M. G. Ettlinger, in preparation.

mal effect of the methyl groups would be bathochromic, some steric interference is indicated; thus, there must be less assist from conjugation. The effect of hyperconjugation is as in o-allylphenol, and the reaction proceeds almost as easily.
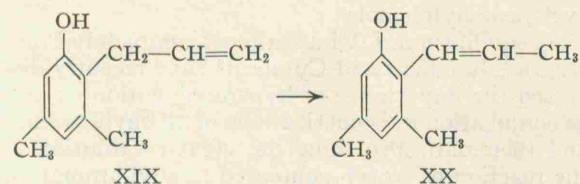
That the difficulty of isomerizing the phenolate is primarily due to the necessarily close approach of a hydroxide ion to the α-carbon atom, and hence to a center of partial negative charge at the o- or p-carbon atom, was shown by the facile isomerizations of the crotylphenoxyacetic acids XXI and XXIII under the relatively mild conditions required to isomerize o-allylphenol.

Experimental

Table II lists the physical constants of the conjugated phenols made from I–VI. p-Crotylphenol[3] (IV), crystallized from heptane, is a crystalline solid, m.p. 39°. The conjugated p-cyclopentenylphenol was identical with the compound prepared previously[4] in the isomerization catalyzed by palladium-on-charcoal.

Mixtures of 10 g. each of I–VI, 10 g. of potassium hydroxide and 30 cc. of methanol were heated with solvent take-off until the flask temperature reached 110°. The clear solutions were then refluxed at 110° under inert gas for 100 hours. The percentage conjugation of I–VI, estimated by ultraviolet spectra, were found to be 80, 3, 60, 30, 3–4 and 1–2%, respectively.

When 0.1 mole each of I–VI was heated in solutions of potassium hydroxide (10 g.) in diethylene glycol[10] (100 cc.) at 165–170° for one hour, no isomerizations were observable. o-Allylphenol and XIX are largely isomerized under these conditions.

When each of I–VI was heated with an equal weight of potassium hydroxide at 200° for 4 hours, each of the conjugated phenols was obtained in better than 80% yields. With equal weights of sodium hydroxide or with small amounts of potassium hydroxide, there was little or no isomerization. To illustrate the need for excess alkali further, 14.8 g. (0.1 mole) each of I and IV was heated with 33.5 g. (0.6 mole) of potassium hydroxide in methanol, and 29.6 g. (0.2 mole) each of I and IV was heated with 13.4 g. (0.2 mole) of potassium hydroxide in methanol. Each mixture was treated as in the first experiments described, and was heated in the same oil-bath at 110° for 40 hours. There was no isomerization of the phenols treated with equivalent amounts of alkali; and 68% in the o-crotylphenol (I) and 36% in the p-crotylphenol (IV) treated with excess alkali.

The conjugated phenols are unstable in air, but stable under nitrogen in the icebox. Exposed to air, the conjugated phenols' ultraviolet spectra show diminishing intensities of the maxima at 250–263 mμ characteristic of conjugation, and the emergence of maxima suggesting the formation of unconjugated phenols or phenyl ethers. Thus, when a sample of p-1-butenylphenol was exposed to air for two months, the maximum at 261 mμ originally of log e 4.29 had a log e 3.9, and there was a new maximum at 227.5 mμ, log e 3.85, and new minima at 222.5 mμ (3.84) and 242.5 mμ (3.65).

p-Crotylphenyl Allyl Ether.—The reaction of allyl chloride with aqueous sodium p-crotylphenolate quantitatively yielded the ether, a colorless oil, b.p. 85–87° (0.5 mm.), m.p. −25 to −23°, n^{25}D 1.523.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.76; H, 8.66.

2-Allyl-4-crotylphenol.—Heating the ether at 200° for three hours yielded (95%) the phenol, b.p. 87–88° (0.1 mm.), n^{25}D 1.540.

Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.18; H, 8.60.

2-Allyl-4-crotylphenyl Allyl Ether.—This compound prepared similarly is a colorless oil, b.p. 116–119° (0.7 mm.), n^{25}D 1.524.

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.71; H, 9.00.

The Claisen rearrangement (200°, 3 hours) of this ether yielded (95%) 2,6-diallyl-4-crotylphenol (VII), a colorless oil, b.p. 122–125° (0.6 mm.), n^{25}D 1.5392. Its infrared spectrum in carbon disulfide shows strong bands at ca. 10.0 and 11.0 μ indicative of terminal unsaturation R—CH=CH$_2$, and at 10.37 μ indicative of a trans double bond R—CH=CH—R.[11]

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.00, 84.25; H, 9.03, 9.05.

The reaction of 2,6-diallyl-4-crotylphenol with an equal weight of potassium hydroxide in methanol at 110° as above (6 hours) yielded as the sole product 2,6-dipropenyl-4-crotyl-

(10) J. H. Fletcher and D. S. Tarbell, THIS JOURNAL, **65**, 1431 (1943).

(11) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1412 (1948); N. Sheppard and G. Sutherland, *Proc. Roy. Soc. (London),* **A196**, 195 (1949).

TABLE III

	M.p., °C.	Solvent of cryst.	Analyses,[a] % Found C	Analyses,[a] % Found H	0.1% HOAc–EtOH λ_{max}, mμ (log e)	λ_{min}
XXI[b]	135–136	Water	69.80	7.00	.	
XXII	101–102	Heptane	69.61	6.91	252.5(4.14), 297.5(3.63)	232.5(3.89), 274(3.31)
XXIII[c]	80–81	Water	69.84	6.80		
XXIV[d]	128–129	Aq. ethanol	69.72	7.16	260(4.37), 287(infl., 3.42) 302.5(infl., 3.17)	226.5(3.51)

[a] Calcd. $C_{12}H_{14}O_3$: C, 69.88; H, 6.84.   [b] Prepared from crude o-crotylphenol; XXI is the only isomer sparingly soluble in toluene–heptane.   [c] Prepared from p-crotylphenol, m.p. 39°.   [d] Prepared both by alkali isomerization of XXIII and from p-1-butenylphenol, m.p. 85–86°.

phenol (VIII) which formed white clusters of soft needles from heptane and melts at 60°. Its infrared spectrum in carbon disulfide shows no bands at 10.0 and 11.0 μ and a strong band at 10.35 μ.

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.77, 84.07; H, 8.82, 8.98. $\lambda_{max}^{EtOH–0.1\% HOAc}$ 237.5 mμ (log e 4.61); 257.5 mμ (infl. log e 4.09); 324 mμ (log e 3.69). λ_{min} 295 mμ (log e 3.30).

2,6-Dipropenylphenol (IX) prepared similarly from 2,6-diallylphenol[12] forms white needles from heptane and melts at 77–78°.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.69; H, 8.67. $\lambda_{max}^{EtOH–0.1\% HOAc}$ 237.5 mμ (log e 4.60); 255 mμ (infl., log e 4.02); 317.5 mμ (log e 3.67). λ_{min} 287.5 mμ (log e 3.29).

2-Propenyl-3,5-dimethylphenol (XX).—2-Allyl-3,5-dimethylphenol[13] (XIX) was treated with an equal weight of potassium hydroxide in methanol at 110° for 20 hours to form XX in good yield. The product formed soft needles from heptane, m.p. 69–70°.

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.17; H, 8.70. XIX: $\lambda_{max}^{EtOH–0.1\% HOAc}$ 216 mμ (log e 4.04), 277 mμ (infl., log e 3.26) 283 mμ (log e 3.29). XX: $\lambda_{max}^{EtOH–0.1\% HOAc}$ 220 mμ (log e 4.38); 254 mμ (log e 4.00); 297 mμ (log e 3.42). λ_{min} 239 mμ (log e 3.87); 279 mμ (log e 3.24).

Butenylphenoxyacetic Acids (XXI–XXIV).—When the mixture of I and IV made by the reaction[3] of phenol with butadiene is treated with chloroacetic acid, the *ortho* isomer XXI is easily separated from XXIII through the former's lesser solubility in toluene and heptane. The acids XXI and XXIII were isomerized to XXII and XXIV, respectively, in methanolic potassium hydroxide (110°, 6 hours). The physical constants of the isomers are listed in Table III.

