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Correspondence

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R. B. WOODWARD COPE AWARD LECTURE
CHICAGO, AUGUST 28, 1973

SLIDE 1

Arthur Cope[1] and I both worked in Cambridge for many years. Although his activities were carried on at M.I.T and mine at Harvard, our paths crossed frequently, and it was my great privilege to be counted among his friends. Consequently, I think I may be allowed to say a few words which express my very personal view of the man whose memory we are all gathered here to honour.

First

Arthur Cope was a gentleman. He was unfailingly kind and courteous. Firm and persuasive in his views, he was at once soft-spoken and well-spoken, always fair and balanced. He looked for, and found, the best in those with whom he was associated, as friends, colleagues or co-workers.

Second

Arthur Cope was an outstanding scientist. His work was characterised by boldness and originality in concept, and by scrupulous adherence to the highest experimental standards in execution.

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[1] Arthur Clay Cope
b. 27 June 1909
d. 4 June 1966

> Of his many brilliant contributions, I shall select one for special comment since it seems particularly appropriate to this occasion: Arthur Cope first established himself, internationally, as a major figure in our science, through his beautiful series of studies on what has come to be known as the Cope Rearrangement——an important reaction which we now recognize as falling within the generalized category of symmetry-allowed [3,3] sigmatropic changes!

- In the light of these brief remarks, you will certainly appreciate that I feel it a very particular honour and a very special privilege to stand here before you, as the recipient, with Roald Hoffmann, of the first Arthur C. Cope Award.

- But every privilege carries with it some kind of responsibility, and I have, here, at this moment, a responsibility which I cannot but regard as a heavy one——that of presenting to all of you a lecture, appropriate to the occasion, and, it may be hoped, of some general interest to an audience among whose members there must certainly be a wide diversity in background.

WHAT TO DO?

- The Principle of Conservation of Orbital Symmetry——for whose enunciation Professor Hoffmann and I are being honoured here today——powerful though it be, can be very simply stated, and almost as easily explicated. Those things Professor Hoffmann and I have done, on numerous occasions, in lectures and in writing[2]; AND to be entirely candid, neither Professor Hoffmann nor I any longer find it à propos to expound principles which have already, in a spectacularly short time, become an integral, indispensable and powerful part of the basic theoretical structure of organic chemistry. Let me not be misunderstood here: for my part, at least, I still find it most thrilling to re-live those marvelous moments of discovery and personal enlightenment. But, to expound the details in public has become, at best, supererogatory.

SO, there is one direction in which I could not foresee a solution to the problem of discharging my responsibilities here this afternoon. Another possibility which I considered was that I might review, from one or another among a number of points of view, some of the consequences of our work. To do that completely, in a lecture, would be a mammoth—indeed an impossible task—since literally thousands of publications during the last eight years describe investigations which have at the very least been influenced by, if indeed not directly stimulated by our work. AND I may say, parenthetically, that I feel on fairly safe ground in hazarding the surmise that some of the loveliest results were discovered in direct response to the challenge, deliberately hurled, in our definitive paper, under the heading VIOLATIONS: There are none!

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[2] Our definitive paper, setting forth our views *in extenso*, first published simultaneously in German and English in *Angewandte Chemie* [in 1969], has been reissued in book form in German, English, Japanese, Russian, Italian, Spanish, Czech, and Chinese editions.

SO, A complete review was obviously out of the question. Could one pick and choose among the plethora of possibilities? I might describe the derivative investigations which we have ourselves carried out in Cambridge, but these represent—and it could not be otherwise—only the tiniest fraction of what has been done, and they are not of special significance.

Could I describe the number and kinds of new reactions which have been predicted and found, the old ones which have been re-interpreted or understood for the first time, the applications to this or that special field? OR, could I select, from the huge volumes of available material, particular examples which to me personally seemed especially beautiful, or particularly significant? On reflection, it seemed to my mind that to choose the former course would be in some measure self-serving, and the latter, invidious.

WELL, THEN, here I stand with the problem still before me. WHAT TO SAY? And now, the solution. I present it with considerable diffidence, since what I am about to describe is highly personal, idiosyncratic, and very far removed from the kind of lecture with which I am familiar!!

FOR almost 50 years, now, I have been involved in an affair with chemistry. It has been throughout—and still is—a richly rewarding involvement, with numerous episodes of high drama and intense engagement, with the joys of enlightenment and achievement, with the special pleasures which come from the perception of order and beauty in Nature—and with much humour. In the relatively recent past, with Professor Hoffmann, I have had the extreme good fortune—such as is given to few individuals—to participate in a major fundamental contribution to the basic theoretical fabric of our science; that is the judgement of your awards committee, and of the chemical community as a whole; and I should be less than candid, were I to say otherwise than that I concur.

NOW, we may pose this question: have there been factors in my personal chemical history which played a significant role in my ultimate involvement in the enunciation of the Principle of Conservation of Orbital Symmetry?

At one extreme, one might conclude that each of many of my chemical experiences was a step in a logical progression leading inexorably to the observed phenomenon. At the other, one might well say that such phenomena are essentially bolts from the blue, without history of antecedents. I, personally, am disinclined to accept either of those conclusions. Indeed, I feel that we are here penetrating into almost unknown territory, and that one draws any conclusion only at great peril of being very wide off the mark. Nevertheless, I hope that you may find it interesting to hear certain historical facts, from which you—or those who follow us—may be tempted to your—or their—own deductions.

AND, if these facts are indeed without special significance in the context in which I am placing them, I may at least dare to hope that some of them may simply engage your interest in their own right.

2nd SLIDE

Archibald Scott Couper[3]. This may seem a strange way to start our excursion, especially since at first blush, it may seem to settle the initial question I have put in favour of the no history/no antecedents position. In 1858, Archibald Scott Couper was a 27-year-old Scotsman, studying chemistry in the laboratory of Adolphe Wurtz in Paris. He had toyed with philosophy and architecture(!) before settling down to chemical studies. Having pursued the latter for, I believe, something on the order of little more than a year, he prepared a paper entitled On a New Chemical Theory[4], which, after some delay, was published in the Comptes rendus of the French Academy of Sciences. In that literally astonishing paper, one may see presented, for the first time, STRUCTURAL FORMULAE, identical with those we use today—and these are of course the most fundamental theoretical tools of organic chemistry.(1)

NOW, August Kekulé is rightly given credit for his recognition of and insistence upon the quadrivalency of carbon, and for his brilliant later proposal of the structure of benzene. But he was not, as many believe, the father of structural chemistry.(2) Indeed, in his famous 1858 paper "On the Constitution and Metamorphoses of chemical Compounds and the Chemical Nature of Carbon"[5], he makes very clear his belief at that time that chemical substances adopted diverse

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[3] Couper: b. 31 March 1831
Townhead, Kirkintilloch
Dumbartonshire

[4] C.r. 46, 1157-60 (1858) Séance du lundi, 14 juin 1858.

[5] Liebig's Annalen der Chemie 106, 129-59 (1858).

structures in response to the influence of attacking reagents; and for many years thereafter he continued to use, in his own papers, the cumbersome and often obscure "TYPE" formulae of GERHARDT(3) and LAURENT.(4) He was, in truth, too much under the influence of the theoretical and physical chemists of the time, who were inordinately opposed to the idea of fixed chemical structure—so much so that, until 1886, the infant Berichte d. ~~d~~Deutschen ~~c~~Chemischen Gesellschaft, born in 1868, would only print structural formulae using dotted-and-dashed lines; the use of solid lines to represent nearest-neighbour relationships would have imputed too much reality to an hypothesis which leading theorists of the day simply would not accept.

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SO, Archibald Scott Couper deserves recognition for the introduction of structural formulae as we know them. And another scientist, ALEXANDER BUTLEROW, working in the relatively obscure provincial town of KAZAN, in Imperial Russia, was the foremost protagonist of the basic principle that organic compounds possess fixed structures.(5)

NOW, Couper has received little credit for his brilliant contribution, no doubt largely because not long after his paper was published, he returned to his mother's home in Sctoland, went mad, and played no further role in chemistry.

OF WHAT RELEVANCE is this history to the story of my personal scientific saga? I will admit freely that in some measure, I have just arbitrarily seized this occasion to right what I consider a grievous historical injustice. BUT, there are connections. We can dismiss the obvious ones briefly and in a jocular vein. It is true that like Couper, I bear Scottish blood. But I left my mother's home early, never to return. Let there be no unduly adverse implications here. Glad as I was to escape the maternal wing, I know that my mother was a powerful and very helpful positive force in my development. To conclude this category, I did not go mad—or if I did, at least I think I have been able, relatively successfully, to conceal the more obviously anti-social manifestations of the condition.

TO RETURN to a more serious vein, let me point out that what I have described are the origins of the structural theory of static molecules. Now let us examine a familiar and succinct statement of the operational imperatives which have been deduced from the Principles of Conservation of Orbital Symmetry.

<u>3rd SLIDE</u>

Note that this is a purely <u>geometric</u> statement, that is, in a chemical context, a <u>structural</u> statement. AND the point I want to make is that in a broad sense, the ideas which Professor Hoffmann and I have developed represent an extension to dynamic, reacting systems, of those basic structural concepts which have served chemists so well in dealing with static systems.

For the present, let us now leave this topic with the thought in mind that from the first awakening of my interest in chemistry, I have found its history absorbing, and have been particularly entranced by the concept of <u>bonding</u> in the most general sense.

<u>4th SLIDE</u>

NOW WE BEGIN! In that connection, I have been told that Dr. Freeman(6) has been concerned that I might go on for so long that we should have to have a Spanish dinner, if indeed, any at all.(7) When I first considered a lecture in this vein, it seemed to me that it would certainly be, mercifully, a very short one. BUT, as usual, when I really began to think about it, I realized that in fact a grave situation might develop. However, if alone out of consideration for my colleague Roald Hoffmann who has his own piece to say, I shall make a valiant effort to limit the discourse to a respectable number of milli-Woodwards. No doubt, many of you have heard of the unit of lecture time established by the distinguished theoretical chemist Edgar Heilbronner.(8) His procedure was not unlike that of using the spread of the King's arm as a unit of length—the yard; Heilbronner used as a standard the amount of time I devoted to a lecture at Karlsruhe—on orbital symmetry, beginning at 8 p.m.—five hours and twenty minutes. Thus, the usual 50-minute exposition favoured by most professors constitutes a lecture of ca. 156 milli-Woodwards.

- SO, let us leap forward about 10 years: Now we see the young Woodward at the bench in his modest home laboratory. On the wall before him, boldly emblazoned in chalk, is a symbol.

5th SLIDE

- There it is, and I shall discuss it after a brief excursion about the bench. From time to time I have heard about myself the legend that, as a boy, I had performed all of the experiments in Ludwig Gattermann's classic manual "The Practical Methods of Organic Chemistry"—a famous book which played a major role in the training of generations of young German students in experimental organic chemistry.(9) About that legend, I can say now that—to the best of my recollection at this point in time (!)—it is substantially true. I had found, and purchased, in one of the delightful second-hand bookshops which then existed in Cornhill in old Boston, a copy of an English translation of, let us say, the 11th German edition—I really don't remember precisely which it was—of that superb work; AND I had been able to mobilize the materials and resources which enabled me to carry out at least a major portion of the experiments described therein.

BUT, of perhaps more relevance to this narrative, while I was enjoying the delights of experimentation, I was also reading intensively. I was fortunate in having at hand an excellent public library—when I say at hand, I mean in this instance at the distance of a 3½ mile walk, which was considered nothing in those days—even by me!—though my extensive early experience in that connection may have something to do with my present loathing for ambulatory exercise. In any event, I found there a wealth of material, which I devoured avidly. I can recall such books as those by J. B. Cohen,(10) A. Bernthsen,(11) and R. Anschütz(12) and more especially, F. Henrich's Theories of Organic Chemistry.(13) Incidentally, [A. W.] Stewart,(14) who wrote about chemistry in a particularly fascinating way, also was the author of engaging mystery novels under the nom de plume of J. J. Connington; that fact may well have had something to do with the generation of the passion—which I still retain—for the latter literary genre.

IN my early chemical reading, I was equally captivated by the extraordinary wealth of factual material, and by the theoretical discussions—though of course it is the latter which are of the greater interest in the present context.

NOW, recall that I am speaking of the second half of the 1920's, before the development of the "English school"(15) of theoretical thought; it will be remembered that Robert Robinson's brilliant and prescient lectures before the Institute of Chemistry of Great Britain and Ireland, presenting an "Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions" were delivered in 1932.(16)

Thus, we are speaking of a time antedating the "English school," and long before the solvolytic wave—some would unfairly say, the solvolytic plaque—swept over a large part of what Charles de Gaulle would have called the Anglo-Saxon chemical community.(17)

SO, the theoretical organic chemical discussion of that period tended to be preoccupied with 3 things:

1st The structure of benzene, in relation to its extraordinary "aromatic" properties
2nd Thiele's theory of partial valency(18)
3rd Electrical effects, as exemplified by the concept of induced alternating polarities in carbon chains.(19)

CONSEQUENTLY, from the very outset of my affair with chemistry, I was deeply steeped in these matters. I will admit that the third rather left me cold, but the first two I found utterly fascinating. NOTE, that they are both concerned intimately with the nature of chemical bonding.

NOW, from my reading, it appeared that almost everyone who had given the matter any thought had his own benzene formula—and I didn't see why I shouldn't have mine—hence the diagram shown on the slide. In the present context, it is interesting in several ways. I think I may be forgiven for not having recognized that it was simply a two-dimensional representation of Ladenburg's prism structure;(20)

6th SLIDE

forgiven, especially if one contemplates the literally astonishing length of time it took the chemical community in general to climb out of its self-imposed two-dimensional prison—and that in the face of the fact that the entire necessary—indeed it should have been compelling—theoretical framework was securely at hand with the proclamation of the tetrahedral carbon atom by van't Hoff just a hundred years ago,(21) and more than 50 years before the time of which I am speaking. Nonetheless, during that very same later time, so eminent a chemist as J. B. Conant was proposing structures such as that shown on the

7th SLIDE

in connection with his brilliant work on chlorophyll.(22) AND indeed, it was not until approximately 1950, with the advent of conformational analysis, through the agency of BARTON,(23) HASSEL(24) and PRELOG,(25) that structural chemistry really at long last took up its proper place in three dimensions.

- NOW, to return to my early personal structure for benzene. We now recognize it not only as Ladenburg's expression for benzene, but also as the actual structure of an entirely different substance—prismane. And it is downright whimsical to call to mind that this highly energy-rich compound—its derivatives are actually explosive—owes its existablility to orbital symmetry factors: its ground state cannot be transformed into the incomparably more stable ground state benzene with conservation of orbital symmetry, and consequently there is a high energy barrier which opposes the transformation.

- I also find it warmly amusing that although various substituted prismanes were first synthesized a few years ago, the first synthesis of the simple hydrocarbon, prismane itself, was announced only very recently, by a former student of mine, Professor Katz[6], at Columbia.(26)(27) During those long-ago days, I spent much time attempting to dream up syntheses of my structure—none of which, alas, were of a character in which I could have even the slightest confidence!

NOW, while I had my own benzene formula, I was not so enamoured of it that I ceased to give attention to those of others. In particular, my imagination was engaged by the relationship between the two conceptually clearly differentiable Kekulé structures:

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[6] T. J. Katz and N. Acton, J. Amer. Chem. Soc. 95, 2738-9 (1973).

In particular, I recognized that if one were to assume the separate existence—however fleeting—of these entities, the conversion of the one into the other might be regarded as a chemical reaction, in fact an addition reaction of an olefin to a diene. Thus was born—in my mind—one of the first chemical reactions of my own design; AND thereby hangs a remarkable tale. I have alluded to my extensive reading in books on chemistry.

Until the point I have now reached in this narrative, I was only dimly aware, through allusions in those books, of the existence of the original journal literature; I now decided that this matter deserved exploration, and I took the forthright step of writing to the German consul-general at Boston—one Baron von Tippelskirch [really!](28)—intimating that I had heard that chemical research was actively pursued in Germany, and that its fruits were described in publications which appeared at regular intervals. Could I enlist his kindness in helping me to procure samples of such publications? The good Baron replied promptly and efficiently in a favourable sense, and indeed, in due course there arrived at my home copies of separate issues—one each—of the Berichte der deutschen chemischen Gesellschaft, the Journal für praktische Chemie, and Liebig's Annalen der Chemie.

IMAGINE my excitement at receiving these treasures! Imaging further my feelings, when I tell you that the issue of the Annalen was Nr. 1 for 1928; and that the concluding paper was one entitled "Synthesen in der hydroaromatischen Reihe," by Otto Diels and Kurt

Alder[7](29)—nothing other, in short, than the now classic paper announcing the discovery of the Diels-Alder reaction—or should I say, *here*, the prototype of the symmetry-allowed [π + s π - s] cycloaddition reaction.

I must emphasize that my reaction to this event was one of the purest pleasure. An idea that I had was one which could be reduced to reality! That seemed to me to augur well for ideas I might have in the future. My pleasure was unalloyed with any dismay that the reduction to practice had been accomplished by others; indeed, to the extent that such factors entered my mind at all, I felt in a sense relieved of a responsibility of which at that time I had become only dimly aware—that of reducing one's own original ideas to practice through experiment.

SO, that is the story of the beginning of a lifetime preoccupation with the Diels-Alder Reaction. I shall now summarize the sequel, I hope briefly. I made use of the reaction in a marginally commendable approach to the synthesis of oestrone during the middle 30's in the course of my work for the Ph.D. degree—I have always rather tended to view my Ph.D. as the first of my honorary degrees. Much later, during the 1950's, I used the reaction, with much greater effect, in syntheses of cholesterol, cortisone and reserpine.(30) AND, over a period of 20 years, beginning in 1939, I pursued a number of investigations explicitly concerned with the detailed course and mechanism of Diels-Alder reactions—those of *furanes* and *fulvenes* with Harold Baer(31) and Virginia Williams,(32) *pyrenes* with

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[7] O. Diels and K. Alder, *Ann.* *460* 98-122 (1928).

Bernard Landau,(33) and cyclopentadienes with Thomas Katz—the results of some of which have actually been published! Of the latter, perhaps the first—a short communication by myself in 1942—and the last—the paper with Katz in 1959,(26) are the most significant in the present context. The former at least exemplifies my willingness to consider bonding in the broadest sense; in it I proposed a generalized two-electron bond between two large π-electron arrays; Robert Mulliken(34) has told me that it had at least a small influence on his impressive contributions to the theory of charge-transfer phenomena. In the paper with Katz, there stands perhaps the first statement—at least, I believe, the clearest early statement, of the possibility—now generally accepted—that in concerted processes, the rate of growth of bond order may differ from one bond to another of those being formed.

IN the remarks just made, I have, perforce, violated the chronology of my narrative. Let us go back to the mid-30's. During that period, as compared with the late 20's, I probably spent relatively more time doing chemistry—as you all know, a demanding and exacting task—as contrasted with thinking about chemistry—an even more demanding and exacting task. Further I had finally agreed with authority, reluctantly, that I must secure my professional credentials—and once committed, I applied myself to awful necessity with a vengeance which cut significantly the time I could devote to personal interests. I should mention that, that exterior commitment did not include courses in organic chemistry—I have never really attended any formal course of lectures in organic chemistry—but it did include many ancillary and totally unrelated disciplines, of the sort that educators feel must be thrust down the throats of aspirant scholars; AND I am not willing to say that I believe they are entirely wrong, provided that they do not go too far.

One of those excursions provides a point of departure for a short personal digression. At that time, at M.I.T., it was necessary to submit a minor as well as a major subject. I selected mathematics, but, in this instance, for the tactical reason that the entire requirement could be met by examination—that meant it required no work or more important, its equivalent, no time. None the less, the fact is that I have always been very fond of mathematics—for one short period, I even toyed with the possibility of abandoning chemistry in its favour. I enjoyed immensely both its conceptual and formal beauties, and the precision and elegance of its relationships and transformations. Why the did I not succumb to its charms? For two reasons, I believe.

FIRST, because by and large, mathematics lacks the sensuous elements which play so large a role in my attraction to chemistry. I love crystals, the beauty of their form—and their formation; liquids, dormant, distilling, sloshing!; the fumes; the odors—good and bad; the rainbow of colours; the gleaming vessels, of every size, shape and purpose. Much as I might think about chemistry, it would not exist for me without these physical, visual, tangible, sensuous things.

SECOND, while in mathematics, presumably one's imagination may run riot without limit, in chemistry, one's ideas, however beautiful, logical, elegant, imaginative they may be in their own right, are simply without value unless they are actually applicable to the one physical environment we have—in short, they are only good if they work! I personally very much enjoy the very special challenge which this physical restraint on fantasy presents.

<u>I do not want to leave</u> the mid-30's without presenting some reflections on the general state of organic chemistry, as I saw it at that time. That was still an age of what seemed to me extreme specialization. There were alkaloid chemists, sugar chemists, hydrocarbon chemists, terpene chemists, metal—organic, heterocyclic, sulfur, etc., and rarely did the protagonists of one of these fields venture into another. This outlook—perhaps understandable in the light of the difficulty—well-known to all of us, now as then, attendant upon getting anything done in any field—none the less seemed to me wrong. I felt that the same body of chemical principle must form the basis for actual operations in <u>any</u> area, and that the barriers which existed were arbitrary and unnecessarily self-imposed. To some extent this specialization continues even now, and there <u>can</u> be justification for it. But by and large I do not commend it. I well remember the story of a former student of mine, who, after taking his degree in Cambridge, not all that long since, proceeded to a post-doctoral fellowship at another of the prominent universities of the Western world. During his stay, he happened at one time to be engaged in conversation with a fellow-worker, who revealed that he was much frustrated in his work; his task involved the transformation of a saturated alcohol into a corresponding α,ß-unsaturated ketone, and he simply had been unable to make any inroads on the problem. "Ok," said my student, "kappageritol has been transformed into bigboobsenone through a simple three-step sequence which seems to be just what you need."

"Honest to God," said his companion, "has that really been done?" "Indeed," replied the ex-Harvard inmate, "and I believe that there are actually several other triterpene alcohols that have been modified in a very similar way." "Ok," replied his colleague, obviously relieved. "Triterpenes—I wouldn't have been expected to know about that. I'm in diterpenes." TOO MUCH!(35)

My own experience has been that it has been almost impossible to read about any facet of chemistry without discerning some degree of relevance or applicability to almost any other area.

NOW, another point about the general outlook of the mid-30's. With rare exceptions, the organic chemists of the day—even the foremost amongst them—were still, as had been their predecessors for generations, actually proud of their ignorance of theory. Speculation was a pejorative word, to be used only contemptuously; woe betide any organic chemist who would try to introduce such nonsense into a discussion, who would try to introduce such nonsense into a discussion, let alone a publication! One is reminded of the Kolbe of a much earlier time, who, suffused with the rich pageantry of organic chemical fact, dripping with operational expertise, simply would not accept the possibility that a simple structural theory—which could be used by any callow student—could be applied to the physical environment he knew so well.(36) In human terms, this attitude may be understandable, given the intricate imperatives of experimental work in organic chemistry, given the fabulous feats which had been achieved without theory, and given also the fact that when, rarely, organic chemists approached theorists for help, they got precious little for their pains.

NEVERTHELESS, I personally—though I would bow to no-one in my respect for facts—felt that these attitudes were all wrong. I knew in my heart and mind that theory—and yes, hypothesis and speculation—would inevitably come into their own and would play a major role. What I could not know then, explicitly, is that just at that time we were at the dawn of a new day, in which that long, bizarre reign of anti-intellectualism was swept away, to the resounding benefit of the science; <u>and</u> that I should myself derive much enjoyment from doing some of the sweeping!

ENOUGH of the mid-30's. In 1937, armed with my fresh Ph.D.—very fresh!—I went to Harvard, to work with Professor Elmer Peter Kohler,(37) as his private assistant; in the following year, I had the inestimable good fortune to be elected to the Society of Fellows. That marvelous institution was founded, at Harvard, by A. Lawrence Lowell,(38) whose conviction it was that scholars should be gentlemen, entirely free to follow their intellectual interests, unencumbered by such Teutonic iniquities as Ph.D. degrees, lecture courses—either to be taken or given—indeed, formal requirements of any kind. Of course, tradition and authority always win some share of the pie, and not all of Lowell's objectives were realized. But that of giving young scholars a period of real freedom most definitely was; the <u>only</u> thing required of a Fellow was—and is—that he dine once a week with his confrères—just over twenty in number, from all disciplines, at the best table in Cambridge. I found it most congenial, and I feel that the period I spent as a Fellow gave me a superb opportunity to lay an excellent foundation for my subsequent activities. One could read, learn, cogitate—even work, if one felt the urge—and plan the future, however unconsciously.

A quarter of a century later, Roald Hoffmann was elected to the Society, and it was during his tenure as a Fellow that our collaboration began.

John Bardeen,(39) who has twice won the Nobel prize in Physics, was a member. Should you wonder about the breadth of the interests of the Fellows, I may make mention of Paul Samuelson,(40) Nobel Laureate in Economic Sciences; if you want still more variety—<u>and</u> balance!—McGeorge Bundy(41) and Daniel Ellsberg!(42)

IN my own case, this splendid period was made the more wonderful through the appearance on the scene of Saul Winstein,(43) who spent the academic year 1939/1940 at Harvard as a National Research Council Post-doctoral Fellow. What a year that was! Saul and I spent by far the better part of it in animated discussions ranging over the whole of organic chemistry. AND it has been a most interesting experience, over the ensuing years, to observe how often many of the ideas we bruited about came to fruition, sometimes by our own hands, frequently through the activities of others, and often in a form surprisingly close to that we had imagined.

I will mention but a single instance, as exemplary of our discussions, and their consequences. Already deeply steeped in the lore of the chemistry of natural products, I was able to bring to Saul's attention the fact that optically active linalool could be converted, through acid catalysis, into optically active α-terpineol.

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Our early discussions of this reaction certainly played a significant role in Saul's subsequent major contributions in the area of complex cations and π-electron participation.

I OBSERVE that the milli-woodwards are marching inexorably on, and we have only reached 1940—though I have mentioned some of the events of the period 1940-1960 out of turn. Let us now jump at once to some further perhaps pertinent incidents of the 1950's.

Organic chemists—and physical and theoretical chemists too—might well have pondered more deeply than they did the fact that the formation of cyclobutanes by the dimerisation of ethylenes was a relatively rarely observed phenomenon. After all, in purely geometric terms, the transition state for the reaction looks superb. I rather fear that what thought

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may have been given to the problem must have followed the shallow course that since cyclobutanes are strained molecules, it is not surprising that their formation is difficult. This reasoning is, of course, both logically and thermodynamically, false. I was certainly as guilty of error in this respect—if indeed not more so—as anyone. Indeed, thinking that I might circumvent the strain problem by substituting a five-membered ring for the four, I suggested to one of my students—Robert Autrey(44)—in the mid 50's, that he attempt to realize the reaction between and allyl cation and an olefin:

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Needless to say, in spite of the most valiant efforts, Autrey found no trace of the desired products. Of course, we now recognize that this, like cyclobutane formation from ethylenes, is a symmetry-forbidden process, and we all know that closely related, but symmetry-allowed reaction between allyl cations and dienes

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has been realized by H. M. R. Hoffmann.(45) Now, when Autrey's efforts had failed, I of all people should have drawn the simple and correct conclusion that for some reason, a high barrier is present which makes that reaction—and the ethylene dimerisation—difficult or impossible of realization. Had I—or someone else—recognized that simple truth, and looked searchingly for the origin of that barrier, the principle of orbital symmetry conservation might have been discovered much sooner! IN my defense, I will point out that, for excellent reasons, one does not ordinarily set much store by negative results.

▸ I TURN NOW to what I used to describe as "the four mysterious reactions." In 1960, I rather felt that, by and large, I had a good understanding of organic reactions—at least in my own perhaps idiosyncratic terms. But whenever I was tempted to become too complacent, there arose in my mind the spectre of these four mysterious reactions. However much I thought about them, they remained for me a true source of bafflement. Here they are:

13th SLIDE

with respect to the first—the isomerisation of precalciferol to Vitamin D—I had done my utmost to convince my friend Hans Herloff Inhoffen(46) that it *must* be acid-catalysed, but he remained unshaken in his position that the reaction was a purely thermal transformation, taking place readily at moderate temperatures—and I knew well that he was among the most scrupulous and careful of experimentalists.

The second case—the Smirnov-Zamkov(47) reaction simply left me open-mouthed, with nothing to say.

In the third case, first investigated by Skell,(48) it was known that a specific one of the halogen atoms was disengaged, but which was not known, and I could not discern a really good case for either.

The fourth case is in a way the most interesting, in that here I came closest to deriving the truth. It involves, as you see, the stereospecific opening, discovered by Emanuel Vogel,(49) of a *cis* disubstituted cyclobutene to a *cis*, *trans* substituted butadiene. I well remember tossing off the suggestion, late one night during one of my notorious Thursday night seminars, that this reaction might involve the *addition* of the relevant single bond, in a *trans* sense, to the double bond! TOO MUCH! HOW CLOSE CAN ONE GET! The only immediate result of this flight of fancy was the formulation on my part of some rather ill-defined notions of the "inherent *trans*-ness" of double bonds, which caused me to lead another student—Bolevant Singh(50)—into an experimental thicket from which we never emerged with any results worth recording.

▸ NEVER waste time and substance licking one's wounds. Rather count one's blessings. How lovely it is to contemplate the fact that A. O. S.—after orbital symmetry—none of these reactions any longer is mysterious!

NOW, let me make a few remarks about the state of quantum chemistry in the early 1960's. First, I should mention that in the early 1930's, at least some of the protagonists of the new quantum mechanics took the view—rather superciliously— that, with the advent of the new discipline, chemistry had had it!: all of its problems were now solved in principle, and soon would be in practice. Soon, gone forever would be the tentative, empirical, experimental, qualitative, heuristic, characteristics of chemistry as we had known it—to be replaced by sure-footed, essentially routine solution of chemical problems, solidly based on unassailable and universally applicable principles, readily translatable into precise, mathematically formulated operational protocols.

THIRTY years later, that flamboyant promise had been far from realized. In fact, the yield for the organic chemist had been rather low. Hückel's 4n+2 rule had generated considerable fascinating and significant work.(51) Pauling's(52) theory of "resonance" had had a good and useful run albeit the ground it covered paralleled closely that encompassed within the non-quantum-derived "mesomerism" of the English school. Many calculations of static properties of molecules had been made, but no one took them very seriously, least of all those who made them, when referring to calculations of others. And that was about it.

NOW, what was my personal position in these matters? It should be emphasized that throughout the period of this narrative my creative imagination, my day-to-day concerns, my persuasive powers—both with respect to my collaborators, and to Nature!—had been in large measure preempted by the not inconsiderable demands of my work in synthetic chemistry. Theory, always of great interest to me, was not, in and of itself, my direct major concern.

NEVERTHELESS, two sides of an important coin should be depicted here. I had always felt—and of course still do—that the synthetic chemist would not go far unless he were to mobilize, and apply, to the best of his ability—and within the limits set by the many other things he must know, AND do—the maximum in the way of principle and theory. Allow me to quote briefly from my memoir on Synthesis, published in Perspectives in Organic Chemistry in 1956.(53)

> .....The structure theory recognized that the maintenance of nearest-neighbor relationships among the elements was responsible for the variety and individuality of the material components of the physical world. The great advance of the recent past has been the recognition of the entities responsible for the maintenance of those nearest-neighbor relationships, and a description in simple general terms of wide applicability and precision, of their fluid nature, and of the laws to which they are subject.
>
> .....modern theory permits synthetic planning, and reduction of plans to practice, on a scale which was hitherto quite as impossible as were the simpler syntheses of the last century before the elaboration of the structure theory.

THE OTHER side of the coin is that to strive to achieve a particular synthetic objective is to put to the most direct and rigorous possible test the validity and applicability of the principles of science—more especially if the achievement of the objective might involve 50, or even upwards of a hundred steps, each of which depends upon the successful completion of the one preceding it.

• SO, in a general way, I had attempted to keep *au courant* with theoretical developments—in addition to carrying on some investigations explicitly concerned with chemical principles—AND I felt that in my synthetic work I was providing some contribution to making the body of chemical theory more precise, and defining—perhaps in some measure extending—its areas of applicability; NOT TO MENTION helping to bring about its use and acceptance by the chemical community in general through demonstrating its power.

▸ *BUT*, to return to quantum chemistry; in the early 1960's my acquaintance with quantum theory in general, and molecular orbital theory in particular, was very far from that of an expert or a specialist. NEVER the less, my view of the prospects for the area was sanguine—conceivably even more so than that of many of the practitioners, some of whom were perhaps discouraged by the relative paucity of advance, and by the small impact their work had had on chemistry as a whole; others might have been frightened by the magnitude of the problems before them, as they saw them. Professor Albert Eschenmoser(54) can testify that about a year before Professor Hoffmann and I began our work on orbital symmetry conservation, he asked me where I thought the future of theoretical organic chemistry might be. I replied, unhesitatingly, "Unquestionably, in quantum chemistry, and specifically in molecular orbital theory," and added that, that future might be sooner at hand than most would suppose. He has told me that my remarks made a most vivid impression on him, and that he has recalled them with wonder subsequent to the recognition of the orbital symmetry control of chemical reactions.

- AND NOW, for a moment, a digression—or is it? I raise the question: Is it possible that my own relative naiveté in quantum chemistry was a positive advantage in relation to the events to come? In my very early remarks, I alluded to the phenomenal insights afforded to Archibald Scott Couper—a young student almost innocent of the science of organic chemistry of his day. And to cite a more recent instance: James Watson(55) and Francis Crick,(56) respectively an ornithologist and a physicist, both manqué, burdened by only the most fragmentary knowledge of structural chemistry, were responsible for the single most significant chemical structure determination of the twentieth century—that of DNA—which led at a stroke to the birth of molecular biology, and permitted a hitherto undreamed-of sophistication in our understanding of genetics.

Perhaps the relatively remote and unsophisticated observer is sometimes the better able to see the forest for the trees? I do not answer this question; I only raise it. And whatever the answer, we must not abandon the precept that continuing advance in science is not possible without painstaking attention to detail from the most knowledgeable point of view possible.

- AND NOW, I approach the climax of my narrative. During 1963 and early 1964, as a superbly gifted member of my post-doctoral group in Cambridge, Dr. Subramania Ranganathan(57) was investigating one of the many lines we explored in seeking to realize our objective of effecting the total synthesis of vitamin B_{12}. Many of you will recognize him, not only for his subsequent original work, but also as the author of those delightful books—Art in Organic Synthesis, Fascinating Problems in Organic Reaction Mechanisms, and Challenging Problems in Organic Reaction Mechanisms. The line which he was following was an intricate one, requiring the utmost in experimental skills, but shorn of the ornament attendant upon its being part of a program for the synthesis of vitamin B_{12}, his work involved the cyclisation of an open-chain hexatriene to a cyclohexadiene. We had analysed the possibilities in great detail, in the light of all available chemical principles, and were convinced beyond shadow of doubt that the reaction would proceed in what we should now describe as a conrotatory fashion, with concomitant establishment, at the termini of the newly-formed single bond, of precisely the stereochemical relationships required at the apposite centers. Lest it might be thought that our analysis had been flawed, I should allude to a paper published, in 1964, by Lewis and Steiner[8], in which the conversion of hexatriene itself to cyclohexadiene is examined from the theoretical point of view in very great detail—except of course that orbital symmetry factors are not taken into account—and the unequivocal conclusion is reached that the reaction must follow what we would now describe as a conrotatory path!

NOW, in the event, our cyclisation occurred smoothly. Further, it was found that irradiation of the product brought about a reversion to a new, geometrically isomeric open-chain triene, which, in turn, could be cyclised to a new cyclohexadiene. This latter, on irradiation, reverted to the original open-chain triene. This was a very pretty set of relationships, and taken by itself, was far from providing any cause for synthetic concern—the more so

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[8] K. E. Lewis and H. Steiner, J. Chem. Soc. 3080-92 (1964).

since, whatever the validity of our reasoning, *one* of the cyclohexadienes *must* embody the desired stereochemical relationships.

BUT, as our investigation proceeded, it became more and more clear that our stereochemical anticipations had been dead wrong. The cyclisations of *both* our hexatrienes had in fact followed a *dis*rotatory course! Here was a real dilemma. I had analysed the situation very carefully in the light of what I regarded as the best contemporary theoretical principles, and I had reached an absolutely wrong conclusion. I was appalled. Now I stood before—so to speak—the 5th "mysterious reaction." AND this one was my very own. To make matters worse, this was not simply a case which I found baffling; it was a reaction which I thought I had understood; now it was abundantly clear that I did not.

THE conviction grew upon me quickly that there *must* be at work here a powerful and overriding, hitherto unrecognized factor.

NOW, recall that the 4th of the "mysterious reactions" to which I alluded earlier involved a *conrotatory* relationship between a cyclobutene and a butadiene. Now I was face to face with an unexpectedly *disrotatory* relationship between a hexatriene and a cyclohexadiene.(58) Here was a situation that was not just one worthy of pondering; it literally cried out for attention.

I REMEMBER very clearly—and it still surprises me somewhat—that the crucial flash of enlightenment came to me in *algebraic*, rather than in *pictorial* or *geometric* form. Out of the blue, it occurred to me that the coefficients of the terminal terms in the mathematical expression representing the highest occupied molecular orbital of butadiene were of opposite sign, while those of the corresponding expression for hexatriene possessed the same sign. From here it was but a short step to the geometric, and more obviously chemically relevant, view that in the internal cyclisation of a diene, the top face of one terminal atom should attack the bottom face of the other, while in the triene case, the formation of a new bond should involve the top (or pari passu, the bottom) faces of both terminal atoms. The central guiding principle was of course that bonding must always involve orbital loci of the same sign. AND, the strikingly contrasting stereochemical paths followed by the two reactions are precisely those which would have been predicted from these simple orbital considerations; it is of course of no consequence that in the case of the butadiene/cyclobutene relationship, the actual reaction which was known at that time was ring cleavage, rather than cyclisation.

- TO DIGRESS again for a moment, I may point out that the highest occupied molecular orbital of π electron arrays has often been described, loosely but aptly, as the valence orbital of the system. Should we discern, in the developments I am now relating, a latter-day reflection of my boyhood absorption, almost 40 years previously, with the partial valence theories put forward by Thiele to rationalize the behaviour of conjugated unsaturated systems?(59)

14th SLIDE

FROM the very beginning, my new orbital ideas had, for my mind, that aura of inevitability which leads one to the conviction that one has discovered the correct solution to a problem, and I was confident that I had found that powerful and overriding, hitherto unrecognized factor which our vitamin B_{12} work had forced me to believe must exist.

AFTER a brief false start in extending these ideas, attributable clearly to my *gaucherie* in the details of quantum chemistry, I very soon realized that I needed more help than was available in my immediate circle, and I sought out Roald Hoffmann, who was well-known to me, though by reputation only, as a brilliant young theoretician, at that time, as I have already mentioned, a member of the Society of Fellows. I told him my story, and then, essentially, put to him the question: "Can you make this respectable in more sophisticated theoretical terms?" He could, and did; AND THUS began our immensely pleasurable, rewarding, and fruitful collaboration. From it, I learned much, AND it led to our five preliminary communications of 1965, to the more highly developed and generalized views described *in extenso* in 1969; to our enjoying together your hospitality here this afternoon. AND as well to uncounted events in the ever more fascinating pageant of chemistry during the last eight years—which it is not my place to narrate here.

I SHOULD LIKE to conclude with a few personal remarks about Roald Hoffmann.(60) His outstanding qualities of mind; his superb capacity to put those qualities to use, his facility in organizing his ideas and transmitting them lucidly to others, are apparent to everyone. I can testify to the astonishing breadth of his interests, to the amazing speed and facility with which he familiarized himself with the facts of organic chemistry, and developed a wonderful intuition about the science—in which he had had only the most casual background. I have observed the intensity of his love for and devotion to chemistry. AND I have seen also that he is sensitive to and respectful of the moods and feelings of others—understanding of and compassionate in respect to their problems. I cannot recall an instance of his having spoken ill of anyone. He is, in short, a man whose wonderful human qualities are commensurate with his genius as a scientist. It is my inestimable privilege to count him as a collaborator and a friend.

- **MAY** I thank all of you most warmly for your attention, your consideration, and your patience.

~~CLAY~~

ARTHUR COPE

(pr: all names: use same types)

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ARCHIBALD SCOTT COUPER

A ground-state pericyclic reaction is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ components is odd.

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↓ Kursiver Buchstabe

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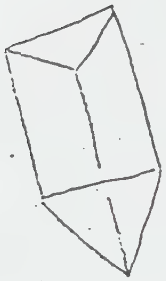
Robert Burns Woodward

b. 10. April 1917

PR 10· kursiv



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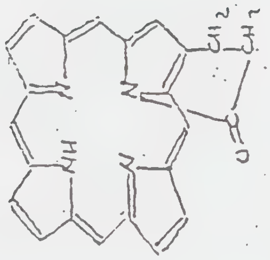

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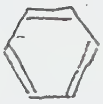

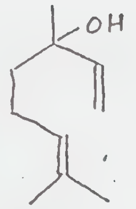
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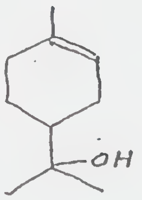
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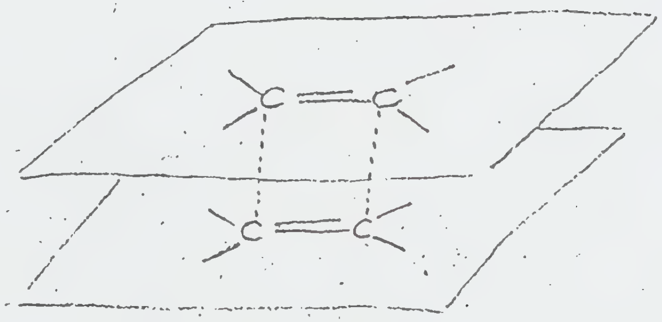
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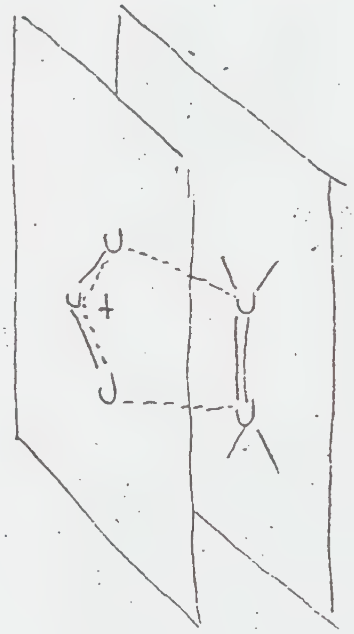

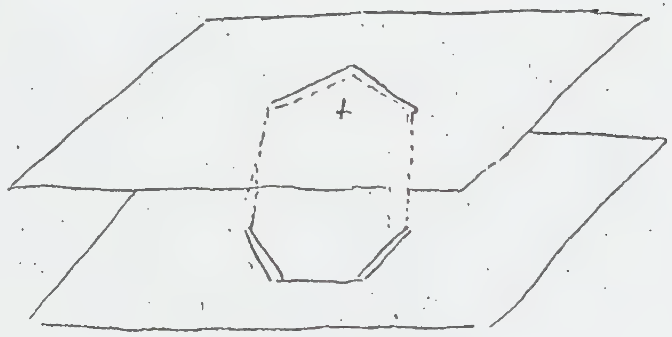

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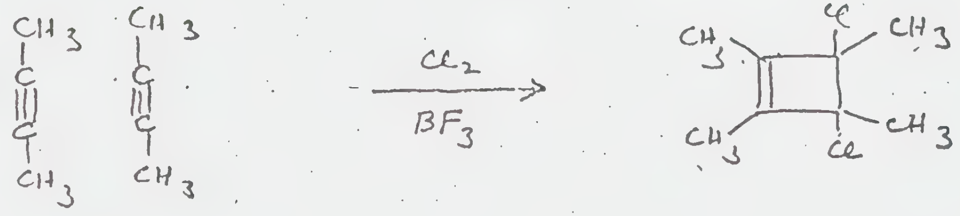
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R. B. WOODWARD COPE AWARD LECTURE

HEADNOTE

The Arthur C. Cope Award was established by the American Chemical Society in 1972 in accordance with the terms of the will of Arthur C. Cope. It is granted "to an individual without regard to age and nationality for outstanding achievement in the field of organic chemistry." In line with these specifications it has been given to one person each year except for the inaugural award in 1973 shared by Robert Woodward and Roald Hoffmann for their orbital symmetry rules for concerted organic reactions. Each received a gold medal, a $5000 honorarium and an unrestricted research grant in-aid of about $15000 each, the exact amount dependent on the Cope fund backing the award. By 1992 the honorarium was $15,000, while the research grant remained at $30,000.

Recipients since 1973 were

1974 Donald J. Cram
1976 Elias J. Corey
1978 Orville L. Chapman
1980 Gilbert Stork
1982 Frank H. Westheimer
1984 Albert Eschenmoser
1986 Duilio Arigoni
1987 Ronald Breslow
1988 Kenneth B. Wiberg
1989 William S. Johnson
1990 Koji Nakanishi
1991 Gerhard L. Closs
1992 K. Barry Sharpless
1993 Peter B. Dervan

In 1973 the award was restricted to recognizing work "the significance of which has become apparent within the five years preceding the year in which the award is to be considered." The 1973 Cope award was given during the fall ACS national meeting in Chicago. Andrew Streitwieser Jr., professor of organic chemistry at the University of California, Berkeley, and 1973 chair of the ACS Division of Organic Chemistry, presided at the award symposium.

Arthur C. Cope (1909-1966) was born in Dunreith, Indiana, and did his Ph.D. work under Samuel M. McElvain at the University of Wisconsin. He taught at Bryn Mawr College and Columbia and finally was Camille Dreyfus Professor at MIT. He was President of the ACS in 1961 and its board chair at the time of his death.

Cope is best known for the Cope Rearrangement largely investigated in the 1940's, the migration of a three-carbon allyl group to a new point of attachment without leaving the molecule. (A. C. Cope, E. M. Hardy, "A Rearrangement involving the Migration of an Allyl Group in a 3-Carbon System," J. Amer. Chem. Soc., 62 (1940) 441-444; A. C. Cope, K. E. Hoyle, D. Heyl, "Rearrangement of Allyl Groups in Three-carbon Systems," ibid, 63 (1941) 1843-1852; H. Levy, A. C. Cope, "Rearrangement of Allyl Groups in 3-C Systems, IV. Hydrocarbons" ibid, 66 (1944) 1684-1688. See also William von Eggers Doering, "50th Anniversary of the Arthur C. Cope Rearrangement," Proceedings of the Robert A. Welch Foundation Conference on Chemical Research, XXXIV (Houston,

Texas: Robert A. Welch Foundation, 1990), 335-340.) Together with C. G. Overberger, Cope successfully repeated Richard Wilstätter's synthesis of cyclooctatetraene, ending a long-standing controversy as to whether the substance had been made.