(12) K. v. Auwers, *Ann.*, **422**, 174 (1920).

(13) K. v. Auwers and E. Borsche, *Ber.*, **48**, 1716 (1915).

MILWAUKEE 12, WISCONSIN

Unsaturated Phenols.   IV.   Crotylphenols

By Alfred R. Bader

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

(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) and 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.
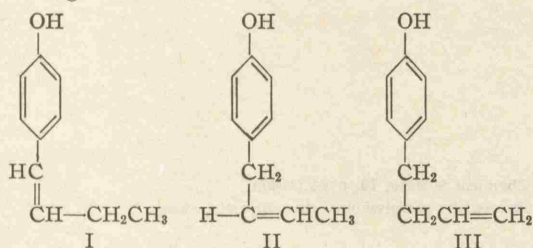
Low temperature crystallizations of the highest boiling butenylphenol fraction yielded a crystalline solid, m.p. 39°, the infrared spectrum of which shows a strong band at 10.35 μ, indicative of a symmetrically disubstituted trans double bond and no bands at 10.1–10.2 and 11.0 μ, characteristic of the 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 these wave lengths in the spectra of the butenylphenols obtained with the other catalysts. Theoretically,

n-butylphenols 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-

(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, vinylically 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., 80%), b.p. 53–90° (0.1 mm.), $n^{25}D$ 1.539, $\lambda_{max}^{EtOH-0.1\% HOAc}$ 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); $\lambda_{max}^{EtOH-0.1\% HOAc}$ 225 mμ (log ϵ 3.99), 279 mμ (log ϵ 3.29); λ_{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°; $\lambda_{max}^{EtOH-0.1\% HOAc}$ 215.0 mμ (log ϵ 3.94), 271.5 mμ (log ϵ 3.24), 277.5 mμ (log ϵ 3.20); λ_{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 was 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[6] 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.

(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.

Unsaturated Aromatic Amines; A Novel Synthesis of Indoles

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By John E. Hyre and Alfred R. Bader

Unsaturated Aromatic Amines; A Novel Synthesis of Indoles

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

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

(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 res-

onance stabilization of the rearranged ion III; in the anilinium ion II
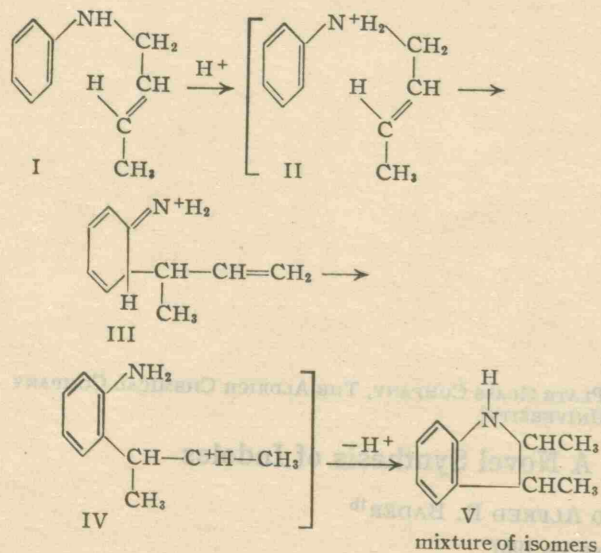
(4) L. Claisen and E. Tietze, Ber., 59B, 2344 (1926).
(5) W. J. Hickinbottom, J. Chem. Soc., 1981 (1934).
(6) Y. A. Arbuzov, Doklady Akad. Nauk, S.S.S.R., 63, 531 (1948).
(7) J. Danforth, U. S. Patent 2,495,890 (Jan. 1950).
(8) A. Steche, Ann., 242, 371 (1887).
(9) P. L. Julian and H. C. Printy, THIS 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).
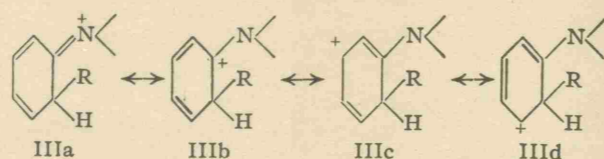
the charge cannot be distributed by resonance.

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}D 1.5614, d^{25}_{25} 0.9737.

Its toluenesulfonamide[30] melts at 69°; the benzenesulfonamide forms needles from aqueous ethanol, m.p. 82–83°.
Anal. Calcd. for $C_{16}H_{15}NSO_2$: 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.

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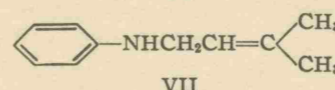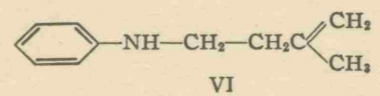
Anal. Calcd. for $C_{11}H_{15}N$: C, 81.93; H, 9.38. Found: C, 82.20, 82.10; H, 9.37, 9.50.

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^{EtOH}_{max} 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

(12) W. Weith, Ber., 9, 457 (1876).

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^{EtOH}_{max} 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, 5.28.
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^{EtOH}_{max} 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.

(13) L. Wolff, ibid., 21, 125 (1888).
(14) M. Padoa and C. Chiaves, Gazz. chim. ital., 38I, 236 (1908).

MILWAUKEE, WISCONSIN
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Unsaturated Phenols.   V.   The Reaction of Isoprene with Phenol

By Alfred R. Bader and William C. Bean

[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]

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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-

(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).

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.
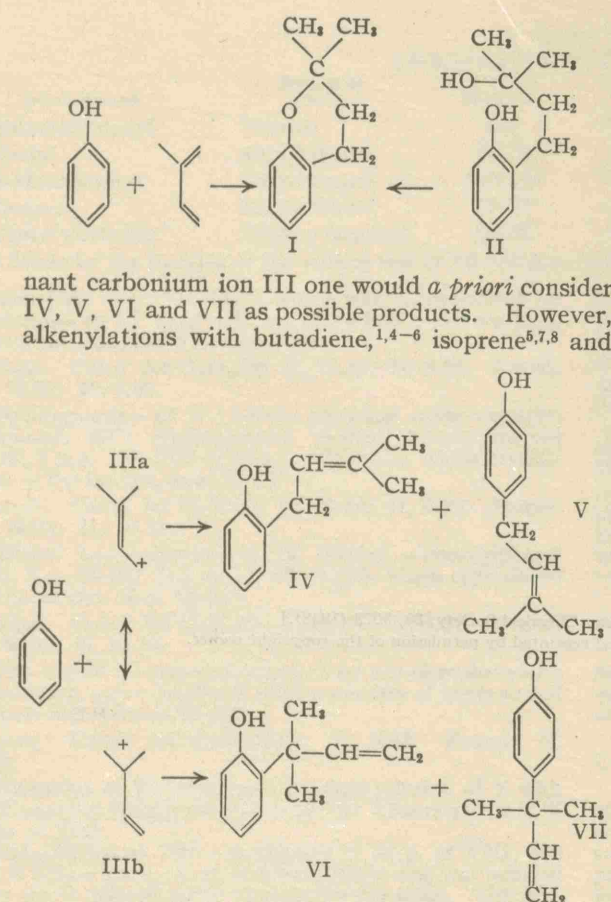
nant carbonium ion III one would *a priori* consider IV, V, VI and VII as possible products. However, alkenylations with butadiene,[1,4-6] isoprene[5,7,8] and 2,3-dimethylbutadiene[7] have shown that the products from the alkenylations with conjugated dienes are derived from that resonance hybrid of 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.
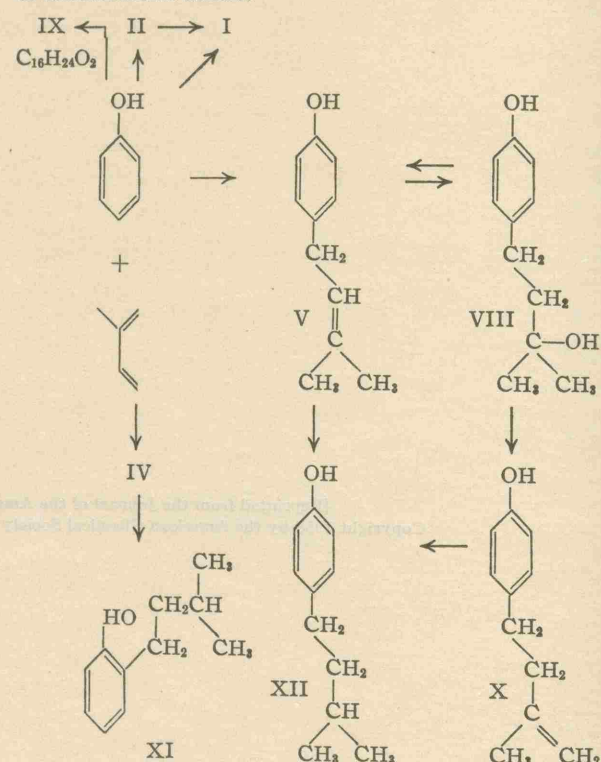
From the reaction of phenol with isoprene catalyzed by 71% phosphoric acid[9] at 20°, we obtained six products. The phenolic fraction yielded the 3-methylcrotylphenols IV and V and the crystalline tertiary alcohols II and VIII: the ethereal fraction consisted of 2,2-dimethylchroman I and an alcohol IX, $C_{16}H_{24}O_2$, 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=CH₂[11].