Woodward's complete Cope Lecture is reproduced here, transcribed from a handwritten copy kindly supplied us by Roald Hoffmann. RBW's footnotes have been augmented only by adding final page numbers to the references he cites. These footnotes are indicated by superscripts. We have added endnotes, indicated by numbers in parentheses.

RBW's sketches for his slides are reproduced courtesy of the Harvard University Archives.

[July 20, 1993 / a:COPEHEAD.RBW]

ROBERT B. WOODWARD'S 1973 COPE AWARD LECTURE

Sample pages from RBW's hand-written and not previously published lecture. A copy of the lecture was kindly supplied to the editors by Roald Hoffmann.

Slide 1

R.B. Woodward address
Chicago Aug. 28, 1973

Arthur Cope and I both worked in Cambridge for many years. Although his activities were carried on at M.I.T. and mine at Harvard, our paths crossed frequently, and it was my great privilege to be counted among his friends. Consequently, I think I may be allowed to say a few words which express my very personal view of the man whose memory we are all gathered here to honour.

<u>First</u> Arthur Cope was a gentleman. He was unfailingly kind and courteous. Firm and persuasive in his views, he was at once soft-spoken and well-spoken, always fair and balanced. He looked for, and found, the best in those with whom he was associated, as friends, colleagues or co-workers.

<u>Second</u> Arthur Cope was an outstanding scientist. His work was characterised by boldness and originality in concept, and by scrupulous adherence to the highest experimental standards in execution.

rthur Clay Cope
b. 27 June 1909
d. 4 June 1966

Of his many brilliant contributions, I shall select one for special comment →

→ since it seems particularly appropriate to this occasion: Arthur Cope first established himself, internationally, as a major figure in our science, through his beautiful series of studies on what has come to be known as the Cope Rearrangement – an important reaction which we now recognise as falling within the generalized category of symmetry-allowed [3,3] sigmatropic changes!

- In the light of these brief remarks, you will certainly appreciate that I feel it a very particular honour and a very special privilege to stand here before you, as the recipient, with Roald Hoffmann, of the first Arthur C. Cope Award.

- But every privilege carries with it some kind of responsibility, and I have, here, at this moment, a responsibility which I cannot but regard as a heavy one – that of presenting to all of you a lecture, appropriate to the occasion, and, it may be hoped, of some general interest to an audience among whose members there must certainly be a wide diversity in background.

WHAT TO DO?

The Principle of Conservation of Orbital Symmetry — for whose enunciation Professor Hoffmann and I are being honoured here today — powerful though it be, can be very simply stated, and almost as easily explicated. Those things Professor Hoffmann and I have done, on numerous occasions, in lectures and in writing |; AND to be entirely candid, neither Professor Hoffmann nor I any longer find it à propos to expound principles which have already, in a spectacularly short time, become an integral, indispensable and powerful part of the basic theoretical structure of organic chemistry. Let me not be misunderstood here: for my part, at least, I still find it most thrilling to re-live those marvellous moments of discovery and personal enlightenment. But, to expound the details in public has become, at best, supererogatory.

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of others, and often in a form surprisingly close to that we had imagined.

I will mention but a single instance, as exemplary of our discussions, and their consequences. Already deeply steeped in the lore of the chemistry of natural products, I was able to bring to Saul's attention the fact that optically active linalool could be converted, through acid catalysis, into optically active α-terpineol.

9th SLIDE

Our early discussions of this reaction certainly played a significant rôle in Saul's subsequent major contributions in the area of complex cations and π-electron participation.

▷ I OBSERVE that the milli-Woodwards are marching inexorably on, and we have only reached 1940 – though I have mentioned some of the events of the period 1940 – 1960 out of turn. Let us now jump at once to -- some pertinent incidents of the 1950's.

further perhaps

Organic chemists – and physical and theoretical chemists too – might well have pondered more deeply than they did the fact that the formation of cyclobutanes by the dimerisation of ethylenes was a relatively rarely observed phenomenon. After all, in purely geometric terms, the transition state for the reaction looks

Cope Lecture

Sequence for Endnotes

1 Couper
2 Kekulé
3 Gerhardt
4 Laurent
5 Butlerov
6 Freeman
7 Spanish dinner
8 Heilbronner
9 Gattermann
10 Cohen
11 Bernthsen
12 Anschütz
13 Henrich
14 Stewart
15 English School
16 Robinson
17 Solvolytic plague
18 Thiele
19 Alternating polarities
20 Ladenburg
21 van't Hoff
22 Conant
23 Barton
24 Hassel
25 Prelog
26 Katz
27 Nancy Acton
28 Tippelskirch
29 Diels, Alder
30 Reserpine et al
31 Harold Baer
32 Virginia Williams
33 Bernard Landau
34 Mulliken
35 Slur
36 Kolbe
37 Kohler
38 Lowell
39 Bardeen
40 Samuelson
41 Bundy
42 Ellsberg
43 Winstein
44 Autrey
45 H.M.R. Hoffmann
46 Inhoffen
47 Smirnov-Zamkov
48 Skell
49 Vogel
50 Bolevant Singh
51 Hückel
52 Pauling
53 RBW essay in Todd
54 Eschenmoser
55 Watson
56 Crick
57 Ranganathan
58 Conrotatory and disrotatory
59 RBW comment re Slide 14
60 Roald Hoffmann

[July 20, 1993 / NOTENOS.RBW]

R. B. WOODWARD COPE AWARD LECTURE

ENDNOTES

(1) Archibald Scott Couper (1831-1892); studied humanities and classical languages in Glasgow, and logic and metaphysics in Edinburgh under Sir William Hamilton who was noted for his success in developing critical powers in his students. Around 1855 in Berlin, he began his studies of chemistry, and then moved to the laboratory of Charles Adolphe Wurtz (1817-1884) in Paris. Couper examined chemical formulas as if they were words in a foreign language seeking to discover the language's structural patterns. He thereby discovered carbon's apparently unique ability to form chains and also its participation in rings, in a molecule such as cyanuric acid. He asked Wurtz to submit his paper to the Académie française des Sciences for publication, but Wurtz procrastinated and Kekulé's paper on the same subject was published first. Couper then turned to Jean Baptiste André Dumas (1800-1884; Professor in Paris and for a time French Minister of Agriculture) and his paper appeared ("Sur une nouvelle theorie chimique". Comptes rendus de l'Académie des Sciences, 46 (1858), 1157-1160). It contained the formulas RBW mentioned with lines between atoms. When his longer paper "On a New Chemical Theory" appeared in English (The London, Edinburgh and Dublin Philosophical Magazine and Journal of Science [4] 16 (1858), 104-116; reprinted in O. T. Benfey, Classics in the Theory of Chemical Combination, New York, 1963, pp. 136-150)

the lines were dotted. The magazine probably followed the practice later adopted by the Berichte der deutschen Chemischen Gesellschaft, as RBW mentions, on the premise that solid lines imply too much of a claim to physical reality. Couper's work was misunderstood and criticized, or else ignored and Kekulé and Hermann Kolbe (see below) attempted to repeat Couper's experimental work on salicylic acid and failed, thus casting doubt also on his experimental competence. Kekulé's biographer and successor at Bonn, Richard Anschütz (1852-1937) duplicated Couper's experiments by following directions exactly. They have been further confirmed more recently (A. G. Pinkus, "On the Structure of Couper's Compounds" Journal of Organic Chemistry 26 (1961), 682-686). Anschütz in the Kekulé biography (see next note and note 12) and Leonard Dobbin ("The Couper Quest" Journal of Chemical Education 11 (1934) 331-338; "On a New Chemical Theory and Researches on Salicylic Acid. Papers by Archibald Scott Couper" Alembic Club Reprint No. 21 Edinburgh: E. and S. Livingstone, Ltd., 1953) unearthed much information on Couper and his work. On returning to Scotland, Couper in 1859 suffered a nervous breakdown and carried on no further significant intellectual work.

(2) Friedrich August Kekulé (1829-1896), born in Darmstadt, was professor of chemistry at Ghent, Belgium, Heidelberg and Bonn. He had planned to study architecture, but on hearing Liebig's lectures at Giessen, he turned to chemistry. In 1857,

simultaneously with William Odling (1829-1921) of the Royal Institution and Oxford, he showed that carbon had a valence of four. The following year, a month prior to Couper, he published his paper "Über die Constitution und die Metamorphosen der chemischen Verbindungen and über die chemische Natur des Kohlenstoffs" (Annalen der Chemie und Pharmacie 106 (1858), 129-159; translated by O. T. Benfey, Classics op cit, 109-131) in which he discussed carbon's ability to form chains. At an 1890 celebration in Berlin on the 25th anniversary of his proposal of a ring structure for benzene, he told of reaching his ideas regarding carbon chains and the benzene ring in daydreams or reveries (Halbschlaf), carbon chains in London, rings in Ghent. The speech has been much used by psychologists and others in discussions of creativity, often translating Halbschlaf erroneously as dreams. (See Albert Rothenberg, "Creative Homospatial and Janusian Processes in Kekulé's Discovery of the Structure of the Benzene Molecule." in Wotiz below). For a translation of his speech see O. T. Benfey, "August Kekulé and the Birth of the Structural Theory of Organic Chemistry in 1858" Journal of Chemical Education 35 (1958), 121-23. Kekulé's account has been questioned by some who suggest he invented it rather than reveal his debt to earlier chemists. (see for instance John Wotiz, editor, The Kekulé Riddle, Vienna, Illinois: Cache River Press, 1993.) Yet Kekulé spoke of standing on the shoulders of others and mentioned C. F. Gerhardt, W. Odling,

A. W. Williamson, and C. A. Wurtz as having contributed to the maturing of his ideas. (see Richard Anschütz: August Kukulé, Leben und Wirken, Berlin: Verlag Chemie. 2 Volumes 1929.)

(3) Charles Frédéric Gerhardt (1816-1856) was born in Strasbourg, France and taught at Montpelier and Strasbourg. He discovered anhydrides of monocarboxylic acids. With Auguste Laurent, he clarified the distinctions between atomic, molecular, and equivalent weights, and set up a comprehensive system of classification for organic compounds. (See also next note.)

(4) Auguste Laurent (1807-1853) organic chemist, crystallographer, artist and composer, was born in La Folie near Langres, France. He was trained at the School of Mines, became assistant to Dumas at the Central School of Arts and Manufacturers in Paris, and then Professor of Chemistry in Bordeaux and Assayer of the Paris Mint. While working in Antoine J. Balard's laboratory he became the guide and inspiration of Pasteur in the latter's crystallographic studies. He isolated and characterized anthracene and phthalic acid.

Assisted by Gerhardt, Laurent developed an extensive systematization of organic compounds to replace the dualistic system of Berzelius. The type formulas proposed by Laurent and Gerhardt represented organic compounds as substitution products derived from the inorganic "types" H_2, HCl, H_2O, NH_3, with organic "radicals" such as C_2H_5 or $C_2H_3O_2$ replacing the hydrogens and linked by curly brackets. (See S. C. Kapoor, "The Origins of Laurent's Organic Classification," Isis 60 (1969), 477-527. J.H. Brooke, "Laurent, Gerhardt and the Philosophy of Chemistry," Historical Studies in the Physical Sciences 6 (1975) 405-29.)

(5) Alexander Mikhailovich Butlerov (1828-1886): Professor of Chemistry at Kazan and St. Petersburg, Russia, and Rector of the University of Kazan, 1860-1863. In 1857-1858 he visited Kekulé in Heidelberg and Couper in Paris and worked out in great detail the consequences of the structural theory. He coined the term 'chemical structure' insisting that for every compound there was only one such structure that could be known from its properties and reactions. ("Einiges über die chemische Struktur der Körper", Zeitschrift für Chemie, 4 (1861) 549-560. See also Alan J. Rocke, "Kekulé, Butlerov, and the Historiography of the Theory of Chemical Structure," British Journal for the History of Science, 14 (1981), 27-57.) This structure—the manner of linking of its atoms—was distinct from the as yet unknown physical structure, the location of atoms in space. Kekulé was often still using several 'type formulas' to describe a single substance. Butlerov presented his views at a congress of scientists and physicians in 1861 in Speyer, Germany, pointing out in his lecture that all his ideas were essentially present in Couper's papers of 1858. He contributed to the understanding of isomerism and tautomerism in organic compounds and carried out numerous organic syntheses. (Henry M. Leicester,

"Contributions of Butlerov to the Development of Structural Theory," Journal of Chemical Education, 36 (1959) 328-9; G.V. Bykov, "The Origin of the Theory of Chemical Structure," ibid 39 (1963) 220-4.)

(6) Jeremiah P. Freeman, Notre Dame University, Indiana, was Secretary-Treasurer of the ACS Division of Organic Chemistry and was presumably in charge of the dinner following the lectures.

(7) Woodward refers here to the practice still common in Spain and Latin America of dining very late, since long mid-day breaks are still often observed, followed by work much later into the evening.

(8) Edgar Heilbronner was born in Munich in 1921. He obtained his Ph.D. with Leopold Ruzicka at the Eidgenössische Technische Hochschule, Zurich, where he taught prior to his move to the University of Basel to become director of its institute of physical chemistry. A leading physical and theoretical chemist, he is particularly known for his chemical applications of photoelectron spectroscopy, his cigars and his raconteurship.

(9) Ludwig Gattermann (1860-1920) was born in Goslar, Germany, and did his doctoral research in Göttingen under H. Hübner until the latter's death just before the work was completed. He taught in Göttingen, Heidelberg, and Freiburg. Known for his Laboratory Methods of Organic Chemistry, a 1932 translation by W. McCartney of Edinburgh, of the twenty-second German edition

of Die Praxis des Organischen Chemikers (the first edition [1894] was called Anleitung für das organisch-chemische Praktikum). Heinrich Wieland of Freiburg and later Munich prepared the revised, 19th, and subsequent editions). Gattermann's book became almost a bible of organic chemistry. It appears in the most unlikely places—even in the chemical "examination" for Primo Levi in Auschwitz concentration camp which assigned Levi to take part in the adjoining chemical industry operation. (Primo Levi If This is a Man New York: Orion Press, 1959).

(10) Julius B. Cohen, (1859-1935) was born in Manchester, studied at Owens College (the later Manchester University), under Carl Schorlemmer, then with Adolf Baeyer in Munich, and became professor of chemistry at Manchester and Leeds (where he was succeeded by C. K. Ingold). In 1907 he published Organic Chemistry for Advanced Students, which expanded in subsequent editions into three volumes on reactions, structure, and synthesis. Cohen in October 1921 in a letter to Arthur Lapworth suggested the use of G.N. Lewis's shared electron pairs to represent covalent bonds in Lapworth's explanations of organic structures and reactions. This led directly to the "English School" (cf. note 20; Cohen's letter is quoted on p. 458 in Robert E. Kohler Jr., "The Lewis-Langmuir Theory of Valence and the Chemical Community, 1920-1928," Historical Studies in the Physical Sciences 6 (1975) 431-468.) Cohen's Practical Organic Chemistry, which first appeared in 1887 as

The Owens College Course of Practical Organic Chemistry, was revised and edited numerous times and was still used as a laboratory text in London University in the forties. He also wrote Theoretical Organic Chemistry (1900; second edition 1917), and with Arthur G. Ruston Smoke: A Study of Town Air (1896, second edition 1925).

(11) August Bernthsen, born in 1855, wrote Kurzes Lehrbuch der Organischen Chemie (1887) which by 1919 in its fourteenth edition contained 672 pages. It was translated by George McGowan (revised edition 1889) as Organic Chemistry, and by J. J. Sudborough, as A Textbook of Organic Chemistry (1926; new enlarged edition 1931).

(12) Richard Anschütz (1852-1937) was born in Darmstadt, obtained his Ph.D. in Heidelberg and studied with R. Fittig before moving to Bonn as assistant to Kekulé. Following Kekulé's death he succeeded him as director of the Chemical Institute. He wrote the standard two-volume biography August Kekulé, Leben und Wirken (Berlin: Verlag Chemie, 1929) and in preparing for it unearthed important information about A. S. Couper and J. Loschmidt.

(13) Ferdinand Henrich was born in 1871 and became professor at Erlangen, Germany. He wrote Neuere theoretische Anschauungen auf dem Gebiete der Organischen Chemie (1908) which was shortened in the second edition of 1912 to Theorien der Organischen Chemie. It was translated and enlarged in 1922

from the fourth German edition of 1921 by Treat B. Johnson of Yale and Dorothy A. Hahn of Mount Holyoke College.

(14) Alfred Walter Stewart (1880-1947), chemist and writer, was born in Glasgow and became professor of chemistry at Queen's University, Belfast. He wrote Stereochemistry (1907, 1919); Recent Advances in Organic Chemistry (eight editions, 1908-1948); Recent Advances in Physical and Inorganic Chemistry (six editions, 1909-1930); and also wrote 27 novels, of which all but the first two were detective stories (as J(ohn) J(ervis) Connington), among them The Dangerfield Talisman (1926) and Murder in the Maze (1927). (George B. Kauffman, "Alias J. J. Connington: The Life and Work of Alfred W. Stewart (1880-1947), Chemist and Novelist," Journal of Chemical Education 60 (1983), 38-40.)

(15) This name is usually applied to the ideas and influence of Robert Robinson (1886-1975) of Oxford and Christopher K. Ingold (1893-1970) of University College, London, who put forward in the 1930's theories as to the influences of electrical factors on the properties of organic molecules and the course and ease of chemical reactions (R. Robinson, Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions, London 1932; C.K. Ingold Structure and Mechanism in Organic Chemistry, Ithaca: Cornell University Press, 1953, second edition 1979. See also Martin D. Saltzman, "The Robinson-Ingold Controversy: Precedence in the Electronic Theory of Organic Reactions," Journal of

Chemical Education, 51 (1980) 484-8. The origins of the "English School" are discussed in detail by Kohler (ref 10)). With these ideas and the language developed with them, large bodies of chemical facts and numerous chemical reactions could be subsumed under a remarkably small number of principles. Organic chemistry was beginning to become rational and predictable.

(16) Robert (later Sir Robert) Robinson (1886-1975) was born in Rufford/Chesterfield, England, and obtained his Ph.D. with William Henry Perkin Jr. in Manchester. He worked from time to time in the family company and taught mainly in Manchester and Oxford. He received the Nobel Prize in 1947 for his synthesis of natural products. He was an early pioneer of physical organic chemistry. (Robert Robinson, Memoirs of a Minor Prophet: 70 Years of Organic Chemistry, 1976; Trevor I. Williams, Robert Robinson, Chemist Extraordinary, Oxford: Oxford University Press, 1990.) [41] (See also note 15 above.)

(17) The "Solvolytic plague" presumably refers to the countless papers and controversies that attempted to clarify the role of classical and non-classical organic cations generated by "solvolysis" of precursors. In this work, new terms emerged such as intimate ion pairs and internal return. See Paul D. Bartlett, editor, Non-Classical Ions. Reprints and Commentary (New York: W. A. Benjamin 1965. Edward M. Arnett, Thomas C. Hofelick, George W. Schriver, "Carbocations", in Maitland

Jones Jr., and Robert A. Moss, editors, Reactive Intermediates 3 (1985) 189-226).

(18) F. K. Johannes Thiele (1865-1918) was born in Ratibor, Germany (now Poland), studied in Breslau and Halle (under Jacob Volhard), and taught in Halle, Munich, and Strasbourg. In 1910 he became editor of Justus Liebig's Annalen der Chemie. To explain the fact that 1,3 butadiene $CH_2=CH-CH=CH_2$ often adds two bromine atoms at the ends of the molecule and that benzene adds bromine only with great difficulty, he proposed that "double bond" was a misnomer, that carbons at such bonds retained a residual valence, or combining capacity, which can be satisfied by a similarly bonded adjacent carbon. (J. Thiele, "Zur Kenntnis der ungesättigten Verbindungen," Justus Liebig's Annalen der Chemie, 306 (1899), 87-266; 319 (1901), 129-143.) Since benzene has a cyclic conjugated system, all residual valences are satisfied leading to its lack of reactivity. His theories served as direct precursors of modern electronic theories. He was also the first to demonstrate isomerism among inorganic compounds (NH_2NO_2 and $H_2N_2O_2$). On the context of Thiele's theories and their relation to the Diels-Alder reaction (note 29 below) see Jerome A. Berson, "Discoveries Missed, Discoveries Made: Creativity, Influence, and Fame in Chemistry", Tetrahedron 48 (1992) 3-17, especially 7-13. (See also fn. 59 below.)

(19) Alternating polarities: The idea that an atom with a partial positive or negative charge would induce an opposite charge in

an adjacent carbon atom, and this charge alternation would then continue along a chain of carbon atoms, was proposed by Arthur Lapworth (1872-1941) in "Latent Polarities of Atoms and Mechanism of Reaction," Memoirs of the Manchester Philosophical Society 64 (1920) 1-16 (see note 10 and its Kohler reference).

(20) Albert Ladenburg (1842-1911) was born in Mannheim, Germany, and took his Ph.D. at Heidelberg, drawn to chemistry by R. Bunsen and G. R. Kirchhoff. He worked with Kekulé in Ghent in 1865 during the year that Kekulé proposed his benzene formula, with C. A. Wurtz in Paris, and with C. Friedel at the École des Mines where he began studies on organic silicon compounds. In 1869 he suggested his prism formula for benzene as one alternative to Kekulé's proposal ("Die Gleichwertigkeit der 6 Wasserstoffatome im Benzolring", Berichte der deutschen chemischen Gesellschaft, 2(1869) 140-272.) He taught at Heidelberg, Kiel, and Breslau (now Wroclaw, Poland), making major contributions to alkaloid structure determinations and synthesis.

(21) Jacobus Henricus van't Hoff (1852-1911) was born in Rotterdam, Netherlands, and studied in Delft, Leyden, Bonn with Kekulé, and in Paris with Charles Adolphe Wurtz, and did his doctoral work at Utrecht. He taught at the Veterinary College in Utrecht where he wrote his 1874 paper on the tetrahedral distribution of carbon valences (cf. his La Chimie dans l'Espace, Rotterdam, 1875), and then in Amsterdam and Berlin.

He also made major contributions to the study of solutions for which he received in 1901 the first Nobel Prize in chemistry. (John W. Servos, <u>Physical Chemistry from Ostwald to Pauling</u>. Princeton: Princeton University Press, 1990; O. Bertrand Ramsay, editor, <u>Van't Hoff-Le Bel Centennial</u>, Washington, D.C.: American Chemical Society, 1975; O. Bertrand Ramsay, <u>Stereochemistry</u>, London; Philadelphia: Heyden, 1981; Ernst Cohen, <u>J. H. van't Hoff, Leben und Wirken</u>, Leipzig, 1912.)

(22) We have not been able to find the formula RBW discussed in any of Conant's series of fourteen "Studies in the Chlorophyll Series" (<u>Journal of the American Chemical Society</u>, 1929-1934). Woodward's structure is that of the tetraazohydrocarbon from which he claims Conant's chlorophyll formulas is derived. Conant's formulas never correspond to this particular skeletal structure but two formulas in Conant's paper XI (<u>J. Amer. Chem. Soc.</u> 55 (1933), 839-849) come close. At least one of them shows a bond that angles back from the nitrogen and forms part of a ring that is stereochemically impossible by what was known of bond lengths and bond angles even at that time. Woodward must have drawn this from memory. If a reader finds his formula in Conant's writings, the editor would be delighted to learn of it.

James Bryant Conant (1893-1978) was born in Dorchester, Massachusetts, obtained his Ph.D. with Elmer P. Kohler at Harvard where he taught chemistry and rose to become President of the University from 1933-1953. He made major contributions to the elucidation of chlorophyll's structure. During World War II he chaired the National Defense Research Committee and had oversight of the early Uranium Committee. On returning to Harvard after the war he introduced history of science courses for the general student. He became the United States High Commissioner to Germany in 1935 and then ambassador until 1957.

(23) Derek H. R. Barton was born in 1918 in Gravesend, Kent, and did his doctoral work with Ian M. Heilbron and E. R. H. Jones at Imperial College, London. His interest in terpenes and steroids led him to Hassel's papers on cyclohexane (see note 28 below). As visiting lecturer at Harvard from 1949 to 1950, he discussed the implications of those findings with R. B. Woodward and used them to explain some data that puzzled Louis Fieser. He presented his ideas in a brief article ("The Conformation of the Steroid Nucleus", <u>Experientia</u> 6 (1950), 316-320), focussing on the relative stabilities of chair and boat forms of cyclohexane rings and the bonds radiating from them.

For this pioneering "conformational analysis" he shared the 1969 Nobel Prize with Otto Hassel. Barton taught at Imperial College, became director of the French Centre National de la Recherche Scientifique, and then joined Texas A & M University. He is now Sir Derek Barton. (Derek H. R. Barton. <u>Some Recollections of Gap Jumping</u>. Washington D.C.: American Chemical Society. (<u>Profiles, Pathways, and Dreams</u>, series editor Jeffrey I. Seeman), (1991); see also Ramsay, Stereochemistry, (note 25)). [69-71, 92]

(24) Odd Hassel (1897-1981) was born in Christiana (now Oslo), Norway, studied at the University there and received his Ph.D. in Berlin. He taught at the University of Oslo and did X-ray and electron diffraction studies on cyclohexane, showing that cyclohexane exists largely in the chair form. Because of World War II, when the Nazis imprisoned him for a while, his studies were at first not widely known. He received the Nobel prize jointly with Derek H. R. Barton in 1969 ("The Cyclohexane problem", Tidsskrift for Kjemi, Bergvesen og Metallurgi 3 (5) (1943), 32-34, translated by Kenneth Hedberg, N. L. Allinger and E. L. Eliel (eds.), Topics in Stereochemistry, Vol. 6 pp. 11-17, New York, Wiley-Interscience, (1971); see also Ramsay, Stereochemistry, (note 21).

(25) Vladimir Prelog was born in 1906 in Sarajevo, Bosnia-Herzegovina, studied in Zagreb and obtained his doctorate under E. Votocek in Prague. He carried out industrial and pharmaceutical research in Prague and Zagreb and taught in Zagreb, then moved to Zurich, Switzerland, to evade the Nazis. There he joined his countryman Leopold Ruzicka at ETH, whom he later succeeded as head of the organic chemistry laboratory, and received the Nobel Prize in 1975 jointly with John W. Cornforth. In the 1940s he and Arthur Cope independently discovered transannular reactions involving interactions from one side of a ring to the other. They met at the ACS Diamond

Jubilee Meeting in New York in 1951 and divided the field between them. Prelog has made pioneering contributions to stereochemistry and conformational analysis, applying the new insights to the understanding of the structures of antibiotics and other natural products. R. S. Cahn, C. K. Ingold, and Prelog developed the R,S system of designating the spatial arrangement of atoms and groups bonded to carbon. He and Ruzicka sought to bring Woodward to Switzerland, culminating in the establishment of the Woodward Research Institute in Basel in 1963 under the aegis of CIBA, later Ciba-Geigy. (Vladimir Prelog: My 132 Semesters of Chemistry, Washington D.C.: American Chemical Society (Profiles, Pathways and Dreams, series editor Jeffrey I. Seeman) 1991; see also Ramsay, Stereochemistry, (note 21.)) [69, 76-78, 86]

(26) Thomas Joseph Katz was born in Prague, Czechoslovakia, in 1936 and received his Ph.D. from Harvard in 1957. Professor at Columbia University, his main fields are non-benzenoid aromatic compounds, organometallics and organic synthesis. [98, 100, 103]

(27) Nancy Vaughan Acton, born in New York in 1937, obtained her Ph.D. at Bryn Mawr College in 1963. She joined the faculty at Bedford College, London, working particularly on polynuclear aromatic systems.

(28) Kurt Wilhelm Viktor von Tippelskirch was born in Neu Ruppin/ Brandenburg in 1880, studied law in Lausanne, Munich, Leipzig, and Berlin and joined the German foreign service in 1909. He

served at the German consulate in Shanghai 1911-1918, was vice-consul in Amsterdam, joined the Peace section of the foreign office in 1920, and from 1926 until his retirement in 1938 was consul in Boston. He died in Siberia in Soviet internment in 1943.

(29) Otto Diels (1876-1954) was born in Hamburg and obtained his Ph.D. with Emil Fischer in Berlin. He taught at Kiel. He and his doctoral student Kurt Alder (1902-1958, born in Königshütte) studied what has become known as the Diels-Alder reaction for which they received the Nobel Prize in 1950. Alder later taught at Cologne. The award-winning reaction involved formation of a six-membered ring from a conjugated diene (C=C-C=C) and an alkene (C=C). [17 and 98 (this volume pp's 00 and 00), 100.]

In their 1928 paper, Diels and Alder predicted the use of the reaction in natural product synthesis, but this was not done until Woodward and Louis H. Sarett's syntheses of cortisone (RBW [54]; L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns, J. M. Constantin, "Stereospecific Total Synthesis of Cortisone," <u>J. Am. Chem. Soc.</u> 74 (1952), 4974-6), and Gilbert Stork's of cantharidin (G. Stork, E. E. van Tamelen, L. J. Friedman, W. W. Burgstahler, "Cantharidin. A Stereospecific Total Synthesis," <u>J. Am. Chem. Soc.</u> 73 (1951), 4501).

On the background of the Diels-Alder reaction and its connection with the Woodward-Hoffmann rules see J. A.

Berson (note 18). On the early history of the reaction see M. C. Kloetzel "The Diels-Alder Reaction with Maleic Anhydride," Organic Reactions 4 (1950) 1-59; H.L. Holmes, "The Diels-Alder Reaction: Ethylenic and Acetylenic Dienophiles", *ibid*, 60-173.

(30) On oestrone (estrone) see [6, 7]; on cholesterol [51-53]; on cortisone [54, 60 (this volume p. 00)]; on reserpine [84, 85, 93 (this volume p. 00)].

(31) Harold Baer, born 1918, New York. After his Ph.D. from Harvard in 1943 he moved to Columbia University's College of Physicians and Surgeons, and Tulane University Medical School, followed by positions at the National Institutes of Health, and at the Food and Drug Administration specializing in allergenic products. [20, 30, 35]

(32) Virginia Rice Williams was born in North Little Rock, Arkansas in 1919. She obtained her Ph.D. in biochemistry from Louisiana State University in 1947 and then joined its faculty, with particular interest in enzymology.

(33) Bernard Robert Landau, born 1926, Newark, N.J. He obtained his Ph.D. at Harvard in 1950 and M.D. at Harvard Medical School in 1954, practiced medicine and then became director of the department of biochemistry at the Merck Institute of Therapeutic Research. In 1970 he joined the faculty at Case Western Reserve University.

(34) Robert S. Mulliken (1896-1986) was born in Newburyport, Massachusetts. He obtained his Ph.D. from the University of

Chicago where he taught most of his life. His Nobel Prize in 1966 recognized his development of the molecular orbital method for the understanding of bonds and the electronic structure of molecules (Robert Sanderson Mulliken, Life of a Scientist: An Autobiographical Account of the Development of Molecular Orbital Theory, edited by Bernard J. Ransil (Berlin/New York: Springer-Verlag, 1989); D. A. Ramsay and J. Hinze, editors, Selected Papers of Robert S. Mulliken (Chicago: University of Chicago Press 1975))

(35) RBW's coining of this chemical name appalled some recent readers, who described it as sophomoric and insensitive. Unfortunately it reflects the fact that RBW's chemical audiences even in the seventies were preponderantly male and such persiflage seemed still at times to be condoned. Yet no hint of laughter is audible on the audiotape of his lecture, available for a time from ACS. R. B. Woodward, according to the tape, began his presentation with: "Professor Streitwieser, Ladies and Gentlemen——or in these asexual days, should I say Gentle Persons...". Thus he was aware of changing sensitivities.

(36) Hermann Kolbe (1818-1884): Professor of Chemistry at Marburg and Leipzig, Germany. He carried out numerous organic chemical researches and made significant theoretical contributions, particularly in the study of organic radicals and their significance in the construction of molecules. He is best known for his total synthesis of acetic acid CH_3CO_2H

from its elements and for his vehement opposition to van't Hoff's proposal that the valences of a carbon atom were directed to the corners of a tetrahedron (H. Kolbe, "Zeichen der Zeit," Journal für praktische Chemie 1877, [2], 15, 473-477. Alan J. Rocke: The Quiet Revolution: Hermann Kolbe and the Science of Organic Chemistry, Berkeley: University of California Press, 1993). He was an outspoken critic of speculations that seemed to go beyond demonstrable data, fearing a return to prescientific myth-making.

(37) Elmer Peter Kohler (1865-1938) was born in Egypt, Pennsylvania. After obtaining his Ph.D. with Ira Remsen at Johns Hopkins University, he joined the faculty of Bryn Mawr College and was the first to teach a course in organic chemistry there. At Harvard he was renowned for his research and even more for his teaching, and one year served as dean of the graduate school. During World War II he helped the British organize the evacuation of civilians by railroad, and was head of research in a section of the U.S. Chemical Warfare Service.

(38) A. Lawrence Lowell (1856-1943), lawyer, political scientist, and educator, was President of Harvard from 1909 to 1933 during which time he reorganized the University's educational system and curriculum. After retirement he became head of the Motion Picture Research Council.

(39) John Bardeen, born 1908 in Madison, Wisconsin, obtained his Ph.D. in physics from Princeton University and taught at the

The Society of Fellows, The Society of Fellows of Harvard University, Harvard
University Press, 1959.)

University of Minnesota, then moved to the United States Naval Ordnance Laboratory, and Bell Telephone Laboratories, and then to the University of Illinois. He twice won the Nobel Prize in physics, in 1956 with Walter H. Brattain and William Shockley for the invention of the transistor, and in 1972 with Leon Cooper and John Schrieffer for superconductivity studies.

(40) Paul Anthony Samuelson, born 1915 in Gary, Indiana. After earning a Ph.D. from Harvard, he taught economics at the Massachusetts Institute of Technology for forty-five years and won the Nobel Prize in economics in 1970 in the field of economic analysis.

(41) McGeorge Bundy, government official and educator, was born in Boston in 1919, graduated from Yale with an A.B., taught at Harvard (where for eight years he was also dean of the faculty of arts and sciences) and New York University. He was Assistant to the President for National Security for John F. Kennedy 1961-3, and for Lyndon B. Johnson 1963-6, and then became President of the Ford Foundation.

(42) Daniel Ellsberg, economist, political scientist, and author, was born in 1931 in Chicago, and was educated at Cambridge and Harvard Universities, obtaining his Ph.D. in economics from the latter. He volunteered for service in the U.S. Marine Corps, advised John F. Kennedy on military policy while the latter was Senator from Massachusetts and then joined the Rand Corporation. During Lyndon Johnson's presidency, he advised Robert S. McNamara, and later Robert Kennedy and Henry

Kissinger. Beginning as an enthusiastic supporter of the Vietnam War, he changed to a bitter critic, culminating in his releasing the "Pentagon Papers" to the New York Times. The court case against Ellsberg was dismissed, the judge citing serious government misconduct.

(43) Saul Winstein (1912-1969) was born in Montreal, Canada, obtained his Ph.D. with Howard J. Lucas at the California Institute of Technology, and taught at the University of California, Los Angeles, where he became one of the leading physical organic chemists of his time.

Winstein is probably best known for his controversy with Herbert C. Brown on the "non-classical carbonium ion" (Paul D. Bartlett, a) "The Scientific Work of Saul Winstein," Journal of the American Chemical Society 94 (1972) 2161-8, and b) Non-Classical Ions. Reprints and Commentary, New York: W. A. Benjamin, 1965; Edward M. Arnett, Thomas C. Hofelick, George N. Schriver, "Carbocations," in Maitland Jones Jr. and Robert A. Moss (editors) Reactive Intermediates 3 (1985) 189-226). [80]

(44) Robert Lewis Autrey was born in 1932 in Indio, California. He obtained his Ph.D. at Harvard in 1958 and taught at his alma mater Reed College, followed by the University of Rochester, Harvard, and the Oregon Graduate Center. He then entered industry, becoming manager of research and development at Nerco, Inc. in 1983.

(45) H. M. R. Hoffmann and D. R. Joy, "Cycloaddition of Allylic Cations to Conjugated Dienes: Stereochemistry," *Journal of the Chemical Society* B (1968), 1182-86.

(46) H. H. Inhoffen and K. Irmscher, "Progress in Chemistry of Vitamin D and Its Derivatives," *Fortschritte der Chemie organischer Naturstoffe* 17 (1959), 70-123; H. H. Inhoffen, "Aus der Chemie der antirachitischen Vitamine," *Angewandte Chemie* 72 (1960), 875-881.

Hans Herloff Inhoffen, born 1906 in Hannover-Döhren, obtained his Ph.D. with Hermann O. L. Fischer in Berlin, taught at the Universities of Göttingen, Marburg, and Braunschweig and, before Marburg, was director of the central research laboratory at Schering A.G. He synthesized estrone, which RBW had attempted in his Ph.D. research, as well as vitamins A and D. The synthesis of ß-carotene was completed independently by Inhoffen and by Paul Karrer. He published articles jointly with RBW in 1953 and 1968 [62, 153].

(47) I. V. Smirnov-Zamkov, "Formation of a Cyclobutene Ring in the Chlorination of Dimethylacetylene," *Doklady Akad. Nauk SSSR* 83 (1952), 869-71; I. V. Smirnov-Zamkov and N. A. Kostromina, "The Reaction of Sulfuryl Chloride with Dimethylacetylene," *Ukr. Khim. Zhur.* 21 (1953), 233-9.

(48) P. S. Skell and S. R. Sandler, "Reactions of 1,1-Dihalocyclopropanes with Electrophilic Reagents. Synthetic Route for Inserting a Carbon Atom between the Atoms of a

Double Bond," Journal of the American Chemical Society 80 (1958), 2024-5.

Philip Skell, born in New York in 1918, obtained his Ph.D. in 1942 at Duke University with Charles R. Hauser, and taught at Pennsylvania State University. He has studied free radicals, carbenes, and carbocations.

(49) Emanuel Vogel, H. Kiefer, and W. R. Roth, "Bicyclo[4.2.0]octa-2,4,7-triene," Angewandte Chemie 76 (1964), 432-3, Angewandte Chemie, International Edition, 3 (1964), 442- .

Vogel was born in 1927 in Ettlingen, Germany, and studied under Rudolf Criegee in Karlsruhe, doing research on cyclobutene and cyclobutadiene. Prior to his Habilitation in 1957 he spent six months with Arthur Cope at MIT (see headnote). His studies of small and large ring systems supplied examples for the later Woodward-Hoffmann rules, and of the Cope rearrangement, as well as demonstrating the power of the Hückel (4n+2) rule (fn. 51). In 1961 he was called to be professor at Cologne University.

Wolfgang Roth, professor at Ruhr Universität Bochum, worked with Doering on the stereochemistry of the Cope rearrangement (W. von E. Doering, W. R. Roth, "The Overlap of Two Allyl Radicals or a Four-centered Transition State in the Cope Rearrangement," Tetrahedron, 18 (1962) 67-74; also see Doering in Headnote).

(50) Bolevant Singh: The editors could find no information about him.

(51) Erich Hückel (1896-1981) born in Charlottenburg, Germany, obtained his Ph.D. in Göttingen with Peter Debye, and taught at the universities of Stuttgart and Marburg. Debye and Hückel are well known for their theory that explained why salt solutions behave as if they are not completely ionized.

His application of molecular orbital theory in 1931 to cyclic conjugated systems ("Quantum-theoretical Contributions to the Benzene Problem. The Electron Configuration of Benzene and related Compounds," Zeitschrift für Physik 70 (1931), 204-286) largely unrecognized by German organic chemists in the 1930's, made possible the prediction of those, like benzene, of considerable stability and aromatic properties. Such structures contain 2,6,10,14 etc. unsaturation electrons in their rings.

(52) Linus Carl Pauling was born in 1901, in Portland, Oregon, and obtained his Ph.D. from the California Institute of Technology, where he then served on the faculty and as an administrator. He moved to the University of California at San Diego and to Stanford University, and became president of the Linus Pauling Institute of Science and Medicine. He obtained the Nobel Prize in chemistry in 1954 for his pioneering studies of chemical bonding, and the Nobel Peace Prize in 1962 for mobilizing the world's scientists to end nuclear testing in the atmosphere. He proposed the helical structure of many proteins and has been investigating the health effects of large doses of vitamins (Linus Pauling, The

Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry. Ithaca, New York: Cornell University Press, 1939; Second Edition 1940, Third Edition 1960).

(53) R. B. Woodward "Synthesis" in Perspectives in Organic Chemistry, Sir Alexander Todd, editor. New York, Interscience Publishers, Inc., 1956, p. 155-184. [51]

(54) Albert Eschenmoser, born in 1925 in Erstfeld, Switzerland, obtained his Ph.D. with Leopold Ruzicka and Placidus Plattner at ETH, Zurich where he now teaches. An organic chemist, renowned for his skill in synthesizing complex molecules, he collaborated with Woodward on the synthesis of vitamin B_{12}. They constructed complementary halves of the molecule and each found a way of combining them. During the work Woodward encountered the puzzling ring-closure data that led to the orbital symmetry rules, his Cope Award with Hoffmann, and Hoffmann's Nobel Prize. Eschenmoser received the Cope Award in 1984. (Albert Eschenmoser, Claude E. Wintner, "Natural Product Synthesis and Vitamin B_{12}," Science 196 (1977), 1410-1420; RBW: [154 (this volume p. 00), 168, 172.)

(55) James D. Watson, molecular biologist, was born in Chicago in 1928, and obtained his Ph.D. at Indiana University. As an undergraduate at the University of Chicago he was "principally interested in birds" (James D. Watson, The Double Helix, New York, Atheneum, 1968, p.21). He held research fellowships in Copenhagen, Cambridge, England, and at the California

Institute of Technology, then taught at Harvard before becoming director of the Cold Spring Harbor Laboratory and more recently and concurrently (and briefly) director of the National Center for Human Genome Research. He won the Nobel Prize in 1962 with Francis H. C. Crick and Maurice H. F. Wilkins for their elucidation of the structure of DNA. (J. D. Watson, F. H. C. Crick, "A Structure of Deoxyribose Nucleic Acid." Nature 171 (1953), 737-8. See also Robert Olby, The Path to the Double Helix, Seattle: University of Washington Press, 1974; Franklin H. Portugal, Jack S. Cohen, A Century of DNA, Cambridge, Mass.: MIT Press, 1977.)

(56) Francis H. Crick, biologist and educator, was born in 1916, graduated from University College, London, and obtained his doctorate from Cambridge University. He worked at the Medical Research Council Laboratory of Molecular Biology for twenty-eight years, then at the Salk Institute for Biological Studies in San Diego, California. With James D. Watson and Maurice H. F. Wilkins he shared the 1962 Nobel Prize for physiology and medicine (note 55). (Francis Crick, What Mad Pursuit: A Personal View of Scientific Discovery. New York: Basic Books, 1988.)

(57) Subramania Ranganathan worked at the Woodward Research Institute in Basel, and has been on the faculty of the Indian Institute of Technology in Kanpur. In addition to the three books mentioned by RBW, the first of which was coauthored by Nitya Anand and Jasjit S. Bindra (San Francisco, 1970), and

the others by Darshan Ranganathan (San Francisco, 1967 and New York, 1972), he wrote with Darshan Ranganathan The Appreciation of Molecular Transformations in Organic Chemistry (Delhi, India, 1975); Art in Biosynthesis: The Synthetic Chemist's Challenge (New York, 1976); and Further Challenging Problems in Organic Reaction Mechanisms (New York, 1980). In addition to his work leading to the vitamin B_{12} synthesis and the Woodward - Hoffmann rules, he was a member of Woodward's group that made cephalosporin C, the synthesis Woodward described in his Nobel lecture included in this volume, p. 00. [139, 142]

(58) When a molecule contains a carbon-carbon double bond the four atoms attached to the doubly-bonded carbons are in a plane. When one of the bonds of a double bond in a conjugated polyene chain is broken to form a new bond, planarity is lost and the attached groups rotate around the axis of the bond either in a clockwise or anti-clockwise direction. In the ring formations discussed by Woodward and Hoffmann, two such double bonds lose their planarity. Conrotary motion means the two sets of rotation are in the same direction. Rotations in opposite direction are disrotatory. (On the forerunners of the Woodward-Hoffmann rules, see Jerome A. Berson, note 18 above.)

(59) In his lecture, Woodward commented regarding slide 14: "There you see a visual expression of Thiele's views of interactions within a conjugated system, with some partial valences left over."

(60) Roald Hoffmann was born in 1937 in Zloczow, Poland (now Ukraine) and lived much of the war hiding from the Nazi occupiers. He came to the United States in 1949, attended Stuyvesant High School, Columbia University, and Harvard, where he gained the M.A. in physics and Ph.D. in chemical physics. He moved to Cornell in 1965 where he is now John A. Newman Professor of Physical Science. For his part in elucidating the orbital symmetry rules he was awarded the Nobel Prize in chemistry in 1981, sharing it with Kenichi Fukui of Kyoto University who had reached similar conclusions independently. He describes his research field as applied theoretical chemistry.

At Columbia, Hoffmann was influenced by poet Mark Van Doren and has himself published several volumes of poetry. He was host on the 26-part television series "The World of Chemistry," and collaborated with the artist Vivian Torrence in a traveling exhibition of her collages with his commentaries and meditations, "Chemistry Imagined." This has also appeared as a book (Washington D.C.: Smithsonian Institution Press, 1993.)

Hoffmann was awarded the American Chemical Society's highest award, the Priestley Medal, in 1990. [131, 133-6, 150, 161-3, 171, 174, 193. For papers 131, 133, 134 and 148 see this volume pages 00.]

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Ted

Alfred - Here is an early version. It's been edited some. Please suggest changes, additions etc.

Thanks, Ted

For [illegible]

ROBERT BURNS WOODWARD
1917—1979

Elected For. Mem. R.S. 1956

By Lord Todd, O.M., F.R.S., and Sir John Cornforth, F.R.S.

Reprinted without change of pagination from
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Volume 27, November 1981

RBWoodward

ROBERT BURNS WOODWARD

10 April 1917 — 8 July 1979

Elected For. Mem. R.S. 1956

By Lord Todd, O.M., F.R.S., and Sir John Cornforth, F.R.S.

In his lifetime Robert Burns Woodward made outstanding contributions spanning almost the whole range of theoretical and experimental organic chemistry. In preparing this biographical memoir the authors were of the opinion that separation of biographical detail from a discussion of his scientific contributions would make for greater clarity in presentation. Accordingly the memoir is presented in two parts—a personal biography of R. B. Woodward (by A. R. T.) and a discussion of his scientific work (by J. W. C.).

Personal Biography

(A. R. T.)