(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).

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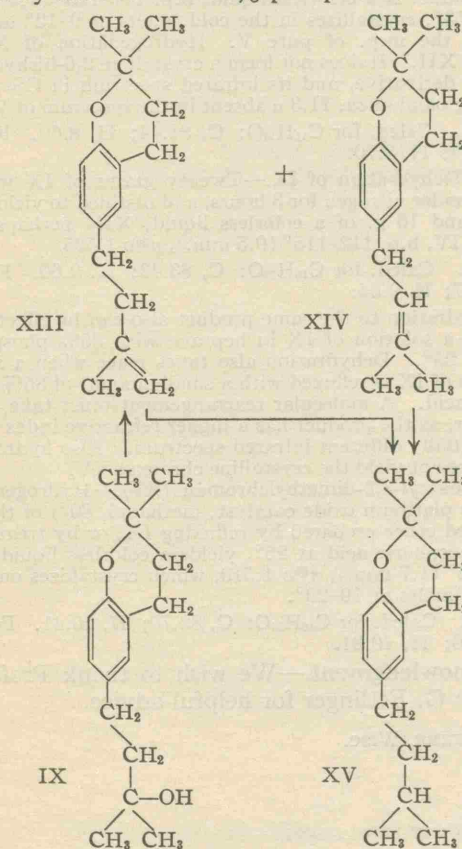
The dehydration of VIII yields one of two products, depending on conditions. In the presence of acid or iodine the predominant product is V characterized by its spectrum and bishydroxymethyl derivative. When, however, VIII is heated at atmospheric pressure without catalysts, dehy-

(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 phos-

phoric 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)-

(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.
(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	$C_{13}H_{16}O_2$	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 re-

(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.

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

BY ALFRED R. BADER AND WILLIAM C. BEAN

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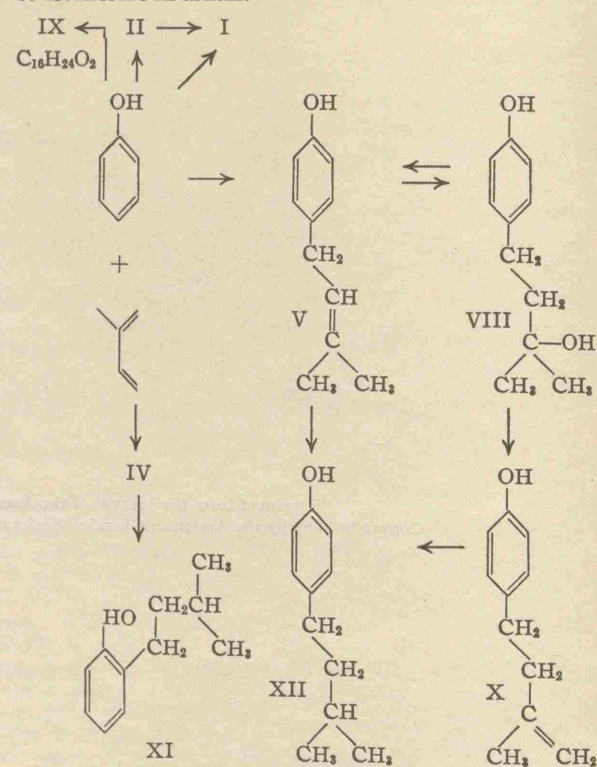
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The 3-methylcrotylphenols IV and V prepared in these alkenylations could not be obtained crystalline. The *p*-isomer V, however, was easily characterized by its 2,6-bishydroxymethyl derivative, m.p. 110–111°, and the reaction of *p*-substituted phenols 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.
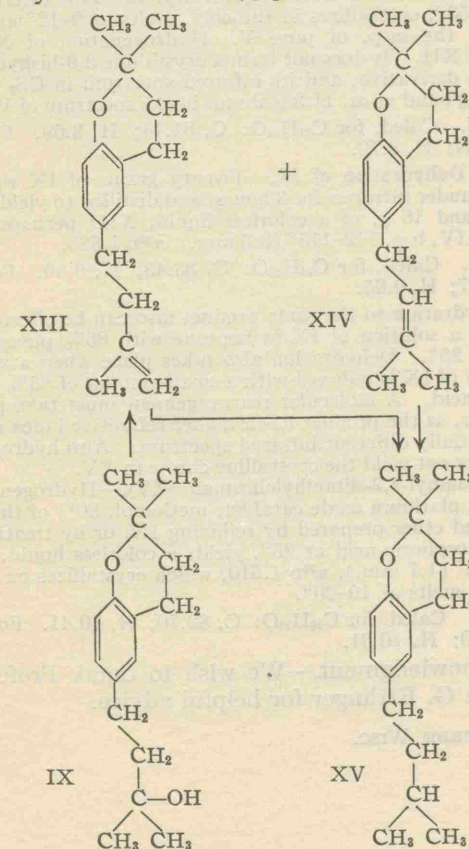
The dehydration of VIII yields one of two products, depending on conditions. In the presence of acid or iodine VIII is dehydrated easily to V characterized by its spectrum and bishydroxymethyl derivative. When, however, VIII is heated at atmospheric pressure without catalysts, dehy-

(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,[5] 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 phos-

phoric 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 $C_{12}H_{16}O_4$: 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)-

(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.

p-Substituent	Solvent of crystn.	M.p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	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 re-

(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.

fluxing 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.

MILWAUKEE, WISC.

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

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

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

(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, *Gass. 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-methyl-indoline 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-benzyl-oxyaniline, 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-propyl-

(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 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).

aniline, and gaseous hydrogen. The analogous reaction of N-cinnamylaniline yielded 2-phenyl-quinoline and o-cinnamylaniline. No indolines or indoles were found in any of these reactions.
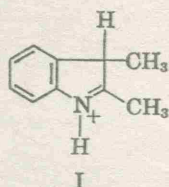
As o-allylaniline[2] yields 2-methylindoline when treated with hydrochloric acid at 190–200°, it seems likely that in the formation of 2-methylindoline discussed in this paper, o-allylaniline is an intermediate. However, to explain the formation of 2,3-dimethylindoline and 2,3-dimethylindole from N-crotylaniline, 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-crotyl-aniline 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-methyl-indole, 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
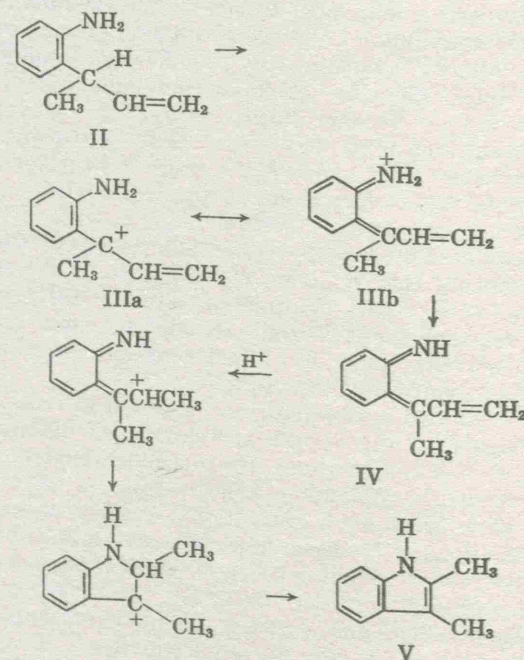
(11) Contrary to Hurd and Jenkins,[2] we think that the Claisen rearrangement does not necessarily involve electron transfer from the hetero-atom to the benzene ring but will be facilitated in amine salts compared to free amines because of delocalization of the positive charge in the transition state.[1b]

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-methylindoline.

Fraction B, 2-methyl-3-propylindole was redistilled, b.p. 131–132° (1.1 mm.), λ_{max}^{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-methyl-naphthalene. 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 - propionyl-indole,[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, $n^{26}D$ 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

(12) B. Oddo, *Gass. 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-tetrahydro-quinoline 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^{24}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-propyl-indole 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.

(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).

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, λ^{EtOH}_{max} 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^{55}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.

(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^{24}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^{24}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.

Hydrogen Peroxide–Vanadium Pentoxide Oxidation of Cyclohexenes

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Hydrogen Peroxide–Vanadium Pentoxide Oxidation of Cyclohexenes[1a]

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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-cyclo-

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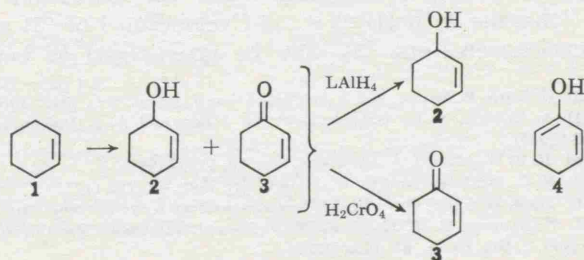
(1)(a) Presented before the Organic Division at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.; (b) Department of Chemistry, Oklahoma State University, Stillwater, Okla.; (c) Heidenheimer Chemisches Laboratorium, Heidenheim an der Brenz, Germany.

(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 repeated 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 λ_{max}^{EtOH} 225 mμ (ϵ 3905) while the reported[2] 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 infrared 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

(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 through the enol **4** suggests that some **3** may have reacted with boric acid. 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 chroma-
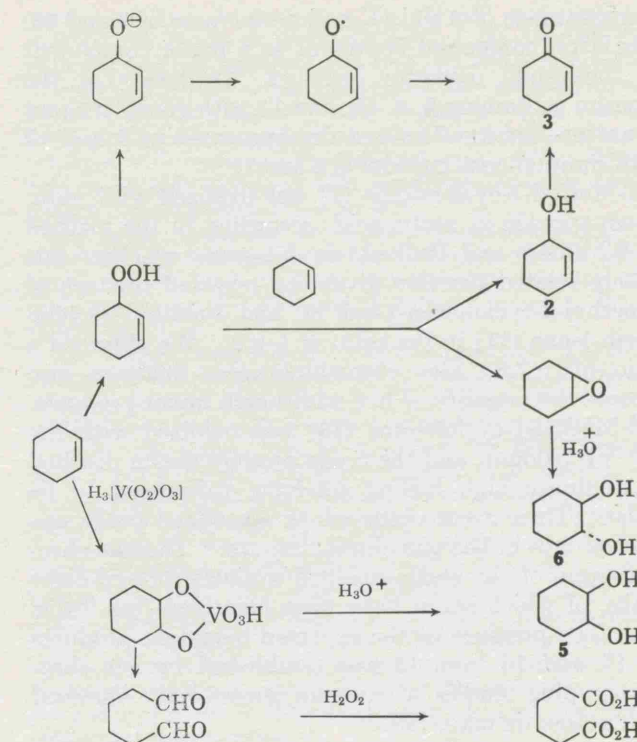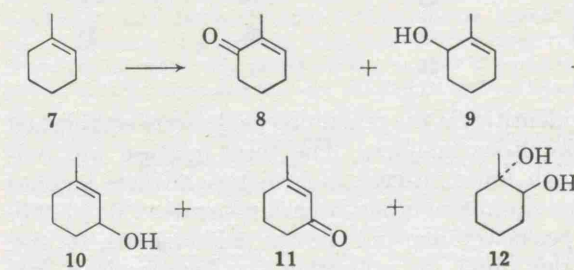

Figure 1

togram 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).

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 methyl-cyclohexene	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 alc. (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 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.
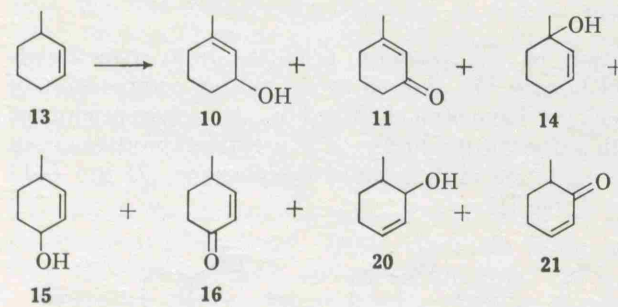
The identities of the remaining peaks were established in a circuitous manner. The total mixture was oxidized with Jones' reagent to a mixture of three ketones with gas chromatography peaks in the ratio 1.0:1.7:3.0. These peaks were shown to be due to ketones **21**, **16**, and **11** in this order, 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
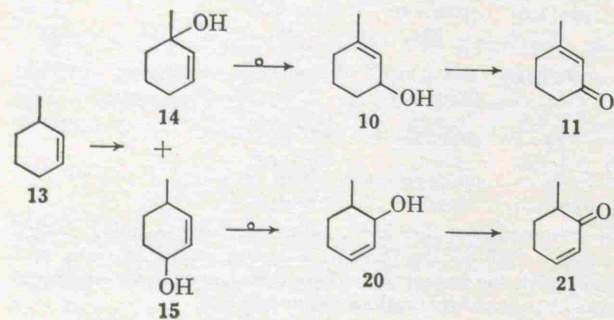
place during the HP–VP oxidation of 3-methyl-1-cyclohexene (**13**). The products **10**, **11**, **20**, and **21** are presumed to form as shown (bottom, col. 1).

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.
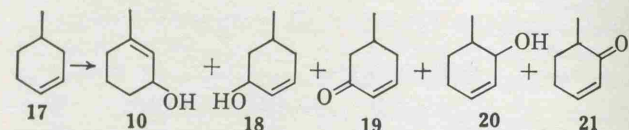

While **13** yields both the normal oxidation products, **15** and **16**, and the products of the allylic shift, **20** and **21**, we were unable to detect **15** and **16**, the corresponding products produced by allylic shift accompanying **18** and **19** in the oxidation of **17**.

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 filtered 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 supernatant 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 milliliters 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**); 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

(16) D. Dusterhoft of Lakeside Laboratories kindly carried out these determinations.

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-dinitrophenylhydrazone derivatives of authentic 6-methyl-2-cyclohexen-1-one (**21**), 4-methyl-2-cyclohexen-1-one (**16**), and 3-methyl-2-cyclohexen-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

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; λ_{max}^{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, λ_{max}^{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 λ_{max}^{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 λ_{max}^{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 isomeriza-

tion 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).

(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).