Robert Burns Woodward was born in Boston, Massachusetts on 10 April 1917, the only child of Margaret Burns and Arthur Woodward. His father died in October 1918 at the early age of thirty-three; in effect then Bob Woodward never knew his father and, indeed, he never referred to him in my presence save to say that he was of English antecedents. Bob's mother was born in Glasgow and he was very proud of his Scottish descent, claiming (I do not know with what justification) a relationship to Scotland's national poet Robert Burns. Left badly off by the premature death of her husband Mrs Woodward had to work hard and long to support her son whose early upbringing was therefore far from luxurious but was sustained and enriched by a devoted mother to whom he was deeply attached. Both his primary and secondary education were received in the public schools of Quincy, the Boston suburb where he lived. Attracted to chemistry at a very early age he carried out quite elaborate experiments in a laboratory which he set up in his home thereby causing, we are told, frequent concern to his mother and to the neighbours. Even in those early days the young Woodward was a non-conformer who did not take well to school routine and discipline although he was certainly recognized by his teachers as a boy of quite unusual ability. He left high-school in 1933 with an outstanding scholastic record and an aversion to games involving physical exercise which remained with him throughout his life.

Our knowledge of these early days is fragmentary, but on the occasion of his obtaining his doctorate from the Massachusetts Institute of Technology the *Boston Globe* on 9 June 1937 devoted no less than three columns to an account of his career. In this article Bob Woodward's career at school was summarized in the following paragraph:

> 'As a boy in short pants in Quincy Grammar School, Massachusetts he consistently brought home report cards dimmed with a pair of D's—for *conduct* and *effort*. The Woodward youngster, who was always fooling in the cellar with a chemistry set, received three double promotions—hurdling the 4th, 7th and 10th grades—all the while whispering in classes, blowing bubble gum, being the last one 'in' after recess and pulling the little girls' long curls. Dr Woodward—ask anyone in Quincy—was a hellion.'

Whether or not the *Boston Globe* reporter was accurate in his description we do not know, but we do know that chemistry was not Woodward's sole interest in school; while there he developed a deep interest in mathematics and in literature of all types, which remained with him throughout his life. There must surely have been some good and perceptive teachers at Quincy in those days.

In the autumn of 1933 at the age of sixteen the young Bob Woodward presented himself for enrolment at the Massachusetts Institute of Technology to study chemistry. His enrolment or, better, the sequel to his enrolment, caused a good deal of consternation for he quickly made it clear that he wanted to spend all his time as an undergraduate in the library and the laboratory, to take the final examinations without attending the set courses, and to forget about compulsory courses in physical education. It goes almost without saying that these proposals were never fully accepted by the Institute authorities and Woodward himself has stated that he was excluded from M.I.T. for inattention to formal studies at the end of the Fall term of 1934. The Institute authorities, however, generously allowed him to re-enrol in the Fall term of 1935 and he took the B.S. degree in 1936 (but only after a brief but highly intensive effort in the gymnasium in order to fulfil one of the basic requirements for graduation). Once the obstacle of physical training had been removed there were no more formal barriers to his progress and he completed his doctorate in the spring of 1937 when only twenty years of age. It may be noted in passing that his problems with physical education had nothing to do with health or physique, for Woodward was a powerfully built and remarkably strong man—but he loathed physical exercise. That he was permitted to follow such an extraordinary course of study and to emerge a graduate of M.I.T. was undoubtedly due to the perspicacity and persistence of Professor James F. Norris who early recognized that this brash but extraordinarily self-assured youngster was, like himself, an unshakable optimist with a passion for chemistry and an inordinate capacity for hard work, but also had in him at least some of the signs of genius. In 1937 Professor Norris observed 'Woodward is brilliant but, unlike some scholars, he will not burn out suddenly. We are convinced that he will make a distinguished name for himself in the scientific world.' How right he was!

Immediately after taking his Ph.D. Woodward took a post for the summer session at the University of Illinois. This was not a success on either side. As his friend Professor Paul Bartlett has put it 'this short contact with the grass roots left him less than a naturalized mid-westerner'. Woodward and the Illinois Chemistry Department parted, to their mutual satisfaction, in the autumn of 1937 and he returned to Boston to take up an assistantship under Professor E. P. Kohler at Harvard University. As it turned out he was to remain at Harvard and adorn its school of chemistry without a break until his death forty-two years later. Quickly recognized by Kohler as quite unusually gifted Woodward was elected Junior Prize Fellow of the Harvard Society of Fellows in 1938. This appointment gave him complete freedom to devote as much time as he wished to study and research, and also enabled him to savour and enjoy the cultural life of Harvard and to indulge further his taste for mathematics. In later years Bob frequently looked back with nostalgia to this period and continued to hold the Society in great affection throughout his career. During the three years he held the Fellowship he produced several short papers dealing with experimental problems including one (5) on the introduction of angular methyl groups and, in 1941, the first (11) of a series of papers (11, 12, 15, 16) in which he correlated ultraviolet absorption spectra with structure among αβ-unsaturated ketones and conjugated dienes. Equally important, perhaps, it was during this period that he began to work out ingenious and increasingly plausible schemes for the total synthesis of quinine, cholesterol, and other complex natural products. To put such schemes to the test was hardly possible for one man and he developed a hunger for collaborators which could not be satisfied while he remained a single-handed member of the Society of Fellows with no access to students. It was doubtless for this reason rather than for any love of undergraduate teaching that he resigned his Fellowship in January 1941 to become Instructor in charge of the advanced organic laboratory in the Harvard University Chemistry Department. In this position he, by his enthusiasm, soon attracted a number of students to collaborate with him in research carried out mainly outside normal working hours at night and on Sundays and by 1944 when he was promoted to the rank of Assistant

Professor he had already published papers with eight junior collaborators. From then onwards the number of his collaborators and the scale of his activities increased rapidly. Promoted Associate Professor in 1946 and full Professor in 1950 he became Morris Loeb Professor of Chemistry in 1953 and in recognition of his outstanding contributions was appointed Donner Professor of Science in 1960. In this position, which he occupied until his death, he was freed from all formal teaching duties and could devote his entire time to research.

During his long association with Harvard the size of his research group grew continually and to it flocked young organic chemists from every corner of the globe; he must have had in total something like four hundred junior collaborators, most of them at postdoctoral level. In addition to these he stimulated, and in part directed, the efforts of research groups in a number of industrial firms with which he was associated as a consultant. From 1963 onwards he had a further group in Basle where, while continuing his work at Harvard he directed the Woodward Research Institute, set up by Ciba Ltd specifically that he might there pursue research on any topic he wished, in the valid belief that progress in synthetic organic chemistry must inevitably lead, at shorter or longer range to progress in the chemical industry. In keeping with his extraordinarily retentive memory Woodward had an unusual capacity for directing simultaneously, and in detail, the work of many individuals. When twitted on one occasion about the large size of his research group he is reported to have replied that bearing in mind the rate at which the average graduate student produced results there was no obvious limit to the number he could keep up with—an arrogant statement perhaps, but one with more than a germ of truth in it!

It was, I believe, Woodward's first paper (11) on the relation between structure and absorption spectra of αβ-unsaturated ketones that first drew world wide attention to him as a new and rising star in the chemical firmament. It was typical of his constant search for improved methods of structural elucidation, that he should have sought thus early in his career to relate absorption spectra to functional groups, even when the theoretical basis for such relations was not yet understood and his work on αβ-unsaturated ketones gave a very substantial spur to the use of electronic spectra in structural organic chemistry. In many ways his 1941 paper (11) reflects both Bob Woodward's interests in, and approach to, organic chemistry. He had wide interests and made monumental contributions both in theory and practice, but the main area of his first-hand engagement with chemistry was the investigation of natural products. This field of interest he described in his own words as 'endlessly fascinating in itself, and one which presents unlimited and unparalleled opportunities for the discovery, testing, development, and refinement of general principles'. How true that description is can be clearly seen in his own record of achievement. For him theory rested on experimental fact and without experimental proof it was, in his view, worthless. He always expressed admiration for the classical work on structure determination by degradative methods but, realising that the introduction of physical methods of analysis could relieve structural work of much drudgery, he sought continually to develop and promote their use by organic chemists. His pioneering work on the use of ultraviolet absorption spectra in structural chemistry had its origin in the frequent occurrence and importance of αβ-unsaturated ketones among steroids and terpenoids, and he was later a pioneer in the use of infrared and nuclear magnetic resonance spectroscopy; indeed, without his enthusiasm and drive the use of these techniques in organic chemistry would have been much slower to develop, and their almost revolutionary impact on the science delayed. Synthesis—the culmination of work on a natural product—was the area to which Woodward devoted his main efforts and the one in which his artistry and his mastery of reaction mechanisms could be seen at their outstanding best. There was little in the way of serendipity about his syntheses, and every step was carefully planned in advance. To use his own words again 'Synthesis must always be carried out by plan and the synthetic frontier can be defined only in terms of the degree to which realistic planning is possible, utilizing all of the intellectual and physical tools available'. But in the course of synthesis any novel or unexpected result whether of a main or a side reaction was always noted and explored by him. It was his determination to understand, and by the power of thought to predict, that enabled him to make his important contributions to our understanding of the mechanism of chemical reactions as exemplified in the Woodward–Hoffmann rules on the conservation of orbital symmetry in cyclisation reactions.

From his earliest days working in his home laboratory in Quincy he was fascinated by the beauty of molecular structures and by the making and breaking of chemical bonds, especially in relation to stereochemical control. It was perhaps for this reason that he so admired the work of Archibald Scott Couper whom he regarded as the real father of structural organic chemistry but whose contribution, although in Woodward's view more important, was regrettably much less known and recognized than that of Kekulé. Bob was both interested in, and very knowledgeable about, the early history of organic chemistry and Couper's role in the development of structural theory was discussed with the writer on many occasions. In a curious kind of way he rather identified himself as a kind of modern Couper but was determined that his contributions to theory would not be similarly neglected. By the time he entered M.I.T. his lifelong interest in the Diels–Alder reaction had already been aroused by reading the original paper of these authors (*Justus Liebigs Annln Chem.*, 1928, **460**, 98) and indeed he used the reaction in some preliminary experiments on the synthesis of oestrone (6) carried out in the mid-thirties. During this period he was also engaged in extensive reading and in planning his first major venture in natural product chemistry, the total synthesis of quinine which he published (with W. E. Doering) in 1944. It was then too that he attracted the attention of Dr E. F. Land of the Polaroid Corporation, with whom he established a fertile professional and personal relationship which was to last throughout his career, and it was indeed the Polaroid Corporation which supported this, his first major synthesis. The quinine synthesis displays clearly the features which characterized all Woodward's synthetic work—meticulous planning based on available knowledge of reaction mechanisms, derived from wide reading and original thought with a built-in flexibility able to cope with the unexpected.

During the period of World War II Woodward played an important part in the joint Anglo-American effort on penicillin and he was indeed the first to postulate the correct structure of that antibiotic. It was through the penicillin work that he first swam into the ken of Robert Robinson, although real contact between those two chemical giants was really established somewhat later through their mutual interest in strychnine and other indole alkaloids. Initially relations were, on Robinson's side at least, rather frosty for he was somewhat taken aback by the young American's aggressive self-assurance; but he soon recognized Woodward's ability and the two became fast friends, each recognizing in the other the same basic passion for organic chemistry. These two men, each perhaps the leading organic chemist of his generation, were very different in personality yet essentially similar in their interests—reaction mechanism on the theoretical side, with natural products as the central feature of their activity, and biogenetic theory as a less prominent but none the less abiding interest. There were, of course, marked differences within these interests. On the theoretical side Woodward's interest was in chemical bonding, whereas Robinson was much more concerned with electrochemical theories of reaction, i.e. with electrical effects such as induced alternating polarities in carbon chains. To a degree this difference reflects the difference in the state of theory during the formative years of the two men. But in the approach to synthesis the difference was essentially one of personality. Robinson was much more mercurial and depended much more on spontaneity and adaptability; Woodward rarely depended on spontaneity—all was carefully considered and planned beforehand. Had they been true contemporaries they could have made a remarkable team! As it is, those privileged to know these two men have had a rich and unforgettable experience.

From 1944 when he published his quinine synthesis Woodward's record is surely unparalleled by that of any other organic chemist in this century, and perhaps in the whole history of the science. Between 1944 and his death thirty-five years later, he completed total syntheses of patulin (1950), cholesterol (1951), cortisone (1951), lanosterol (1954), lysergic acid (1954), strychnine (1954), reserpine (1956), chlorophyll

(1960), the tetracyclines (1962), colchicine (1963), cephalosporin C (1965), prostaglandin $F_{2\alpha}$ (1973) and—that monster among natural products—vitamin B_{12} (1972), the last named being in part a cooperative effort with Albert Eschenmoser. To this impressive list must be added the structural elucidation of, among others, patulin (1949), terramycin (1952), aureomycin (1952), cevine (1954), magnamycin (1956), gliotoxin (1958), oleandomycin (1960), streptonigrin (1963), tetrodotoxin (1964). He also made notable contributions to the synthesis of peptides and polypeptides and to biogenetic theory in the indole alkaloid, steroid and macrolide fields. In keeping with his steadfast belief that the power of thought and understanding could master any material problem and his delight in the beauty of chemical structures he made outstanding contributions to theoretical aspects of his subject. His early work on the absorption spectra of αβ-unsaturated ketones has already been mentioned; this was followed by his recognition of the structure and aromaticity of ferrocene and other metallocenes (1952) by the 'octant rule' in the rotatory dispersion of ketones and finally by the brilliant contribution in collaboration with Roald Hoffmann on the conservation of orbital symmetry in cyclo-additions—a contribution which some have compared in importance to Kekulé's announcement of the cyclic formula of benzene. These matters will be touched upon in more detail in the section of this memoir devoted to Woodward's scientific contributions but they are mentioned here to give an idea of the quite outstanding range and brilliance of the man—features evident in him from an unusually early age.

The writer (A. R. T.) had a fleeting encounter with Bob Woodward in Boston in 1938 but our first real personal contact and the start of a lifelong friendship was in 1948 when he visited England as a side trip on his first visit to Europe as American Swiss Foundation Lecturer—a visit vigorously promoted by Leopold Ruzicka and Vlado Prelog. Thus began not only his lasting friendship with Prelog but also his long and close association with Switzerland and its chemists. Efforts to have him leave Harvard and settle at the Eidgenössische Technische Hochschule in Zürich, although vigorously pursued, were unavailing but in the end a method deepening and rendering permanent his Swiss association was found in 1963 when Ciba Ltd—largely at the instigation of Albert Wettstein—created the Woodward Research Institute alongside the company's headquarters in Basle. There Woodward was able to carry out part-time direction of a group of research workers on topics not unconnected with the company's interests but essentially of his own choosing. There he directed a series of brilliant studies on cephalosporin antibiotics—work which he presented in Stockholm on the occasion of his receipt of the Nobel Prize for Chemistry in 1965. In addition, towards the end of his life a new series of synthetic antibiotics—the cephems—was discovered in the institute, while some of Bob's other qualities were recognized by his appointment to the Board of Directors, first of Ciba Ltd, and then of its successor Ciba-Geigy Ltd. While it is true that the Basle institute revolved round Woodward himself it is sad that a laboratory which produced so much in its sixteen years of life should have been closed down following his death. Even before the creation of the Woodward Institute Bob's visits to Europe, and indeed to many overseas countries, had become rather frequent for he was greatly in demand as much for his brilliance as a lecturer as for the outstanding results of his research.

Bob Woodward was a brilliant lecturer who had many of the qualities of a first-class actor; his lectures were not merely brilliant expositions of his work—he imparted to them more than a touch of the theatre. His equipment for a lecture was, during most of his career, invariable. Until late in his career he eschewed the use of slides; instead he carried with him a small black box containing a selection of coloured chalks and a carefully folded duster. Every step in his chemical story was illustrated by formulae drawn on the blackboard with consummate artistry and meticulous accuracy, with chalks of various colours. There was nothing slapdash about Woodward's lectures and they were indeed carefully rehearsed. The somewhat theatrical style, with continuous drawing and redrawing of complicated chemical formulae, had as one of its main objects a slowing down of the presentation so as to increase the ease with which it could be appreciated by his audience. Moreover, when coupled with his histrionic ability, it gave his public lectures—invariably entitled 'Recent advances in the chemistry of natural products'—something of the flavour of an evangelical gathering. Certainly I have never seen any other scientist who could hold an audience of chemists—and especially young chemists—spellbound not just for one hour but for several hours on end. He undoubtedly strove deliberately to make the length of his lectures legendary—he himself claimed as his record a lecture at Karlsruhe which was said to have lasted 5 hours and 20 minutes! Yet there was nothing artificial or specious about either his work or his lectures; his own passion for chemistry shone through everything he did, and it was this I believe which made him idolized by young organic chemists throughout the world.

The actor in Woodward or, better put, his feeling for the theatre and the use to which it could be put, was evident not only in his lecturing style. It appeared also in other ways and notably in his addiction to unusual hours for work and for discussions. His famous Thursday night seminars with his group in his room in the Harvard laboratory, which began in the evening and lasted well into the small hours, provide another example. Here many brilliant ideas would emerge, apparently spontaneous and unpremeditated, and some at least of his audience got the impression that all that was necessary to produce brilliant ideas was a bottle of whisky and several packs of cigarettes (for Bob was an inveterate smoker and a heavy—although not excessive—drinker). In this they were wrong; the style of his seminars concealed—as did his showmanship in the lecture theatre—the immense amount of reading and thinking Bob Woodward put into the preparation of his lectures and his apparently spontaneous contributions to seminars. For he was an extremely hard worker, a voracious reader and he had a quite extraordinary memory for detail. But he strove continually to build an image of himself as a unique person indifferent to, if not immune from, the trials of everyday life; his other well known foibles like his invariable blue lounge suit, white shirt and light blue tie were all, I believe, designed to be part of that image. Yet despite his passionate devotion to chemistry, his long working hours and his desire to be recognized as something unique, Woodward read widely outside science, loved parties and was addicted to puzzles and games, provided always that the latter did not entail physical exertion which he abhorred. Just how his scorn for physical exercise originated I do not know, but he made no secret of it. However, it is true that on one occasion I prevailed upon him to play golf and, during a memorable three-family holiday in the Swiss Alps he actually climbed a small mountain! His friend Paul Bartlett once said of him 'He works and plays with equal intensity and endurance. He sleeps only as a last resort'. And indeed there was some truth in this for Bob Woodward was one of those unusual people who sleep much less than most of their fellows; he claimed indeed never to have slept more than three hours out of twenty-four for as long as he could remember. This ability to do without sleep coupled with his incessant smoking, heavy consumption of alcohol and total lack of exercise led him to believe, at least in his middle and later years, that he was in fact different from other people and that he would not be sùbject to the frailties of his fellow men. In this, of course, he was in the end and quite inevitably proved wrong. Nevertheless he did differ markedly from most of his fellow men in a number of ways and notably so in his astonishing chemical and mathematical precocity.

It is, in my experience, not uncommon to find that well known chemists have been interested in their science from early youth and have dabbled with it experimentally in makeshift laboratories in their family homes; but as a rule these activites could best be described as childish dabblings with a subject which for one reason or another attracted them but of which they had little real knowledge or understanding. This was not so with Bob Woodward, who not only had some kind of laboratory in his home at Quincy but had by the time he was twelve years of age repeated in it a considerable range of the standard experiments set out in Gattermann's famous text-book and normally carried out in first-year practical course of organic chemistry in universities at that time. In a remarkable unpublished lecture delivered by him to the American

Chemical Society in Chicago on 28 August 1973 on the occasion of his receiving (with Roald Hoffmann) the first Arthur Cope Award, Woodward stated that while still only eleven years of age he became aware through references in chemical textbooks which he read in the Boston Public Library that there existed journals which regularly published results of chemical research. He accordingly got in touch with the German Consul-General in Boston, Baron von Tippelskirch and through him obtained specimen copies of the three main German periodicals *Berichte der deutschen Chemischen Gesellschaft, Journal für praktische Chemie* and *Justus Liebigs Annalen der Chemie*.* The specimen of the last-named chanced to be the first issue of 1928 and contained the famous paper of Otto Diels and Kurt Alder announcing their discovery of the cycloaddition involving olefines and dienes known as the Diels–Alder reaction. The Diels–Alder paper fascinated Woodward who claimed that prior to reading the paper he had concluded that such a reaction must occur if one were to explain the separate existence—however transient—of the two Kekulé forms of benzene. However that may be, it is certain that his reading of that original paper in the *Annalen* was the start of a lifelong interest, both practical and theoretical, in the Diels–Alder reaction, and so played an important role in the train of events leading finally to the development of the Woodward–Hoffmann rules on orbital symmetry relations. The depth and extent of Woodward's chemical knowledge at this very early age may help to explain not only the wholly unorthodox nature of the course of undergraduate studies at M.I.T. but also why his behaviour was permitted and indeed condoned by Professor Norris and his colleagues there. His astonishing precocity, and his consequent self-assurance in matters chemical, were no doubt responsible for a degree of brashness and arrogance in him as a young man, and he was certainly not universally popular among his fellow scientists. Much of the brashness was lost as he matured and his arrogance diminished as he realized that judgement of others by his standards often did them less than justice; but his scorn for the pretentious and the superficial remained with him throughout his life.

From what has been written above it is clear that Bob Woodward had more than a streak of genius in his make-up, that he had a record of scientific achievement unequalled by any of his contemporaries, and that his name will live and rank among the greatest in organic chemistry. But what kind of man was he? Despite the impression he conveyed to many people he was not a narrow specialist with restricted interests. He read widely and avidly being especially fond of biography and was both interested in and knowledgeable about world affairs. He held very definite and usually very pertinent views on most subjects and he loved a

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* It has not been possible to get details of the correspondence or contacts between Woodward and the Consul-General. Kurt Wilhelm Viktor von Tippelskirch, born at Ruppin in 1878, was German Consul-General at Boston from 1926 to 1938; he died in Siberia in Soviet internment in 1943.

good argument with his friends. His primary interest and indeed his passion was however for organic chemistry. This quite unusual devotion to one science—for he displayed no deep interest in any other—coupled with his precocity set him rather apart from his fellow students in his youth and he formed few friendships. The 'lone wolf' characteristics thus developed remained with him throughout his life and he made few intimate friends. Even his young collaborators who were deeply attached to him rarely had much in the way of contact with the real Bob Woodward who existed behind the facade of indifference to human affairs which he presented to the world at large. He did have a deep interest in mathematics and he confessed that at one point in his undergraduate days he toyed with the idea of making his career in that subject. I recall discussing with him late one evening factors which had influenced us in our respective careers and I asked him why he had taken to organic chemistry rather than mathematics. He confessed that, like myself, he loved the material or, as he put it, the sensuous aspects of organic chemistry—the growth of crystals, the colours, the experimental techniques and even the smells—and was fascinated by the sheer beauty of molecular structures; he was especially attracted by the making and breaking of chemical bonds and by stereochemical control. The need for chemistry to conform to the hard reality of an existing world rather than, like mathematics, to be almost independent of it was a further source of attraction. To Woodward, theory was always subservient to experimental fact and he was inexorably drawn to synthesis not only for the scope it gave for logical thought but also for the finality of its outcome.

Woodward's passion for chemistry and his habit of pursuing it at all hours of the day and night made him difficult to live with and was hardly conducive to domestic harmony. In 1938 he married Irja Pullman whom he had known since schooldays but the marriage which produced two daughters Siiri and Jean lasted only a few years. His second marriage in 1946 to Eudoxia Muller gave him a daughter, Crystal and a son Eric. Doxie, as she was known to all her friends, was a charming and devoted wife but this marriage too, although it lasted much longer than the first also ended in divorce. Bob, although he found it difficult to cope with the very young, loved his children and was always ready to help them in times of trouble; if he had a fault it was perhaps in being at times a little over-indulgent towards them. On the whole he had little time for family life or for holidays. There is a story told of a prospective postdoctoral worker who asked him what holidays he might expect if he joined the Woodward group. Bob it is said replied that he himself sometimes took Christmas Day off.