The Oxidation of Dunnione with Alkaline Hydrogen Peroxide

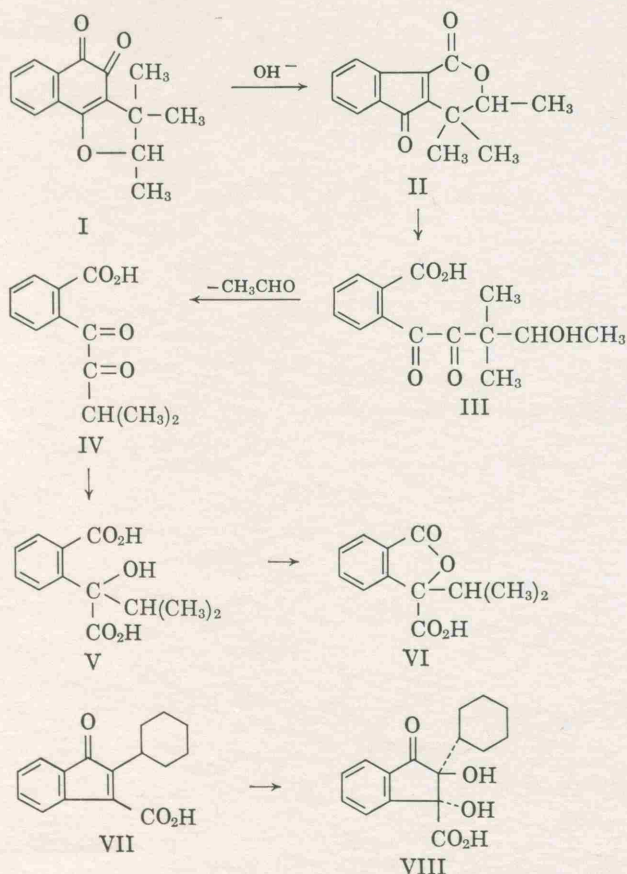Michael A. Oxman, Martin G. Ettlinger, and Alfred R. Bader

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
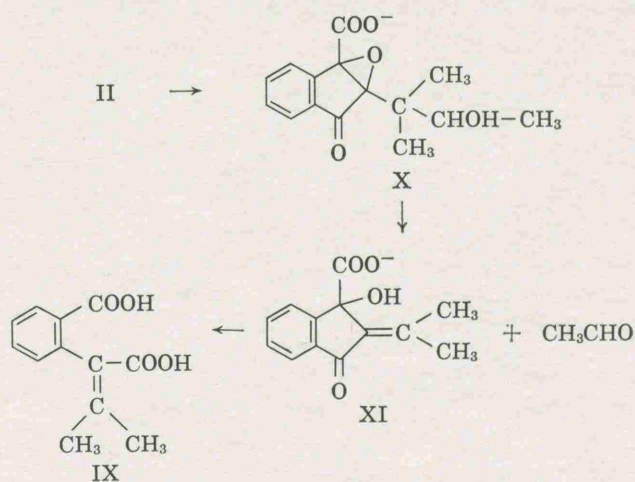
easily cleaves to acetaldehyde and XI. Such cleavages of derivatives of 1,3-diols are well known.[8] The formation[8d] of merolimonol from limonol appears particularly like the present example.

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°; 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 isopropylidene-homophthalic 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

* To Professor Louis F. Fieser

(1) J. R. Price and R. Robinson, *J. Chem. Soc.*, 1522 (1939).
(2) J. R. Price and R. Robinson, *ibid.*, 1493 (1940).
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(5) R. H. Thomson, "Naturally Occurring Quinones," Academic Press Inc., New York, N. Y., 1957, p. 88.
(6) L. F. Fieser and A. R. Bader, *J. Am. Chem. Soc.*, **73**, 681 (1951).

(7) H. J. E. Loewenthal and R. Pappo, *J. Chem. Soc.*, 4799 (1952).
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(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.

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).
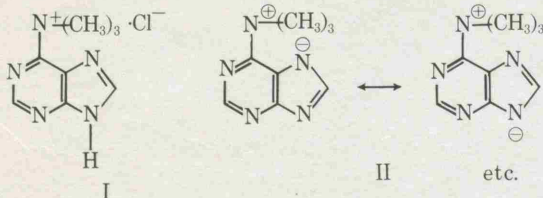
Experimental Section

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* (P₂O₅) 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 D₂O 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.

(1) Alpurine (Trademark applied for).

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

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(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.

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(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).

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Concerning the Mechanism of the Hooker Oxidation

Kwan Lee, Philip Turnbull, and Harold W. Moore*

Department of Chemistry, University of California, Irvine, California 92717

The Hooker oxidation is one of the more remarkable reactions in organic chemistry. A historic example is the conversion of lapachol (**1**, R = H, Scheme 1) to the lower homologue (**2**), a reaction discovered by Hooker and studied in detail by the Fiesers and their co-workers.[1,2] Two important observations are apparent from this example: (1) the prenyl substituent is shortened by one carbon unit and (2) the regiochemical arrangement of the 2-alkyl group and the 3-hydroxy substituent in the product are reversed from their positions in the starting quinone. This unusual reaction and its mechanistic consequences have dominated interest in the Hooker oxidation since the seminal work of Hooker and the Fiesers some 50 years ago. It is surprising that its synthetic potential has not been realized; only recently has work appeared pointing in this direction.[3]

Reported in this note are data supporting the mechanism for the rearrangement initially proposed by Fieser and Fieser in 1948.[2a] Most revealing is the observation that hydroxynaphthoquinone **9**, enriched with ¹³C at the 1-position of the ethyl substituent, rearranged to **10** under Hooker conditions and that the isotope enrichment was observed to be at a quinone sp² carbon atom (Scheme 2).

The synthesis of **9** stems from di-*tert*-butyl squarate (**5**), a reagent previously shown to be a useful precursor to hydroxy quinones.[4] Treatment of **5** with [1-¹³C]-ethylmagnesium iodide followed by hydrolysis (TFAA) gave **6** in 70% isolated yield.[5] Addition of 1-lithio-2,4-dimethoxybenzene (THF) to **6** at −78 °C afforded cyclobutenone **7** in 52% yield. Thermolysis of **7** in refluxing toluene gave the corresponding hydroquinone which was directly converted to quinone **8** (92%) upon Ag₂O oxidation.[6] De-*tert*-butylation (TFA) then gave the desired hydroxynaphthoquinone **9** in nearly quantitative yield.

Oxidation of **9** under Hooker conditions (1. H₂O₂/Na₂CO₃; 2. CuSO₄/NaOH) gave **10** in 72% isolated yield, the structure of which is in complete accord with the

Scheme 1

lapachol, **1** (R=H)

Hooker Oxidation
KMnO₄/NaOH
or
1. H₂O₂/Na₂CO₃
2.CuSO₄/ NaOH

2

3

4

observed spectral properties (Experimental Section). In addition, **10** was independently synthesized from 3-*tert*-butoxy-4-methylcyclobutene-1,2-dione (**12**) as outlined in Scheme 2. Treatment of **12** with 1-lithio-3,5-dimethoxybenzene gave cyclobutenone **13** in 32% isolated yield which was then converted to **10** (78%) upon thermolysis in refluxing toluene followed by Ag₂O oxidation and de-*tert*-butylation. Comparison of the quinone obtained by this sequence with the product of the above Hooker oxidation using a sample of **9** that had not been enriched with ¹³C showed them to be identical in all respects.