Yet on at least one occasion he did have a brief family holiday when immediately after the International Chemical Congress in Zürich in 1955 three families—the Joneses from Oxford, the Todds from Cambridge and the Woodwards from Harvard—spent a few days together in the mountains at Lenzerheide. There for a few days he really relaxed away from his chemistry and in the company of eight children of various ages; he even discarded his legendary blue lounge suit and tie at times and did quite a bit of hill walking. He could indeed relax for short periods and I recall him as a gay and delightful companion on a number of extended trips we made together to Singapore, Australia, Egypt and India and one especially memorable one made with an international group of chemists to Australian mandated New Guinea in 1960. Bob had a strong sense of humour; he was fond of informal convivial gatherings and could be the life and soul of a party. Even at parties, however, he would occasionally let his chemistry bubble up and would convert a section of the gathering into a kind of informal seminar. When this happened the situation could generally be restored by producing for him a new game or puzzle; of such things he was inordinately fond and to them he used to apply himself with an intensity otherwise reserved for chemical problems.

Woodward's precocity and his unusual intellectual gifts readily account for his youthful arrogance and self-assurance but they do not explain what was perhaps his most outstanding personal characteristic—a desire not merely to excel in all he did but to be publicly recognized as indisputably first in all he did. Honours and awards he prized greatly as tangible evidence of this recognition. His habit of giving lectures of inordinate length, his special coloured chalks and blackboard technique, his use of the same lecture title whatever the subject and even his unchanging conventional mode of dress with dark blue lounge suit and pale blue tie were all, I believe, part of a conscious desire to create and perpetuate the legend of a man different from and scientifically superior to all others and one who seemed able to excel almost without effort. I have already alluded to the way in which he sought in these and other ways to conceal from his audiences how hard and how diligently he studied every aspect of a problem and how many young chemists failed to appreciate that behind all of Bob's apparently spontaneous contributions to discussions lay a great deal of hard work—although it is only fair to say that Bob himself never tired of emphasizing to them the need for hard work and hard thought in research.

It is not unusual to meet people who feel a need for public recognition in order that they may be reassured as to the value of their contributions but this could surely not have been the case with Bob Woodward who from his earliest days was fully aware of his unusual ability. His desire to be recognized as a wholly exceptional person extended in varying degree throughout all his activities; it was even evident in his already mentioned addiction to puzzles; shown a new puzzle or even a childish game he would apply himself totally to it and would not rest until he had mastered it—which he usually did in an astonishingly short time. We know little in the way of detail about his early life; but the origin of this overriding urge for public recognition of excellence must surely have had its origin in childhood. And I believe that what we do know is sufficient to provide an explanation. Bob Woodward was in effect a fatherless boy (his father died before he was two years old) supported in none too comfortable circumstances by a widowed mother. As such he would be at a social disadvantage while his very precocity would set him apart from and make him a butt for his contemporaries. Small wonder in these circumstances that he should try to erect a kind of protective screen against the taunts of his fellows and that he should develop a determination to show not only that he was better than them but to make them publicly acknowledge that he was superior to them. And he needed that protective screen, for he was a very sensitive person. Behind the somewhat arrogant style and apparent indifference to mundane problems of his adult years lay the real Bob Woodward—a generous, warm-hearted, somewhat shy and very lonely human being.

The reaction of strangers on first meeting Woodward varied; some were at first repelled by his self-assurance but as a rule this initial repulsion quickly passed. Although he could not be said to suffer fools gladly, he usually contrived to be gentle in his treatment of them. The one thing he would not forgive was what he regarded as scientific dishonesty—the endeavour to claim credit for sloppy work or for contributions properly attributable to other than the claimants. In his later years he travelled widely and was a particularly frequent visitor to Switzerland through his connections with Ciba-Geigy Ltd and with Albert Eschenmoser, his partner in the vitamin B_{12} synthesis. These visits also kept him in close touch with his Swiss friends and especially with Vlado Prelog to whom he was deeply attached. On his Swiss trips he would often stop over in London and became a frequent visitor to Sir George and Lady Porter at the Royal Institution. He had a great affection for Britain and once remarked to me that his ideal was to make money in the United States, work in Switzerland and live in England—a task too complex even for Bob Woodward to perform.

Following the break-up of his second marriage and a period during which he was deeply troubled by the outlook for his children the loneliness which had always been part of his make-up began to become more evident to his friends. For many years his affairs and those of his research group were conducted with great efficiency by his devoted secretary Miss Dodie Dyer. Her premature death in 1976 was a severe blow to Woodward and coming as it did on the top of the breakdown of his family life, seemed to accentuate his loneliness. Certain it is that in the last year or two of his life he was not just increasingly lonely but to his closer friends at least it was clear that he was beginning to look to the future with some apprehension. He had scaled the heights in chemistry in a way that no other man in his generation had done and was universally acclaimed as the world's leading exponent of organic chemistry. But he as well as we could see that with the passage of years a younger man would take his place on the pinnacle of current achievement. One can only wonder what would have been the effect on Bob Woodward of being one day surpassed in public esteem by a younger man. I believe it might well have been disastrous; but that is and will remain mere speculation for the situation never arose. On 8 July 1979 at his home on Memorial Drive, Cambridge, Massachusetts, Bob Woodward was struck down by a massive heart attack and died before medical help could reach him. But he died as he himself would have wished and, I confess, as I would have wished—still at the height of his powers and without the agony of a long illness. We are left to mourn the loss not just of a great chemist but also a generous and loyal friend. Alas! We shall not see his like again.

Scientific work

(J. W. C.)

Woodward published his first paper (1) in 1934, at the age of seventeen. In the succeeding 45 years he produced 196 publications of which around 85 are full papers; the remainder comprises preliminary communications, the text of lectures and reviews. The pace and pressure of his scientific activity soon outstripped his capacity to publish all experimental details: much of his achievement in synthetic chemistry remains in the form of published lectures and short communications, and much is available only in theses and laboratory notebooks at Harvard.

In reviewing Woodward's work I have been assisted by contributions from Professors R. Bonnett (chlorophyll), R. Hoffmann (theoretical chemistry), W. D. Ollis, F.R.S. (alkaloids), the late F. Sondheimer, F.R.S. (steroids), and from Dr J. Gosteli (β-lactam antibiotics). The need for selection and for compatibility of treatment has precluded the use of these contributions *en bloc*, as was possible in our memoir of Robert Robinson (*Biographical Memoirs*, 1976, **22**, 415–527). We are most grateful to these contributors, but I am responsible for the expressions and opinions below. Having re-read all Woodward's publications, with the help of a complete file of reprints kindly supplied by Professor Jeremy Knowles, F.R.S., I conclude that his work is best examined under four headings: Analyses of structure, Analyses of mechanisms, Syntheses, and Generalizations. These will be taken in order.

Analyses of structure

A guerrilla, said Mao Tse-tung, moves among a population like a fish in water. At a certain level of competence, the same can be said of an organic chemist (or an exponent of any other discipline rich in exact detail) moving in the literature of his subject. Woodward's attachment to, and appetite for, the original literature of chemistry was formed very early and stayed with him all his life. He was also blessed with a brain having unusual capacity for storage and phenomenal power of recall and analysis. He must have discovered soon enough that very few scientific papers propound new principles and that most of them add a very small piece to an existing pattern. But this pattern is not the same for every reader and an omnivorous reader with a critical intellect will soon restrict his storage of new information to the things that surprise him. Most of these things, when subjected to a process of intellectual digestion, prove to be reasonable extensions or reinforcements of the pattern already existing in his mind; those that do not will irritate like a broken tooth. Either his personal pattern, or the new information, is wrong; and neither conclusion is bearable.

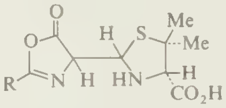
Bob Woodward loved puzzles, and he was always more interested in answering questions than in asking new ones. His knowledge of the chemical literature became encyclopaedic when he was still a very young man and his dazzling power of logical analysis ensured for him a flow of problems from the chemical literature and from contemporaries perplexed by their own findings. His solutions had for him the added spice that others had failed using the same data.

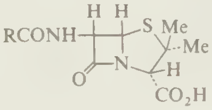
Mostly, these problems were questions of molecular structure. Nowadays, such problems are normally resolved quickly by physical measurements. Nuclear magnetic resonance, and especially computer-assisted X-ray crystallography, have taken much of the intellectual effort out of the pursuit. Woodward made full use of both these tools as they became available, but there is no mistaking the satisfaction in his claim (127) that the structure of tetrodotoxin was deduced from chemical evidence before confirmation by X-ray methods! He knew, none better, that the assignment of a compound's structure from its chemistry is one of the finest exercises of the human intellect. During his career, he contributed to the solution of the structures of the alkaloids strychnine (29, 31), sempervirine (36), cevine (69, 76, 77, 79) tetraphyllicine, ajmalidine, rauvomitine (83) calycanthine (103), dehydroisolongistrobine and isolongistrobine (173, 175, 182); the mould antibiotics patulin (38, 48, 49, 50), penicillin (40, 41), Terramycin and aureomycin (57–59, 61, 66, 72), magnamycin (90, 91, 138), gliotoxin (95), oleandomycin (104) and streptonigrin (123); the Spanish fly vesicant cantharidin (13); the puffer-fish poison tetrodotoxin (127, 128); and the 'iron sandwich' ferrocene (55, 56). Latterly in collaboration with P. Yates, he published several full papers on some intricate puzzles of santonin chemistry (44, 75, 118–120). Scattered throughout his life's record are publications setting straight some aspect of the chemical literature that would not harmonize with his pattern (12, 13, 20, 21, 33, 42, 46, 97, 99, 155, 157, 158).

The extent, variety and richness of these achievements have been obscured by the brilliance of Woodward's successful syntheses, but in many ways they show him most clearly as the supreme exponent and interpreter of the organic chemistry of his time. In problems of this kind, the experimental evidence is often fragmentary, sometimes misleading, nearly always ambiguous. Too many explanations, or none, may seem possible. Woodward used to find his way through the maze of possibilities as a chess grandmaster finds the one winning continuation. Some characteristic examples will be presented here.

Penicillin

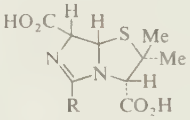
We referred in our biographical memoir of Robert Robinson (pp. 489–491) to the wartime binational effort on the structure and synthesis of penicillin. Woodward's contribution to the structural problem was made in 1944 and circulated, in this country, in the secret communications of the Committee for Penicillin Synthesis. At that time, the structures of degradation products representing, collectively, the entire molecule were known and two structures for the antibiotic had been proposed: the thiazolidine-oxazolone (**1**) and the β-lactam (**2**).





1 R = $PhCH_2$-, *etc.* **2**

The chemical evidence was conflicting. The rearrangement at pH 2 to penillic acid (**3**) and the formation of penicillenic acid (**4**) by the action of heat or of mercuric ion seemed to favour structure (**1**); so did the synthesis (in minute yields) of penicillins by condensation of penicillamine (**5**) with 4-alkoxymethyleneoxazolones (**6**). The sole degradation product containing a β-lactam ring was desthiopenicillin (**7**), obtained by the action of Raney nickel. The lactam (**7**) was far more resistant to hydrolysis than was penicillin and it did not undergo rearrangement in acid.



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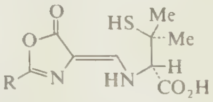

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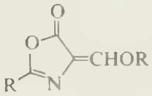

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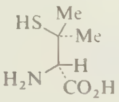

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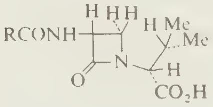

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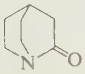

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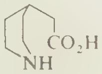
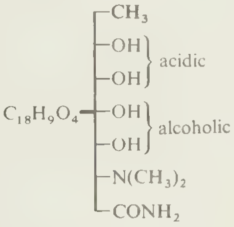


9

On the other hand, the physical evidence (infrared spectra; the acidity of the carboxyl group) was more consistent with the β-lactam structure (**2**). Woodward was always more sensitive to evidence of this kind than was Robinson. In addition, Woodward at the time was fresh from his triumph over the synthesis of quinine (23, 24) and he had been impressed during this work by the complete failure to prepare the lactam quinuclidone (**8**) from the amino-acid (**9**) or its derivatives. He attributed this failure to the circumstance that in this lactam the rigid ring-structure prevents a normal interaction of the unshared electrons on nitrogen with the π-system of the carbonyl group. In normal amides, this interaction suppresses the reactivity of both functions; its absence in the quinuclidone could explain the reluctance of (**9**) to cyclize and the tendency to obtain polymers in forcing conditions. Woodward reasoned that the rigid structure produced by the fusion of two small rings in (**2**) would produce a somewhat similar effect and that this would account for the abnormal reactivity of the β-lactam group of penicillin in comparison with other β-lactams. He plumped for structure (**2**) and Dorothy Hodgkin's X-ray crystallographic work was to prove him right. The formation of penillic acid (**3**) is now thought to proceed by initial rearrangement to (protonated) **1**! It remains a most remarkable rearrangement by any standard.

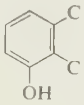
Terramycin and aureomycin

The elucidation of the structure of these two tetracycline antibiotics (57–59, 61, 66, 72) was published in 1952–54 by chemists at the research laboratories of Chas. Pfizer and Co., Inc. at Brooklyn, NY, jointly with Woodward in his role of *deus ex machina* (as it was once described), resolving complications. Terramycin, a yellow crystalline amphoteric substance, has the formula $C_{22}H_{24}N_2O_2$. Conventional chemical and physico-chemical analysis identified seven substituents attached to a core: the partial formula was **10**:



$$C_{18}H_9O_4\begin{cases}-CH_3\\ \left.\begin{array}{l}-OH\\-OH\end{array}\right\}\text{acidic}\\ \left.\begin{array}{l}-OH\\-OH\end{array}\right\}\text{alcoholic}\\ -N(CH_3)_2\\ -CONH_2\end{cases}$$

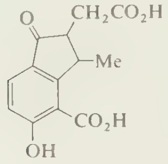
10



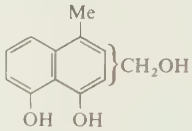
11

The appearance of both salicylic and *m*-hydroxybenzoic acids on alkali fusion of Terramycin pointed to the presence of the partial structure **11**; milder alkaline degradation, however, led to the isolation and identification (in earlier work by the Pfizer team) of terracinoic acid

(**12**), a diabolically deceptive product. Fortunately, when zinc was also present it was accompanied by small amounts of another substance, terranaphthol (**13**) and these two fragments could not come from wholly different parts of the molecule. Moreover, terracinoic acid was optically inactive (unlike Terramycin) although it contains two centres of asymmetry, one of which would resist racemization: this hinted at a complex mode of formation.



12



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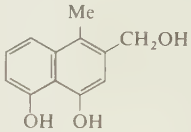
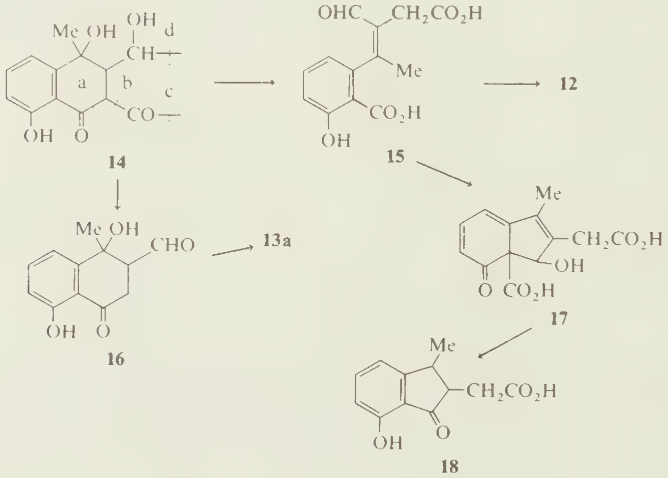


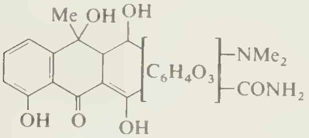
13a

The original full paper (66) should be consulted for the subtle and strong reasoning behind the eventual hypothesis that **12** and **13** represented alternative modes of decomposition of the same portion of the Terramycin molecule, and the formulation of this fragment as **14**. Hydrolytic cleavage at a, c and d can then lead, after dehydration, to the aldehyde **15**, from which **12** is derived by an internal phenol—aldehyde condensation followed by indene and enol-ketone tautomerization. Similar cleavage at b, c and d can yield, after decarboxylation, the aldehyde **16**; this by dehydration and reduction by zinc of the aldehyde group leads to terranaphthol, the correct formulation of which (**13a**) was subsequently verified. A beautiful strengthening of this hypothesis came from the prediction that the phenol-aldehyde cyclization of **15** could take



the alternative course of *ortho* condensation, the intermediate (**17**) then losing carbon dioxide to produce the different hydrindone **18**. This minor product of alkaline degradation was then sought, found and identified by synthesis.

The β-diketone grouping shown in **14** is enolized in Terramycin, the complex chromophore accounting for much of the antibiotic's absorption in the ultraviolet. The ambiguities in the total structure were now much reduced (**19**).



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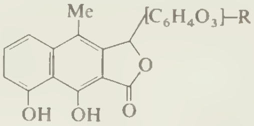
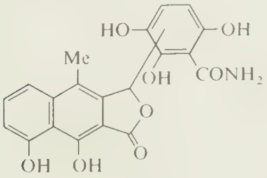


20 R = CONH$_2$
21 R = H

As might be expected, acid degradation of Terramycin aromatized the hydroxy-tetralone **19**, but another change occurred readily to yield a substance, terrinolide, which had the infrared absorption of a γ-lactone and which on the basis of several pieces of supporting evidence was accorded the partial structure **20**. Thus the dimethylamino group had been eliminated and, indeed, stronger acid hydrolysed and decarboxylated the carboxamido group, leaving decarboxamidoterrinolide (**21**). The stability of this substance, and the formation of a pentamethyl ether, supported the suspicion that the $C_6H_5O_3$ group was trihydroxyphenyl. Since this would be a chromophore separate from the naphthalenoid structure, the orientation of its hydroxyl groups could be examined by comparing the ultra-violet spectra of a derivative of **21** and equimolar mixtures of suitably substituted naphthols and various isomers of trihydroxybenzene; among these, only 1,2,4-trihydroxybenzene gave a good fit (the comparison was made with the methyl ethers). Further, the presence of a relatively acidic grouping (pK_a 7.5) in this region of the terrinolide molecule made it probable that the carboxamido group lay between two phenolic hydroxyls. Thus partial structure **20** became **22**. A product of milder acid hydrolysis, apoterramycin, had the benzophthalide structure attached to a moiety in which the dimethylamino group of



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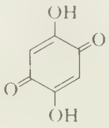

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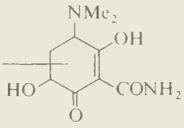
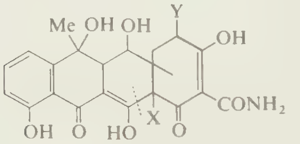


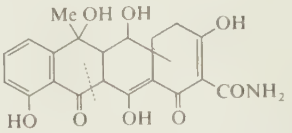
24

Terramycin was still present: the transformation to terrinolide was formally an elimination of dimethylamine. Apoterramycin (which occurred in isomeric α- and *β*-forms) gave 2,5-dihydroxybenzoquinone (**23**) on fusion with alkali. The conditions of formation of this compound clearly indicated that its six-membered carbocyclic ring was already present. Also, apoterramycin had a quite strongly acidic group in this region, indicating that there were at least two carbonyl groups, in α- or β-relationship, in this six-membered ring. The decision in favour of a β-relationship was made by considering the relative difficulty with which the 2,3,6-trihydroxybenzamide structure was generated from apoterramycin: it was not possible to find an arrangement of the substituents in a cyclohexane-1,2-dione ring that would neither be subject to very easy aromatization nor give a 1,2,3-orientation of hydroxyl groups. With a cyclohexane-1,3-dione, on the other hand, an arrangement as in **24** satisfied all experimental findings including the curious fact that a trace of air catalysed aromatization.

Reverting to the structure of Terramycin itself, the partial structure **25** was propounded: the bond joining the enolized carbonyl group to unknown territory was assigned a position adjoining the 1,3-diketone system to account for the ease of cleavage at the dotted line. It was then shown that in **25** X is hydroxyl. Mild reduction of Terramycin by zinc and acetic acid removed, reductively, the dimethylamino group to give a product very similar in its absorption spectra to Terramycin itself. In more vigorous conditions a hydroxyl group was also lost by reduction, and this clearly permitted a new chromophore to arise to which the structure **26** could be assigned and supported by spectroscopic and chemical evidence (e.g. mild alkaline treatment cleaved the molecule at the dotted line and a γ-lactone was formed with the tertiary hydroxyl group). The existence of the enol **26** also excluded attachment of the one linkage remaining unassigned to the carbon atom bearing the group Y (now dimethylamino, by exclusion) in Terramycin, since then the compound **26** would contain a bridged ring violating even the more exact versions of Bredt's rule. The sole remaining expression, **27**, for Terramycin has since been proved entirely correct, and the stereochemistry has been elucidated.



25 X, Y = OH, NMe$_2$



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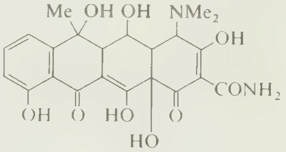
This summary treatment can do no more than suggest the subtlety and depth of the arguments deployed in the full paper (66), and Terramycin is one of the last great structures to be deduced mainly from chemical evidence. Woodward was fortunate in his able team of chemists who provided a wealth of data, but the interpretation is not the less dazzling for that.



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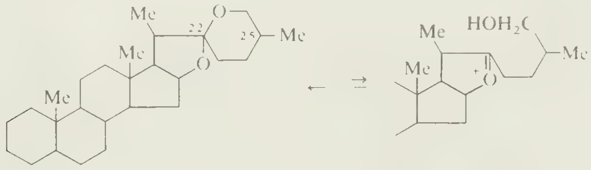
Analyses of mechanisms

Neither Woodward's structural analyses nor his syntheses could have been achieved without mastery of organic chemical mechanism. The development of this mastery clearly owed much to the ideas of Robert Robinson and indeed, Woodward retained Robinson's original 'anionoid' and 'cationoid' for reagents and reactivities now generally called 'nucleophilic' and 'electrophilic' after Ingold's better publicized revision.

The Diels–Alder reaction, and its mechanism, were loves of his lifetime, and he published several papers about it (17, 20, 30, 98, 100). We shall return later to this topic; here, three characteristic examples of his work on mechanism (two chemical, one biogenetic) have been chosen.

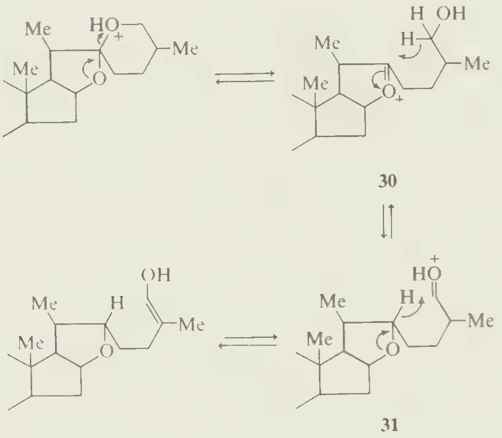
Spirostane isomerization

The steroidal sapogenins, which are the aglycones of foam-forming saponins found in many plants, occur in two stereochemical families called normal and iso, distinguished by the fact that treatment with acid interconverts the two series, the equilibrium strongly favouring the iso form. When the ring-system (**28**) was elucidated by Marker, he made the reasonable suggestion that the isomerization was at C-22 since the sapogenins, now called spirostanes, are ketals that might be expected on acid treatment to form protonated enol ethers (as in **29**) which could *prima facie* recyclize with retention or inversion of the original configuration. Later work led to the very surprising conclusion that this is not so: the normal and iso series are identical at C-22 and differ only at C-25. Moreover, when the isomerization was conducted in deuterium oxide, stably bound deuterium appeared only at C-25.