Tracking the course of the ¹³C label in the conversion of **9** to **10** provides critical information regarding the mechanism of the Hooker oxidation. The ¹³C NMR spectra of these two hydroxynaphthoquinones clearly show that the label is maintained in both compounds and that an sp³ C atom (16.4 ppm) is enriched 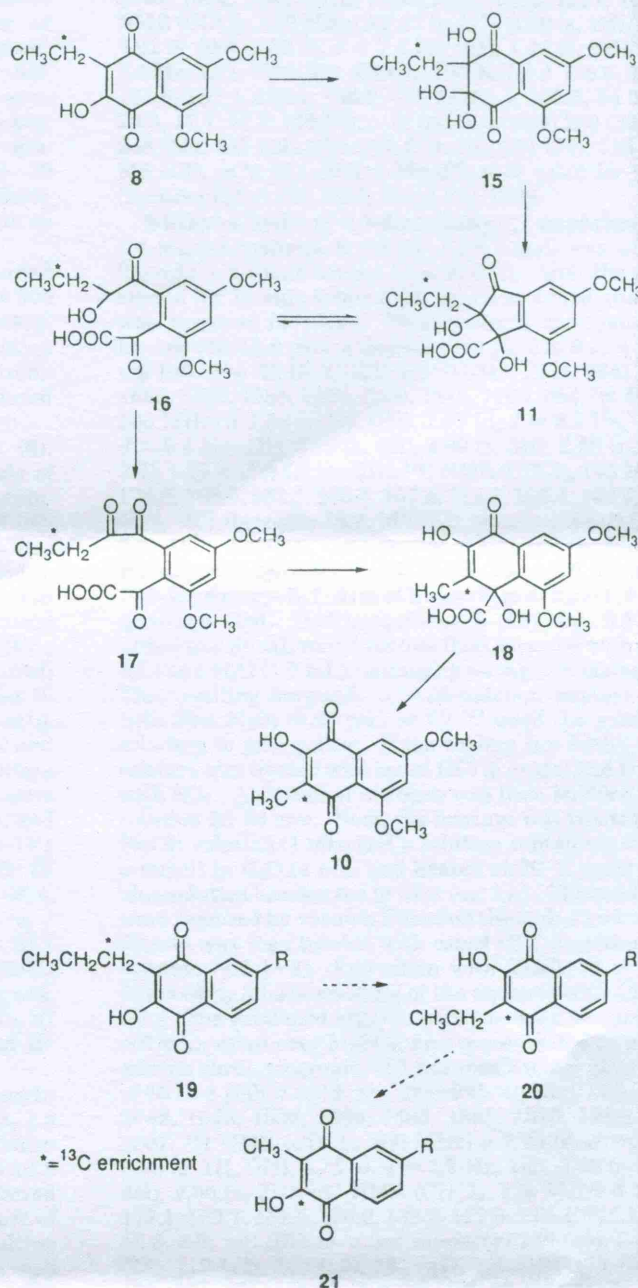in the former and an sp² C atom (122.0 ppm) in the latter. Verification of a direct bond connection between the methyl group (8.8 ppm) and the ¹³C-enriched vinyl carbon (122.0 ppm) in **10** was accomplished by a carbon–carbon correlation (INADEQUATE) experiment. In addition, when a carbon–proton long-range coupling (INAPT) experiment was performed by irradiating the methyl proton absorption, three C-atom absorptions (122, 151, and 184 ppm) were affected. Thus, the vinyl C atom absorbing at 122 ppm is directly attached to the methyl group, the carbonyl C atom (184 ppm), and the vinyl C atom (151 ppm) bearing the hydroxyl group.

Further confirmation of the mechanism was obtained by a structural analysis of an intermediate formed in the rearrangement. In a series of elegant experiments, first reported by Fieser and Fieser and later by Fieser and Bader, an intermediate in the Hooker oxidation was isolated and characterized primarily on the basis of chemical data.[2a,c] For example, when lapachol (**1**) was treated with H₂O₂/Na₂CO₃, *cis*-2-alkyl-1-oxoindan-3-carboxylic acid (**3**) was isolated and subsequently shown to rearrange to quinone **2** upon treatment with CuSO₄/NaOH. Even though the data presented in the above studies are in accord with structure **3**, the rigor of modern NMR analysis is needed. In addition, some confusion arose in 1977 when Otten and Rosazza reported that fermentation of lapachol (**1**) with *Penicillium notatum* gave a polar metabolite they claimed to be **4**, a compound

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(2) (a) Fieser, L. F.; Fieser, M. *J. Am. Chem. Soc.* **1948**, *70*, 3215. (b) Fieser, L. F.; Hartwell, J. L.; Seligman, A. M. *J. Am. Chem. Soc.* **1936**, *58*, 1223. (c) Fieser, L. F.; Bader, A. R. *J. Am. Chem. Soc.* **1951**, *73*, 681.
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(4) Enhsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *J. Org. Chem.* **1990**, *55*, 1177.
(5) For leading references concerning the synthesis of substituted cyclobutenones, see: (a) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350. (b) Gayo, L. M.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896. (c) Reed, M. W.; Pollart, D.; Perri, S. T.; Foland, L.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477. (d) Liebeskind, L. S.; Fengal, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482.
(6) For reviews concerning the ring expansion of 4-aryl, 4-alkenyl-, and 4-alkynylcyclobutenones, see: (a) Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, *5*, 273. (b) Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. (c) Liebeskind, L. S. *Tetrahedron* **1989**, *45*, 3053. (d) Moore, H. W.; Yerxa, B. R. *Advances in Strain in Organic Chemistry*; JAI Press LTD: Hampton Hill, U.K., 1994. For a review of the utility of cyclobutenones in natural product synthesis, see: Bellus, D.; Ernst, B. *Angew. Chem.* **1988**, *100*, 820.

Scheme 2

• = ^{13}C enrichment

Scheme 3

• = ^{13}C enrichment

that had previously been suggested as an undetected intermediate in the Hooker oxidation.[2a,7] This assignment, however, is questionable since the ^{1}H NMR data [δ 7.52 (m, 4H, ArH), 4.97 (t, *J* = 8.0 Hz, 1H, =CH−), 4.82 (s, 3H, OH), 2.87 to 2.13 (m, 2H, CH$_2$), 1.47 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$)] do not list an absorption for a CHOH group, and no ^{13}C NMR data were presented.

Support for an indanone structure for the intermediate in the Hooker oxidation is provided below. Treatment of 2-ethyl-3-hydroxy-5,7-dimethoxy-1,4-naphthoquinone (**9**) with H$_2$O$_2$/Na$_2$CO$_3$ gave a white crystalline solid in 76% isolated yield. ^{13}C and ^{1}H NMR spectra showed the appropriate chemical shifts and both proton and carbon counts to be in accord with structure **11** [^{1}H NMR (CD$_3$OD, 500 MHz) δ 6.78 (s, 2H), 4.90 (s, 2H, OH), 3.81 (s, 3H), 3.80 (s, 3H), 1.95 (q, *J* = 7.3 Hz, 1H), 1.54 (q, *J* = 7.3 Hz, 1H), 0.81 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (CD$_3$OD, 500 MHz) δ 204.9, 165.2, 160.4, 140.5, 140.1, 132.9, 108.0, 98.4, 88.8, 84.5, 57.2, 57.1, 30.6, 9.1]. In addition, a DEPT-90 experiment showed no absorptions in the 50–

(7) Otten, S.; Rosazza, J. P. *Appl. Environ. Microbiol.* **1978**, *35*, 554.

90 ppm region as would be expected for a compound lacking a -CHOH moiety. Furthermore, the IR spectrum shows an intense absorption at 1757 cm^{-1} which supports the existence of a carbonyl group as in an indanone moiety. Finally, the indanone intermediate gave quinone **10** in 66% when subjected to CuSO$_4$/NaOH oxidation.

In conclusion, the following points are noted: (1) synthesis of the ^{13}C-enriched hydroxynaphthoquinone **9** and its rearrangement to **10** provides data in agreement with the mechanism of the Hooker oxidation originally proposed by Fieser and Fieser, i.e. **8** → **15** → **11** → **16** → **17** → **18** (Scheme 3),[2a] (2) synthesis of **9** and its rearrangement to **10** presents a prototypical method for the regiocontrolled construction of specifically labeled quinones and related compounds, e.g., two successive oxidations starting with **19** would result in respectively **20** and then **21**.

Experimental Section

General Procedure. Commercial reagents were used without further purification. Tetrahydrofuran and diethyl ether were
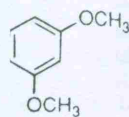
distilled from sodium/benzophenone ketyl immediately before use. Toluene was distilled from calcium hydride. All air- or water-sensitive reactions were carried out in flame-dried glassware under a positive pressure of argon or nitrogen. Air-sensitive solutions were transferred via cannula and were introduced into the reaction vessels through rubber septa. Lithium reagents were introduced via syringe. Reaction solutions were concentrated on a Buchi rotary evaporator at 15–30 mmHg. Column chromatography was performed with E. Merck silica gel (230–400 mesh) employing hexanes/ethyl acetate as eluent.

Instrumentation. Proton and carbon NMR were recorded on a General Electric Ω 500 NMR or a General Electric GN 500 NMR spectrometer. Infrared spectra were recorded on a Perkin-Elmer FT IR spectrophotometer (1600 series). Low-resolution mass spectra (MS) were recorded on a Finnigan 4000 spectrometer and high-resolution mass spectra (HRMS) were measured with a VG Analytic 7070E spectrometer.

3-*tert*-Butoxy-4-([1-^{13}C]ethylcyclobutene-1,2-dione (6). Magnesium ribbon (360 mg, 15 mmol) and a few crystals of iodide were placed in a flame-dried round bottom flask containing anhydrous Et_2O (30 mL). An ether solution (50 mL) of ^{13}C-labeled ethyl iodide (1 g, 6.4 mmol) was then added dropwise over 30 min, and the resulting reaction mixture was heated to reflux for 1 h. After cooling to 0 °C, the gray mixture was transferred via cannula to a solution of di-*tert*-butyl squarate (5) (1.8 g, 8.0 mmol, −78 °C) in dry THF (100 mL). Upon stirring for 30 min, a white solid formed and TFAA (1.5 mL, 10 mmol) was added via syringe. The reaction mixture was stirred for 10 min, and then the reaction was quenched with H_2O (10 mL). The crude mixture was then extracted with Et_2O (200 mL) and H_2O (30 mL) followed by back-extraction of the aqueous portion with Et_2O (2 × 100 mL). The combined organic portions were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography (3:1 hexanes/EtOAc) gave 820 mg (70%) of **6** as a pale yellow oil: IR (CDCl$_3$, cm^{-1}) 2986, 2945, 1791, 1748, 1575, 1558, 1464, 1374, 1307, 1153, 1077, 985; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 2.75 (q, J = 7.5 Hz, 1H), 2.50 (q, J = 7.5 Hz, 1H) (C–H coupling = 29.7 Hz), 1.61 (s, 9H), 1.27 (dt, J = 7.5, 4.7 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 200.3, 197.3, 193.1, 187.5, 88.5, 29.3, 19.1 (largest), 10.6; MS (EI), *m/z* (rel intensity) 143 (2), 100 (29), 99 (100), 87 (16), 83 (3); MS (CI), *m/z* 184 (MH$^+$); HRMS, *m/z* calcd for $C_9{}^{13}CH_{14}O_3$ 183.0976, found 184.1062 (MH$^+$).

3-*tert*-Butoxy-2-ethyl-4-hydroxy-4-(2,4-dimethoxyphenyl)cyclobuten-2-one (7). *n*-Butyllithium (1.6 M in hexanes, 1.5 mL, 2.4 mmol) was slowly added to a solution of 2,4-dimethoxybromobenzene (0.38 mL, 2.6 mmol, −78 °C) in dry THF (50 mL). After stirring for 30 min, the reaction mixture was transferred via cannula to a solution of **6** (386 mg, 2.1 mmol; 9:1 mixture of the ^{12}C isomer and **6**) in dry THF (40 mL). The resulting mixture was stirred for 30 min, and then the reaction was quenched with a 5% NH_4Cl solution (3 mL). The reaction solution was extracted with Et_2O (100 mL) and H_2O (20 mL). The aqueous portion was back-extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography (3:1 hexanes/EtOAc) gave 352 mg (52%) of **7** as a thick yellow oil: IR (neat, cm^{-1}) 3372, 2977, 2398, 2839, 1748, 1614, 1504, 1463, 1371, 1309, 1209, 1159, 1032, 828; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.18 (d, J = 8.2 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 6.43 (s, 1H), 4.92 (s, 1H, OH), 3.83 (s, 3H), 3.76 (s, 3H), 2.1 (q, J = 7.4 Hz, 2H), 1.44 (s, 9H), 1.13 (t, J = 7.4 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 191.9, 177.4, 160.4, 158.2, 130.2, 128.2, 117.8, 104.6, 99.4, 93.4, 83.4, 55.8, 54.9, 28.9, 16.5 (largest), 11.0; MS (EI) *m/z* (rel intensity) 264 (17), 247 (32), 246 (100), 231 (10), 178 (47), 175 (16), 165 (97), 149 (24), 121 (17), 97 (17), 56 (78), 55 (34); MS(CI) *m/z* 321 (MH$^+$), 265, 247; HRMS, *m/z* calcd for $C_{17}{}^{13}CH_{24}O_5$ 321.1657, found 322.1815 (MH$^+$).

3-*tert*-Butoxy-2-ethyl-5,7-dimethoxy-1,4-naphthoquinone (8). A toluene solution (50 mL) of cyclobutenone **7** (180 mg, 0.56 mmol) was placed in a flame-dried round bottom flask and heated to reflux for 1 h. Upon cooling to ambient temperature, Ag_2O (200 mg) and K_2CO_3 (140 mg, 0.95 mmol) were added. After 2 h of stirring, the solvent was removed *in vacuo*. Flash column chromatography (3:1 hexanes/EtOAc) gave 164 mg (92%) of **8** as a yellow solid: mp 91–92 °C; IR (CDCl$_3$, cm^{-1}) 2977,

2940, 1664, 1592, 1570, 1460, 1368, 1352, 1211, 1151, 982; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.22 (s, 1H), 6.66 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 2.56 (q, J = 7.4 Hz, 2H), 1.46 (s, 9H), 1.09 (t, J = 7.4 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 185.6, 180.9, 164.1, 161.3, 157.4, 138.1, 136.2, 113.7, 103.4, 102.5, 84.0, 56.2, 55.6, 29.3, 17.7, 12.8; MS(EI), *m/z* (rel intensity) 263 (33), 262 (100), 248 (15), 247 (49), 220 (14), 219 (45), 151 (14), 115 (3), 106 (6); MS (CI), *m/z* 321 (MH$^+$); HRMS, *m/z* calcd for $C_{17}{}^{13}CH_{24}O_5$ (reduced form) 321.1657, found 321.1629.

2-Ethyl-3-hydroxy-5,7-dimethoxy-1,4-naphthoquinone (9). 1,4-Naphthoquinone **8** (90 mg, 0.28 mmol) was added to TFA (30 mL) in a round bottom flask at 0 °C. After the solution was stirred for 15 min, toluene (30 mL) was added and the solvent was removed *in vacuo*. Flash column chromatography (1:1 hexanes/EtOAc) gave a quantitative yield of **9** as a yellow solid: mp 193–194 °C; IR (CDCl$_3$, cm^{-1}) 3348, 2974, 2941, 1648, 1596, 1566, 1460, 1385, 1357, 1260, 1219, 1160, 984; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.88 (s, 1H, OH), 7.37 (d, J = 2.4 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 2.58 (q, J = 7.7 Hz, 2H), 1.15 (t, J = 7.7 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 184.3, 178.5, 166.5, 162.5, 153.3, 137.5, 112.1, 106.1, 104.4, 102.2, 56.2, 55.8, 16.4 (largest); 12.4; MS (EI) *m/z* (rel intensity) 263 (31), 262 (100), 220 (20), 219 (73), 165 (13), 151 (23), 106 (13), 77 (8); HRMS, *m/z* calcd for $C_{13}{}^{13}CH_{14}O_5$ 263.0875, found 263.0829.