28 **29**

Woodward published his explanation in 1958 (97). He recognized the special features favouring a reversible intramolecular hydride shift of a type still quite rare in organic chemistry. The protonated species **29**, written more suggestively (**30**), was supposed to undergo such a shift leading to the protonated aldehyde **31**, in which the hydrogen on C-25 is liable to exchange by enolization with protons from the medium. This exchange leads to two aldehydes stereoisomeric at C-25. Reversal of the entire process then regenerates the spirostane structure; and the thermodynamically more stable isomer, with the terminal methyl group equatorial, will be favoured. The normal series of spirostanes has axial methyl groups. The cycle, written as he wrote it, is shown below:

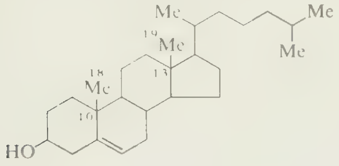


To test the hypothesis, an aldehyde corresponding to **31** was prepared by an unambiguous procedure and shown to produce, on the standard treatment with acid, a spirostane of the iso series in good yield accompanied by small amounts of the normal isomer. No one has challenged this explanation in the twenty-three years of its currency, and no specialist in spirostanes or in reaction mechanisms saw it before Woodward. I had published, in 1953, a less harmonious explanation of the same problem; and was among those who kicked themselves when Woodward's paper appeared.

Biosynthesis of cholesterol

The availability of stable and radioactive isotopes of carbon gave an immense boost to biochemistry after World War II. Konrad Bloch studied the biosynthesis of sterols with their help, and acetic acid was soon identified as a key intermediate providing the total carbon skeleton. Moreover, chemical degradations of cholesterol (**32**) showed that methyl carbons and carboxyl carbons from acetate were incorporated into cholesterol in a definite pattern. The pattern in the side-chain of cholesterol, where m is a carbon originating from acetate methyl and c a carbon from acetate carboxyl, goes like this (**33**)

This pattern and some other evidence revived interest in Robinson's old hypothesis (1934) that the C_{30} polyisoprenoid hydrocarbon squalene was the precursor of the sterols. It was shown experimentally that squalene is made from acetate (in rats) and is further converted into cholesterol. As a polyisoprenoid, squalene can be dissected into six five-carbon units and their labelling, from acetate, should then be as in **34**. Writing the whole squalene molecule in the same notation and folding it according to Robinson's scheme of cyclization we then have **35**.



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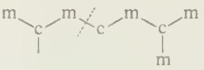

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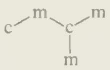

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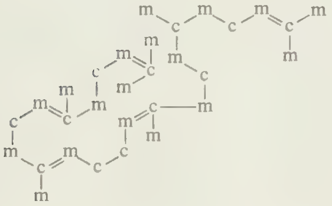

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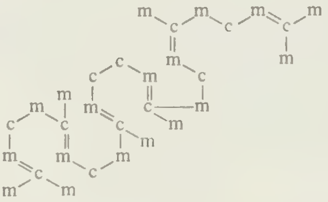

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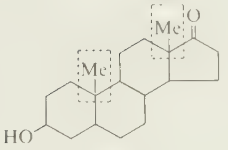

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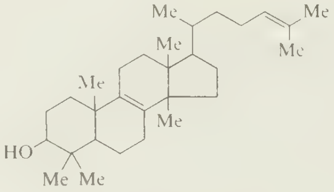


36

Woodward knew at the time (1953) of the recently established structure (**36**) of the wool-fat sterol lanosterol, and he proposed with Bloch (63) an alternative folding of squalene (**37**) that might cyclize to give the lanosterol structure with one methyl shift. For biosynthesis of the sterol skeleton, one difference between these two foldings of squalene was that from **35** C-13 of cholesterol would originate from acetate carboxyl, but from **37** it would come from acetate methyl. A chromic acid oxidation (Kuhn–Roth) of a specimen of epiandrosterone (**38**), derived chemically from cholesterol made biosynthetically from acetate labelled with ^{14}C in the *methyl* group, gave acetic acid. This represented, in its methyl groups, C-18+C-19 of cholesterol, and in its carboxyl groups C-10+C-13 of cholesterol. Chemical degradation of the acetic acid and counting of radioactivity showed unmistakably that one (but not both) of the two positions in cholesterol giving rise to its carboxyl group was derived from acetate methyl. It had recently been found that C-10 was derived from acetate carboxyl; therefore, C-13 was the methyl-derived position.

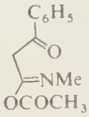
Since that time, the biosynthesis of cholesterol has been elucidated in minute detail. Lanosterol *is* a precursor of cholesterol and the folding of the squalene skeleton for cyclization is as depicted in **37**.

Isoxazolium salts as acylating reagents

Woodward published eleven papers (107, 108, 137, 140, 141, 145–147, 151, 159, 188) on this theme, mostly with R. A. Olofson or D. J. Woodman: the most that he ever published on a single chemical topic.

A neutral product from the very rapid reaction of the N-methyl-5-phenylisoxazolium cation with acetate ion had been observed many years before: it was wrongly assigned the structure **39**. Woodward had started his investigation from the hypothesis that isoxazolium cations with a hydrogen atom at position 3 should be converted by bases to α-ketoketenimines (e.g. **40**).

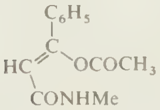
40



39

The hypothesis was correct, and evidence for the transient formation of **40** was obtained. The product from acetate ion, however, was identified as the enol ester **41**. This could not have been formed directly from the ketenimine and it was postulated that the imido-ester **42** and its enol **43** were intermediates.

Thus a method was available for converting a carboxylic acid in mild conditions to an activated ester. As expected, the enol ester **41** reacted easily with amines to form acetamides. The finding was exploited by substituting for acetic acid a series of N-protected amino acids, and by



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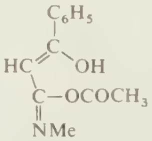

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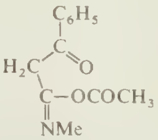
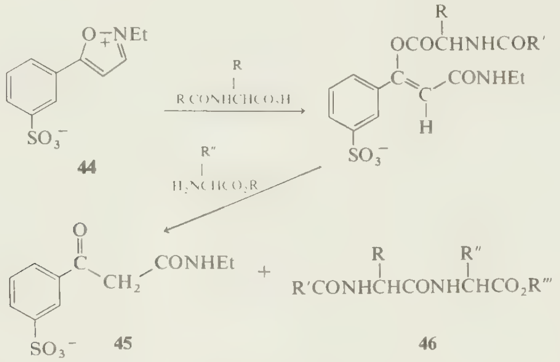
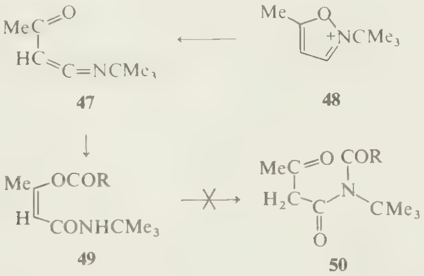


42

using as amines the esters of other amino acids. In this way a peptide synthesis of exceptional smoothness and versatility was developed. The phenylisoxazolium ion was replaced by the sulphobetaine **44** which had the advantage that the end-product **45** remained soluble in water and easily separated from the protected peptide ester (**46**). The whole process is as shown. The betaine **44** is available commercially under the name Woodward's Reagent K.


44 **45** **46**

With *t*-butyl groups attached to nitrogen it was possible to isolate the ketoketenimines (e.g. **47**). The enol esters (**49**) derived *via* **47** from N-*t*-butyl-5-methylisoxazolium salts (**48**) were stable, showing no tendency to rearrange to the diacylimides (**50**)—a rearrangement liable to reduce the yields in peptide syntheses using e.g. the zwitterion **44**. The reagent **48** (as perchlorate) is also on sale as Woodward's Reagent L.


47 **48** **49** **50**

Another paper (159) described how to avoid racemization *via* an oxazolone of the acidic component of peptide synthesis, and the last of the series (188) puts the preferred procedure into *Organic Syntheses*, that practical chemists' Escoffier.

Syntheses

Woodward's fame as a chemist is based principally on his syntheses of natural products. In chronological order he reported syntheses of quinine (1944), patulin (1950), cholesterol and related steroids (1951), lanosterol

(1954), strychnine (1954), lysergic acid (1954), reserpine (1956), ellipticine (1959), chlorophyll (1960), mycarose and cladinose (1962), tetracycline (1962), colchicine (1965), Cephalosporin C (1966), vitamin B_{12} (1973), prostaglandin $F_{2\alpha}$ (1973) and marasmic acid (1976). One of his last papers (194), the text of a lecture, described much progress towards the synthesis of erythromycin, completed after his death and reported by 49 authors in three notes: *J. Am. chem. Soc.*, **103**, 3210, 3213, 3215 (1981).

No one will ever surpass this record; if only because Woodward set new standards for synthesis that others have emulated but not changed. He was among the first to realize that an increasingly useful theory of chemical reactivity, a flood of new reagents and procedures, and new physical methods for examining chemical reactions and their products, had transformed the prospects for planned synthesis of complex molecules. In comparison with Robinson, he invented few new methods; unlike Robinson, he had no need to do so. It was sufficient to have mastery of the chemical theory and practice of his time, and the superb intellectual equipment that enabled him to exercise this mastery on its chosen objects.

A typical Woodward synthesis is noted first and foremost for its planning. Woodward started at a very early age to plan organic syntheses on paper, and he often said that this exercise is one of the best ways to learn organic chemistry. His deep study of the original literature taught him not only the methods which were outstanding for high yields but also the failures and partial failures: the types of reaction to avoid. A long synthesis is always something of a gamble, and it pays heavily to load the dice in one's favour before beginning the game, and to take the greatest risks before the stake is too high. Woodward's discrimination in choosing his approach can scarcely be faulted, and it came from sensitivity to risk and leaving room for contingencies as much as from assessment of advantage.

In the execution of his syntheses Woodward took no physical part. His reputation, established very early, assured him junior researchers of high quality; his business was to direct and inspire them. This is not to say that he ever lost interest in the practice of organic chemistry or the subtleties of handling chemical substances and chemical reactions. If he had, he could not have achieved what he did. Where experimental details are available for a synthesis the procedures are often of great interest. A salient feature of his earlier work was the use of spectroscopy, especially in the infrared, to follow the course of chemical reactions. He, like the present authors, was old enough to have experienced the blinkered frustration of organic chemists faced with unrevealing reaction mixtures, without paper or thin-layer chromatography, without convenient ultraviolet or infrared spectrometry, let alone mass spectrometry or nuclear magnetic resonance; with one quantitative method—elementary analysis—and that almost useless with mixtures. Chemists did what they could with colour reactions and similar tests: a lost art now, except among biochemists who use them still for quantitative analysis. Woodward was among the first to exploit the possibilities of the new photoelectric ultraviolet spectrophotometers, as his earlier papers attest. Infrared spectrometry, with its wider frequency range and the sharper and more characteristic absorption signals associated with specific bonds, was even more liberating, and he became an artist in the interpretation of spectra and their use in following reactions as well as in identifying isolated products. So he could find out without loss of time whether, and often how, a reaction was going wrong. Allied to his superb resourcefulness this knowledge made few obstacles unsurmountable.

The composition and execution of a complex organic synthesis is a human art unlike any other. In one sense, imperfection is excluded: if one step fails, there is no synthesis. But within the class of technically successful syntheses there are those in which the possibilities and sensitivities of matter are expressed in harmony, and one loses the feeling that recalcitrant molecules are being tortured into new shapes. Most of Woodward's syntheses are in that category.

Except for the two earliest, all Woodward's great syntheses have been the subject of published lectures. For him, the delivery of such a lecture was like the performance of a musical work by its composer. His lecturing style, leisurely and somewhat florid, comes over in the printed word (the translator of a lecture on chlorophyll (106) once jibbed at rendering into scientific German 'Fresh from his dramatic conquest of the blood pigment, Fischer hurled his legions into the attack on chlorophyll'!). In contrast, his papers on analysis of structure and his generalizing publications (see later) are models of incisive argument.

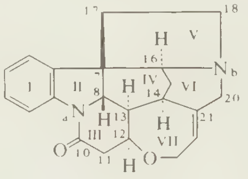
I have chosen to deal with a limited number of syntheses in greater detail than would have been possible in a comprehensive survey. Among so many beauties the choice has been difficult, but the four chosen: strychnine, chlorophyll, Cephalosporin C, and vitamin B_{12}, do show his full range.

Strychnine

Woodward contributed to the final solution of the structure (**51**) of strychnine, and his elucidation of the baffling chemistry of neostrychnine (**52**) is a very fine piece of chemical interpretation (29, 31) backed by experiment. His total synthesis of the alkaloid, announced in 1954 (73), is in many ways his masterpiece. The lecture (81) and the full publication (122) are up to the same standard.

The choice of 2-veratrylindole (**53**; easily made from 4-acetylveratrole phenylhydrazone by a Fischer indole synthesis) as starting-point was influenced by a hypothesis of strychnine biosynthesis (34, 82) that turned out, ironically, to be wrong. But this is not the place to tell the fascinating story of indole alkaloid biosynthesis, and the hypothesis was not too wrong to be useful. Considered as a building block containing already two-thirds of the skeletal atoms of strychnine, **53** is a brilliant choice, as the sequel shows.

Elaboration of the tryptamine (**54**) from this indole followed established procedures: condensation with formaldehyde and dimethylamine gave 2-veratrylgramine, the methiodide of which on treatment with cyanide ion gave a nitrile reduced to **54** by lithium aluminium hydride. In this sequence, and later, the veratryl group is acting as an inert blocker of the reactive 2-position of the indole ring. The tryptamine (**54**) formed a Schiff base (**55**) with ethyl glyoxylate. It had been hoped, quite reasonably, that under acid catalysis this might cyclize to the indolenine (**56**), and the first check in the synthesis was experienced here. Acid catalysis proving unproductive, Woodward had the beautiful idea of using a combination of toluene 4-sulphonyl chloride and pyridine. The former was designed to accentuate the electronegativity of the Schiff base by reacting with its nitrogen and the latter to increase the electropositivity of the indole by helping to abstract its somewhat acidic hydrogen. This device would not work for many formally analogous condensations: it was tailor-made for that special case and it gave the toluene-sulphonylindolenine (**57**) in 64% yield.



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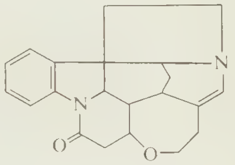

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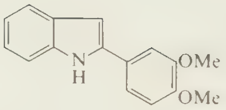

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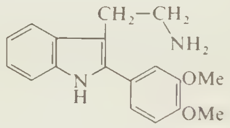
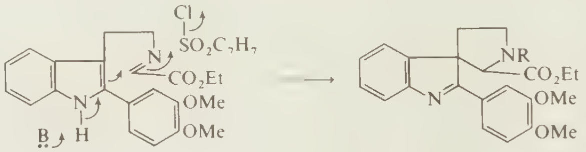


54

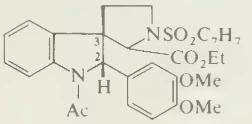
Two centres of asymmetry had been introduced by this reaction and two diastereomeric racemates could have been formed. Only one was



55

56 R = H
57 R = $SO_2C_7H_7$

isolated, and the plan of synthesis was indifferent to this complication since the carbethoxyl group in **57** can be isomerized, if necessary, by basic reagents. The next step, reduction of the indoline by borohydride and acetylation of the newly-formed secondary amine to give **58**, introduced a third centre of asymmetry. Again, the splendid plan made the outcome of secondary importance, though it is probable that the relative stereochemistry at the 2- and 3-positions of the indoline ring was as shown.



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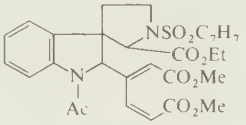
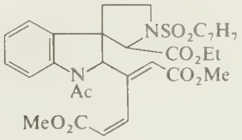


59

Woodward knew, when planning the synthesis, that simple methoxylated aromatic systems could be cleaved by peroxy-acids. When this failed with **58**, he tried ozone in acetic acid and got in moderate yield the triester **59**. Ozone *had* been observed earlier to effect an analogous cleavage (of dihydrocodeine) but even Woodward did not know this at the time! So another minor obstacle was by-passed.

Closure of the six-membered lactam ring III of strychnine was the next part of the plan. It can be seen in **59** that ring-closure to a five-membered pyrrolone is impossible without altering the geometry of a double bond, whereas the stereochemistry of the other double bond, as shown in the tropomer **60**, is favourable for cyclization to a pyridone (**61**). This change occurred smoothly in methanolic hydrogen chloride.



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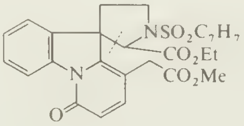
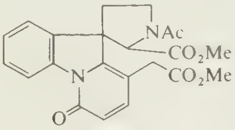


61

It was found necessary, before attempting to close ring IV by a Dieckmann cyclization, to remove the toluenesulphonyl group (hydrogen iodide and phosphorus); this avoided a base-induced cleavage (at the dotted line in **61**). Acetylation and re-esterification (for of course the two ester groups had been cleaved by the reagent) gave the acetyl diester **62**. Methanolic sodium methoxide then gave the cyclized product **63**, a



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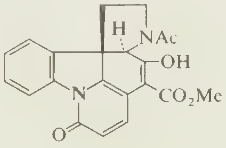
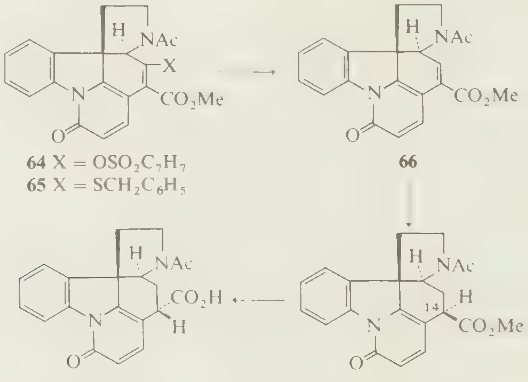


63

persistent and unusually acidic enol. There was no stereochemical problem about the two chiral centres in **63**, since only one relationship between them, and that the desired one, allows closure of the ring.

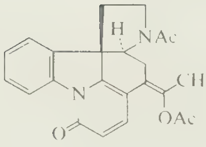
The stability of the enol in **63** allowed the preparation of an O-toluenesulphonyl derivative **64** (not usually possible with β-keto esters) and thence a benzylthio derivative (**65**) which by nickel desulphurization gave the αβ-unsaturated ester **66**. Catalytic hydrogenation then produced the saturated ester **67**, largely in the stereochemical form shown since one side of the αβ double bond in **66** is much more shielded than the other. The epimeric acid **68**, being thermodynamically the stable epimer, was however produced by alkaline hydrolysis of **67**. This outcome had been foreseen in the plan: the configuration at position 14 is 'correct' for strychnine in **67** and not in **68**, but again this was to be corrected later.



64 X = $OSO_2C_7H_7$
65 X = $SCH_2C_6H_5$
66
68
67

This synthetic acid was resolved as the quinidine salt—a favourable case for resolution, since there is plenty of structural asymmetry close to the salt-forming groups in both acid and alkaloid. This, as Woodward pointed out, should lead to greater differences between the two epimers than when the chiral centres are well separated. Further, the laevorotatory enantiomer of the acid **68** was obtainable as a degradation product of natural strychnine, only a small extension of an existing sequence being needed. Thenceforth, the synthesis was continued with material prepared in this way, and the relative configurations shown in the diagrams above became absolute.

The arrival of reinforcements was useful at this stage, for trouble was encountered in constructing ring VI. The solution eventually found, after long search, was simple but by no means obvious. The acid **68** with acetic anhydride in boiling pyridine underwent a change analogous to the well-known Dakin-West reaction and the product (**69**) was the enol acetate of the corresponding methyl ketone. Quite vigorous acid hydrolysis was needed to remove the two acetyl groups and form the methyl ketone (**70**).



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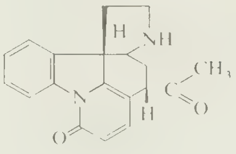
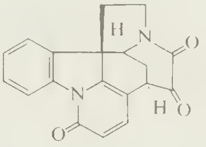


70

When this ketone was treated with selenium dioxide in ethanol, dehydrostrychninone (**71**) was formed directly. The process was not smooth (12% yield) but it is remarkable enough that it succeeded at all where so many apparently more reasonable approaches had failed. Notably, the stereochemistry at position 14 was now correct. Once again, the interlocking ring system prevented any other outcome of the cyclization. Dehydrostrychninone was also available by oxidative degradation of strychnine.



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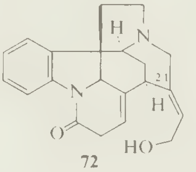
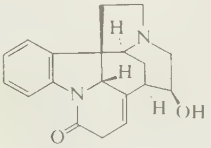
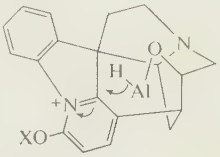


72

It remained to add two carbons to position 21 and to alter the oxidation state of rings III and VI. The objective was isostrychnine I (**72**) since this was known to give strychnine itself when treated with ethanolic potassium hydroxide. The necessary addition of hydrogen to C-12 had to take place on the concave side of the ring system and it was a well-earned piece of good fortune to find that lithium aluminium hydride in boiling ether not only reduced the amide carbonyl group in ring VI but also reduced the pyridone ring, in the desired stereochemical sense and to the desired oxidation level! This reagent does not normally reduce α-pyridones in this manner, and the retrospective explanation was that the hydroxyl group in ring VI, produced initially by the reduction, carried a hydridoaluminium complex favourably situated to donate hydride to the pyridone (itself complexed in the dipolar form by lithium or aluminium in the role of the group X (**74**)). The dihydropyridone would then be stabilized against further reduction. In any case, the product was **73**. How



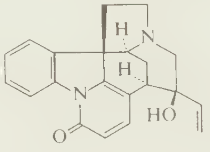
73



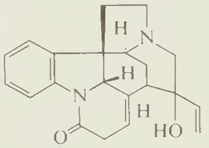
74

Woodward would otherwise have established the correct configuration at C-12 can only be guessed; but here too he had thermodynamics on his side.

The information gained was applied to the vinylcarbinol **75**, obtained from dehydrostrychninone (**71**) by reaction with sodium acetylide followed by partial reduction over Lindlar catalyst. The reduction of this compound by lithium aluminium hydride produced, directly, an allylic isomer (**76**) of the desired isostrychnine (**72**).



75



76

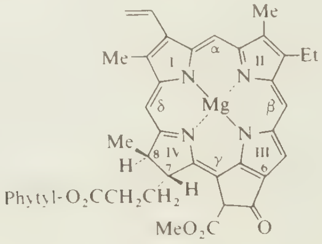
The necessary allylic rearrangement was not easy, but hydrogen bromide in acetic acid at 120° gave a mixture of bromides from which isostrychnine (**72**) was isolated after aqueous acid hydrolysis. Thereby, the synthesis was formally complete, though Woodward characteristically carried through his synthetic isostrychnine to a final yield of a few milligrams of strychnine.