2-Hydroxy-5,7-dimethoxy-3-methyl-1,4-naphthoquinone (10). Hydroxyquinone **9** (131 mg, 0.5 mmol) was added to a 50 mL round bottom flask charged with dioxane (1.5 mL) and H_2O (1.5 mL) containing 64 mg (0.6 mmol) of Na_2CO_3. The resulting burgundy colored reaction mixture was heated with 30% H_2O_2 (0.20 mL) at 60 °C until the solution became colorless to pale yellow. Upon cooling (ice bath), the reaction mixture was treated with concd HCl (5 drops) and H_2O saturated with SO_2. A stream of nitrogen was then bubbled through the solution for 30 min. Next, the mixture was treated with a 25% NaOH solution (1 mL) and a solution containing $CuSO_4$ (0.5 g, 3 mmol) in H_2O (4 mL) and heated at 70 °C until the starting blue solution became red in color (ca. 1 h). The solid components were removed by vacuum filtration through a pad of Celite. The filtrate was then treated with concd HCl, resulting in a yellow solution (pH 1–2). Extraction with CHCl$_3$ (3 × 50 mL) was followed by a back-washing of the aqueous with CHCl$_3$ (2 × 25 mL). The combined organic portions were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography (3:1 hexanes/EtOAc) gave 89 mg (72%) of **10** as a yellow solid: mp 223–225 °C; IR (CDCl$_3$, cm^{-1}) 3433, 2942, 1645, 1596, 1566, 1465, 1389, 1320, 1289, 1208, 1159, 1067; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.25 (d, J = 1.7 Hz, 1H), 6.99 (s, 1H, OH), 6.75 (d, J = 1.7 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 183.8, 181.3, 177.1, 163.7, 161.5, 150.9, 133.0, 122.0, 114.2, 105.1, 103.0, 56.3, 55.8, 8.8; MS (EI) *m/z* (rel intensity) 249 (40), 248 (100), 220 (28), 219 (49), 205 (19), 191 (27), 190 (13), 177 (29), 147 (22), 135 (26), 106 (14), 91 (10), 83 (13), 63 (16); HRMS, *m/z* calcd for $C_{12}{}^{13}CH_{12}O_5$ 249.0718, found 249.0733.

2-Ethyl-4,6-dimethoxy-1-oxoindan-3-carboxylic acid (11). Hydroxyquinone **9** (262 mg, 1.0 mmol) was added to a 50 mL round bottom flask charged with dioxane (5 mL) and H_2O (5 mL) containing Na_2CO_3 (120 mg, 1.13 mmol). The resulting burgundy reaction mixture was next treated with 30% H_2O_2 (0.20 mL) and heated at 70 °C until the solution became a pale orange (1.5 h). The mixture was then cooled on an ice bath and treated with 36% HCl (5 drops) followed by H_2O saturated with SO_2. Remaining SO_2 was purged with a gentle stream of N_2 for 0.5 h. Extraction with EtOAc (3 × 30 mL) and combination of the organic portions was followed by a brine wash and drying ($MgSO_4$). Concentration afforded a yellow oil which gave 224 mg (76%) of **11** as white platelets from CHCl$_3$: mp 148–150 °C; IR (KBr, cm^{-1}) 3468, 3274, 2980, 1757, 1704, 1611, 1500, 1463, 1408, 1357, 1314; ^{1}H NMR (CD$_3$OD, 500 MHz) δ 6.78 (s, 2H), 4.90 (s, 2H, OH), 3.81 (s, 3H), 3.80 (s, 3H), 1.95 (q, J = 7.3 Hz, 1H), 1.54 (q, J = 7.3 Hz, 1H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (CD$_3$OD, 125 MHz) δ 204.9, 165.2, 160.4, 140.5, 140.1, 132.9, 108.0, 98.4, 88.8, 84.5, 57.2, 57.1, 30.6, 9.1; MS (CI), *m/z* (rel intensity) 297 (2), 279 (25), 235 (39), 210 (10), 209 (100), HRMS, *m/z* calcd for $C_{14}H_{16}O_7$ 296.0896, found 297.1011 (MH$^+$).

2-Hydroxy-3-methyl-5,7-dimethoxy-1,4-naphthoquinone (10) from Indanone 11. Indanone **11** (87 mg, 0.29 mmol) was suspended in H_2O (2 mL) and treated with a 25%

NaOH solution (0.80 mL) to afford an homogeneous pale yellow solution. Addition of an aqueous solution (1.5 mL of H_2O) of $CuSO_4$ (277 mg, 1.7 mmol) gave a blue reaction mixture which was heated (10 min) to 70 °C. The resulting burgundy/brown suspension was worked up as described above to give 48 mg (66%) of **10** as orange needles from MeOH: mp 225–226 °C; IR (thin film, cm^{-1}) 3411, 2968, 2921, 1659, 1641, 1629, 1587, 1557, 1455, 1377, 1312, 1198, 1156, 1054; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.263 (s, overlapping with CHCl$_3$, 1H), 6.96 (s, 1H, OH), 6.75 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 184.0, 181.5, 163.8, 161.7, 151.1, 133.2, 122.1, 114.3, 105.4, 103.2, 56.5, 56.0, 8.9; HRMS (EI), m/z calcd for $C_{13}H_{12}O_5$ 248.0685, found 248.0686.

3-*tert*-Butoxy-2-methyl-4-hydroxy-4-(3,5-dimethoxyphenyl)cyclobuten-2-one (13). To a solution (−78 °C) of 3,5-dimethoxybromobenzene (427 mg, 1.97 mmol) in dry THF (15 mL) was slowly added n-BuLi (1.6 M in hexanes, 1.3 mL, 2.15 mmol) via syringe. After 30 min of stirring, the cold solution was transferred via cannula to a THF (15 mL) solution of 3-*tert*-butoxy-4-methylcyclobutene-1,2-dione (300 mg, 1.79 mmol), prepared according to the published procedure.[4] After being stirred for 30 min, the reaction mixture was worked up according to **7**. Flash column chromatography (7:3 hexanes/EtOAc) gave 175 mg (32%) of **13** as a thick yellow oil: IR (neat, cm^{-1}) 3363, 2980, 2933, 2837, 1748, 1593, 1455, 1425, 1389, 1342, 1198, 1150, 1060, 1030, 911; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 6.63 (dd, J = 1 Hz, 2H), 6.37 (d, J = 1 Hz, 1H), 3.758 (s, 3H), 3.756 (s, 3H), 1.81 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 191.5, 179.3, 160.8, 139.9, 124.4, 103.9, 100.1, 92.9, 84.3, 55.3, 28.3, 8.4; HRMS (EI), m/z calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1473.

2-*tert*-Butoxy-5,7-dimethoxy-3-methyl-1,4-naphthoquinone (14). Cyclobutenone **13** (148 mg, 0.48 mmol) was dissolved in p-xylene (9 mL) and heated to reflux under N_2 for 15 min. Upon cooling to ambient temperature, Ag_2O (224 mg, 0.97 mmol) and K_2CO_3 (134 mg, 0.97 mmol) were added and the reaction mixture was stirred for 20 min. Filtration through a pad of Celite afforded a bright yellow filtrate. Removal of the volatiles gave a dark yellow oil which crystallized from hexanes/EtOAc (3:2) as bright orange platelets weighing 115 mg (78%): mp 129–130 °C; IR (thin film, cm^{-1}) 2977, 2931, 2841, 1671, 1643, 1615, 1592, 1564, 1457, 1423, 1372, 1333, 1294, 1156, 1102, 965; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.21 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 2.07 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 184.3, 182.8, 164.0, 161.2, 154.2, 139.0, 135.4, 114.3, 103.9, 102.9, 83.7, 56.2, 55.6, 29.2, 11.2; HRMS (CI), m/z calcd for $C_{17}H_{20}O_5$ 304.1311, found 307.1545 (MH$^+$, reduced form calcd for 306.1467).

2-Hydroxy-5,7-dimethoxy-3-methyl-1,4-naphthoquinone (10) from 14. 1,4-Naphthoquinone **14** (115 mg, 0.38mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with TFA (1 mL). The resulting deep purple solution was stirred for 5 min prior to concentration to an orange solid, which gave 71 mg (75%) of bright orange needles from methanol. All data are in accord with the same hydroxyquinone synthesized by the alternate route.

Supplementary Material Available: Copies of ^{13}C NMR spectra of **6** (and ^{1}H NMR), **7–11**, and **13** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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