The beauty of the synthesis resides principally in the flexible strength of its master plan, and especially in the seemingly effortless disposal of one stereochemical problem after another. There are six centres of asymmetry in strychnine and none of them gave the least trouble. That was no accident.

Chlorophyll a

The chlorophyll synthesis was begun in 1956. It took four years and the efforts of seventeen post-doctoral colleagues. It has never been reported in detail and the published information comes from the preliminary communication (105) and four lectures (106, 110, 116, 117).

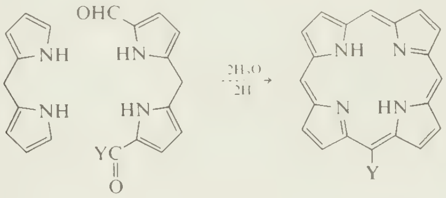
Chlorophyll a (**77**) is a dihydroporphyrin. The structure **77** was proposed by H. Fischer in 1940, without the sterochemical detail which was added (by Linstead) not long before the synthesis began. Woodward



77

started his siege of the molecule by studying profoundly the published chemistry of pyrroles and of porphyrins. These had been the subject of much work by Willstätter, Stoll and especially Hans Fischer. The porphyrins had, for early investigators, the advantage of being deeply coloured stable substances with characteristic absorption bands in the visible region. They could be recognized with a hand spectroscope even when present in minute amounts, and this circumstance delayed the development of high-yielding syntheses. Woodward at first approached the structure (**77**) with scepticism. Simple dihydroporphyrins (chlorins) are easily oxidized to porphyrins; chlorophyll is not. Molecular models suggest that the carbocyclic five-membered ring in **77** is strained, and indeed it can be opened hydrolytically with ease. But it is also closed with ease, which seemed strange. On reflection all this behaviour was attributed to the mutual crowding of substituents attached to the 6, 7 and γ positions, especially in the porphyrin system. The realization that the tetrahedral configuration at position 7 (and consequently of course at 8) not only had a good reason for survival but should also be *formed* readily from a suitably substituted porphyrin reconciled Woodward to the accepted structure and gave him a starting-point for planning the synthesis.

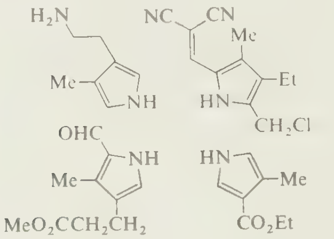
Reviewing the unsatisfactory state of porphyrin synthesis, Woodward was impressed by the ease with which pyrroles condensed, in the α-position, with pyrrole-2-aldehydes to form pyrromethenes. He reasoned that condensation of a dipyrrylmethane (**78**) with a formyl-acyl-dipyrrylmethane (**79**) could lead easily to a porphyrin (**80**).



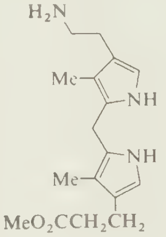
78 **79** **80**

Ideally, the synthesis of chlorophyll would call for an acetic acid group —CH_2CO_2R for the substituent Y, but Woodward's mimosaic sensitivity led him to avoid this since he foresaw possibilities of the whole group being eliminated, instead of a proton, on porphyrin formation. This possibility was averted by lengthening the group by one methylene, with the intention of shortening the resulting propionic chain, —$CH_2CH_2CO_2R$, by one carbon at a later stage. Another group thought too sensitive to carry through a long synthesis was the vinyl group in ring I, and it was decided to use a β-aminoethyl group as its precursor. Thus four monocyclic pyrroles were first prepared, and they are represented in the assembly **81**. Little new chemistry was required, since the manipulation of substituents on the pyrrole ring had been extensively developed by Hans Fischer for his porphyrin syntheses. The β-aminoethyl pyrrole, for example, was made from a known aldehyde by condensation with nitromethane and reduction.

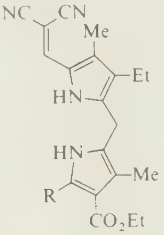
The four pyrroles were then combined in pairs. The left-hand pair in **81** gave the dipyrrylmethane **82** on condensation to a dipyrromethene hydrobromide in methanolic hydrogen bromide, and reduction of this by sodium borohydride. Lacking electronegative substituents, **82** was a very sensitive substance and was best used without isolation. The dipyrrylmethane **83**, formed by acid-catalysed condensation of the right-hand pair of pyrroles, was more stable. It could be acylated in the free α-position by β-methoxycarbonylpropionyl chloride to give the desired, fully substituted dipyrrylmethane **84**.



81



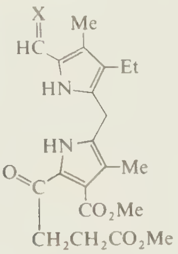
82



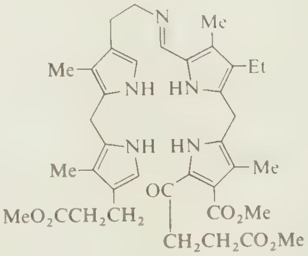
83 R = H
84 R = COCH₂CH₂CO₂Me

Vigorous alkaline hydrolysis now released the masked aldehyde group in **84** and re-esterification yielded the aldehydo-ketoester **85**. It was then already possible to condense the two dipyrrylmethanes **82** and **85** with each other to give the desired porphyrin in yields that were very good by previous standards, but the condensation is obviously ambiguous and did in fact lead to two isomeric porphyrins in comparable amount.

The plan—no doubt it had influenced the choice of a β-aminoethyl group as a precursor of the vinyl group in chlorophyll a—for removing

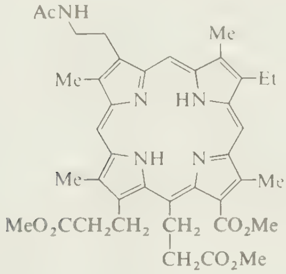


85 X = O:
86 X = NEt:
87 X = S

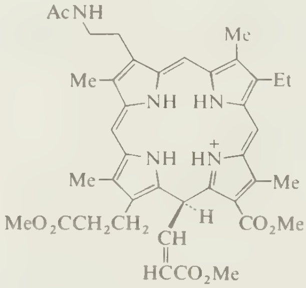


88

this ambiguity was to form a Schiff base (**88**) between the two components before cyclization. It could be expected that the Schiff base would behave as an aldehyde in the cyclization, and there was no possibility of a condensation the 'wrong way round'. In practice, making the Schiff base was difficult because of the sensitivity to acid (needed as catalyst) of the dipyrrylmethane **82**. A way round the difficulty was found by converting **85** to a Schiff base (**86**) with ethylamine. This substance with hydrogen sulphide gave the thioaldehyde **87**, which needed no acid catalysis to form with the sensitive amine **82** the Schiff base **88**. This was at once added to methanolic hydrogen chloride; the intermediate dihydroporphyrin salt was oxidized *in situ* with iodine, and the porphyrin (**89**) was isolated after acetylation with acetic anhydride and pyridine. The overall yield, starting from the dipyrromethene related to **82**, was 50%. About 50 g of the porphyrin was prepared in all, in batches not exceeding 1 g. The experimental conditions were critical but reproducible. This was one of the earliest examples in synthesis of facilitating the course of a chemical reaction by making it intramolecular.



89

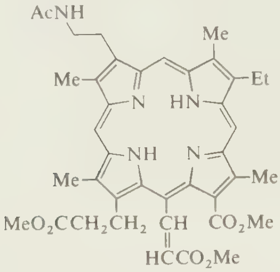


90

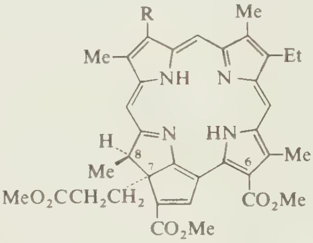
The next stages introduced some extraordinary chemistry, probably not predicted but vindicating remarkably the notion of steric crowding in the lower part of the molecule as shown. In hot acetic acid, in the absence of air, a salt (**90**) was formed of a dihydroporphyrin ring-type which Woodward christened phlorin. He had encountered one of these as an intermediate in the cyclization leading to **89** and had recognized that several prototropic changes had been required to produce it. Given that the propionic side-chain in the γ-position can relieve steric compression by getting itself out of the plane of the porphyrin ring, it was not surprising to find that the γ-position was the final resting-place for a wandering hydrogen.

The two hydrogens necessary to reduce the porphyrin ring could be provided prototropically from the γ-side chain, and so they were. The phlorin salt (**90**) was easily oxidized in air to the porphyrin **91**. When this in turn was heated in acetic acid, prototropy and relief of steric compression took a different course, the product being an equilibrium mixture of starting material, the purpurin **92**, and a trace of an isomeric purpurin in which cyclization had occurred at position 6 instead of position 7.

This happy result had placed a hydrogen atom where it was needed, at position 8, and it was soon to be joined by its neighbour at 7.



91

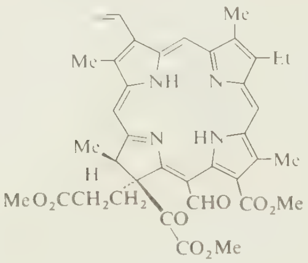


92 R = CH_2CH_2NHAc
93 R = $CH = CH_2$

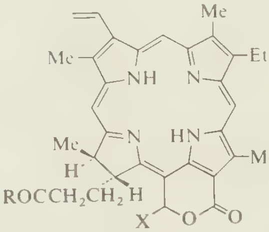
First, however, the opportunity was taken to generate the vinyl group in ring I. This was done by treatment with methyl sulphate and methanolic sodium hydroxide, the Hofmann elimination proceeding, as might have been (and certainly was) expected, very easily to yield the vinyl compound **93**.

The double bond in the carbocyclic ring of **93**, proved to be unusually, selectively, and fortunately labile to photochemical oxidation in air, the product being the keto-aldehyde **94**. Further, the methoxalyl group in **94** had the expected lability to alkali, so that when **93** was treated with dilute methanolic potassium hydroxide it was cleaved and the methoxy-lactone **95** was formed. This was the racemic form of a known substance, isopurpurin 5 methyl ester, from degradation of chlorophyll a. The visible and infrared spectra in solution were identical.

Now was the time for optical resolution, and it was done by crystallizing the quinine salts of the corresponding acid (chlorin 5; **96**). The synthetic specimens of dextrorotatory chlorin 5, and of purpurin 5



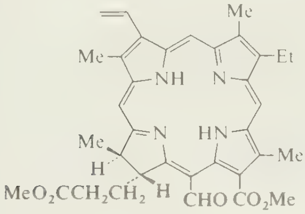
94



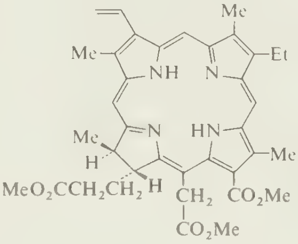
95 R = X = OMe
96 R = X = OH
97 R = OMe; X = CN

dimethyl ester (**98**) prepared from it by the action of diazomethane, were identical with specimens made from chlorophyll by Fischer's procedures.

The synthesis was now nearly complete, for it was already known that hydrogen cyanide converted the aldehyde **98** into the cyano-lactone **97**. The latter was cleaved reductively by brief treatment with zinc and acetic acid; the action of methanolic hydrogen chloride then gave chlorine e_6 trimethyl ester (**99**), identical in every detail with an authentic sample. The remaining steps to chlorophyll a (**77**) had already been traversed (Dieckmann cyclization; replacement of one methyl ester group by a phytyl group; introduction of magnesium. It happened that the natural, optically active form of phytol had been synthesized only in the previous year).



98



99

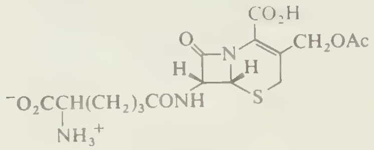
The chlorophyll synthesis posed no real stereochemical problem, since the two substituents in ring IV could be expected to take up positions *trans* to each other when the carbons to which they were attached became tetrahedral. The porphyrin synthesis used was highly ingenious and an advance on existing methods. But most readers will agree that the fascination and chief merit of this synthesis is in the stages between compounds **88** and **95**. Woodward diagnosed the cause of a strangeness in chlorophyll chemistry and laid his plans so that this strangeness—even if he could not predict it in detail—pushed his intermediates along the right path. The practical execution of these steps might well have been impossible without his resource, his awareness, his sensitivity to the slightest clues and his insistence on obtaining the maximum information. It is a thousand pities that the experimental detail remains unpublished.

Cephalosporin C

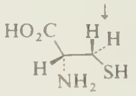
Woodward chose for his Nobel Prize lecture (142–144) the unchanging title that had heralded his earlier achievements: 'Recent advances in the chemistry of natural products'. His subject on this occasion was the synthesis of the antibiotic Cephalosporin C, achieved with the help of seven skilled colleagues at the Woodward Research Institute in Basel. Cephalosporin C (**100**), isolated by Newton and Abraham at Oxford in 1955, is one of the β-lactam antibiotics that have been successful in combating a very wide variety of human and animal bacterial infections.

Woodward had taken part, as mentioned earlier, in the co-operative effort on the penicillins—the first β-lactam antibiotics—during the war.

The fundamental problem in synthesizing this kind of compound is the need to construct a highly strained chemically unstable four-membered ring in the presence of other sensitive groups. We used to compare the problem with the feat of throwing up a tennis ball to lodge on a high shelf—exactly the right amount of energy is needed! When Woodward made the decision to start from L-cysteine (**101**) he met a similar problem head-on, for it was going to be necessary to replace one of the two least reactive hydrogen atoms (arrowed in **101**) in the molecule, and by a group that would allow closure of a tight ring. On the other hand, cysteine was abundantly available; and it had one of the two asymmetric centres of the ring system in the correct absolute configuration.

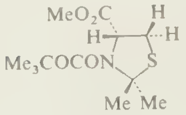


100



101

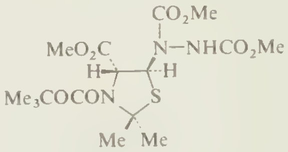
Woodward began by tying up the other groups in cysteine as tightly as he could, so as to make the target atom relatively more susceptible to attack. The form chosen, the N-acylated thiazolidine ester **102**, had the additional advantage that rotation of the methylene carbon in cysteine was no longer possible, so that its two hydrogens were in markedly different steric environments and could be expected to react with unequal reluctance. Many reagents were tried, and finally it was found that when the thiazolidine **102** was heated for 45 hours at 105° with excess of dimethyl azodicarboxylate (**103**) the hydrazo diester **104** was formed almost quantitatively: these conditions were critical. Perhaps it was Woodward's penchant for the Diels–Alder synthesis that first brought this reagent to mind: it was used first by Diels as a philodiene, but with some dienes it had recently been found to prefer allylic addition to Diels–Alder condensation. Woodward considered, and found experimental evidence for his view, that the initial attack of the reagent was on the sulphur atom in **102**. A subsequent hydrogen transfer gave a sulphur ylide that could undergo Stevens-type rearrangement. The hypothesis is pictured below (**105**→**106**→**107**).



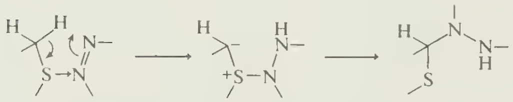
102

$$CO_2Me{-}N{=}N{-}CO_2Me$$

103



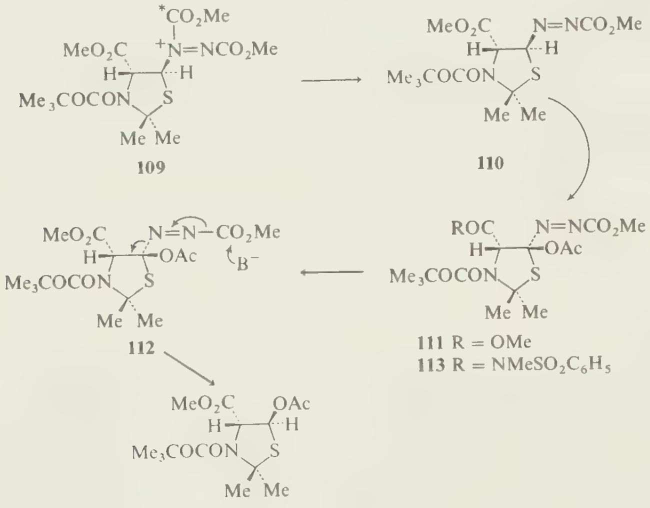
104



105 **106** **107**

The reaction was stereospecific, the new group entering the ring on the side away from the methoxycarbonyl group; but the remaining hydrogen atom had to be brought somehow to the same side as its neighbour before the correct stereochemistry for Cephalosporin was established, and this meant an inversion of configuration at some stage.

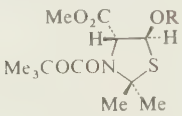
When the hydrazo diester **104** was oxidized with lead tetra-acetate in boiling benzene, the product was principally the *trans* acetoxy-ester **108**, along with a little of the *cis* isomer. The first oxidation product was thought to be the cationic azo compound **109**, which would lose the starred methoxycarbonyl group easily to nucleophilic attack. The resulting azo-ester **110** would then be oxidized to the acetoxy derivative **111**. In this, nucleophilic attack on the azoester carbonyl would lead to loss of nitrogen as shown (**112**); acquisition of a proton from the medium would then complete the formation of **108** and its isomer. Again, experimental evidence in support was obtained by the isolation of an intermediate product (**113**) analogous to **111** in a parallel series.



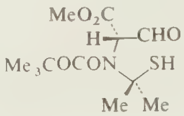
109 **110** **112** **111** R = OMe **113** R = $NMeSO_2C_6H_5$ **108**

To continue the synthesis, the acetoxy isomers were not separated but the total product was submitted to base-catalysed methanolysis (anhydrous methanolic sodium acetate). This gave, from both the *trans* and the *cis* isomers, the *trans* hydroxy compound **114**, the structure of which was confirmed by X-ray crystallographic analysis of the corresponding acid.

The chemistry is remarkable enough, but the very existence of **114** in a reasonably stable, optically active form is perhaps more remarkable still. Tautomerism with the thiol-aldehyde **115** is not only possible but seems actually to occur in the isomerization of the *cis* acetoxy isomer during methanolysis. Moreover, this thiol-aldehyde might lose the elements of thioacetone by further tautomerism and it is also a derivative of formylacetic ester in which enolization (destructive of optical activity at the least) could be expected to occur with great ease: in fact, it seems to revert to the thiazolidine **114** without either of these changes. Finally, in the intermediates **108**, **114** and (later) **117**, there is some likelihood of elimination yielding the thiazoline **116**. Woodward pointed out with relish to his audience these abysses surrounding the small plateau of stability that he had created.



114 R = H
117 R = SO_2Me



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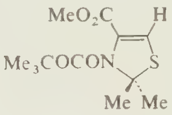
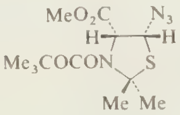


116

In the event, none of these disasters occurred; and further, when the methanesulphonate (**117**) of **114** was prepared it underwent smooth reaction with sodium azide with clean inversion of configuration. The *cis* azido-ester **118** was reduced by aluminium amalgam to the amino-ester **119**, and this on treatment with triisobutylaluminium cyclized with loss of methanol to the fused β-lactam **120**. Both structures **119** and **120** were verified by X-ray crystallography.



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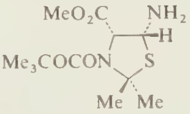

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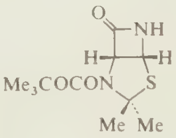
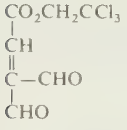


120

The intermediate **120** retained one group somewhat amenable to further substitution—the lactam nitrogen. Because of the sensitivity now built into the molecule, the use of catalysts was to be avoided. To provide the remaining carbon atoms for the cephalosporin nucleus, the powerfully electrophilic carbalkoxymethylenemalondialdehyde **121** was prepared. This was done by oxidizing di-βββ-trichloroethyl tartrate to trichloroethyl glyoxylate, and condensing this with sodium malondialdehyde to an aldol which was dehydrated by heating in octane. The βββ-trichloroethyl ester group was used here and subsequently because it can be removed by reduction with zinc instead of by hydrolysis or catalytic hydrogenation.

The extreme reactivity of **121** was evidently needed. The octane solution was used directly for condensation with **120** and 16 h at 80° were required. The adduct (**122**) was transformed in trifluoroacetic acid at room temperature into the sensitive amino-aldehyde **123**. Construction of the cephalosporin nucleus was almost complete.



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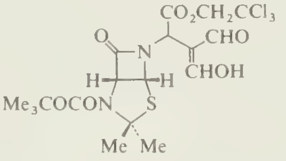

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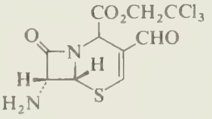
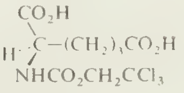


123

The synthesis of Cephalosporin C itself was concluded a little inelegantly by Woodward's standards in that a condensation, effected by dicyclohexylcarbodiimide, between the amino-aldehyde **123** and the trichloroethyl urethane **124** from D-α-aminoadipic acid, gave reaction at both carboxyl groups and consequently required the chromatographic separation of two isomers, after esterification of the surviving carboxyl groups with trichloroethanol and dicyclohexylcarbodiimide. The desired isomer (**125**) was then reduced by diborane to the primary alcohol and acetylated to yield the acetate **126**. In anhydrous pyridine this substance was equilibrated with the prototropic isomer **127**. The equilibrium is unfavourable (**125** : **127** ≈ 4 : 1) and again chromatographic separation was necessary. Finally, reduction of **127** by zinc in acetic acid gave Cephalosporin C (**100**) identical with the natural antibiotic.



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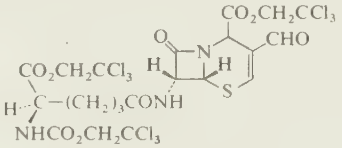

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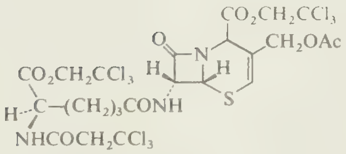

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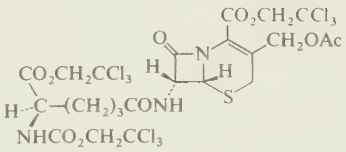


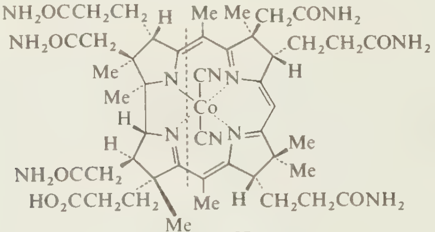
127

The fascination of this synthesis, for the present author at any rate, is in the chemistry of the thiazolidines. Woodward worked on this hard little nucleus like a Japanese netsuke carver.

Several other contributions were made at the Woodward Research Institute to the chemistry of β-lactam antibiotics (169, 185–187, 190, 191, 196).

Vitamin B_{12}

The synthesis of this vitamin was the product of a collaboration between Woodward's research group at Harvard and that of Albert Eschenmoser at ETH Zürich. It has never been published in detail and this account is compiled from three lectures by Woodward (154, 168, 172). These described completion of the formal total synthesis which was complete in 1972. A fourth lecture (195) described the conversion of synthetic cobyric acid (**128**) to the synthetic vitamin; a path that had already been travelled by Bernhauer, Friedrich *et al.* using natural material.



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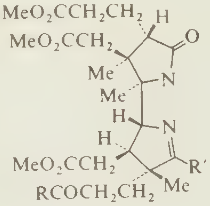
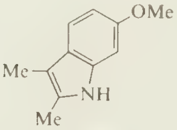


129

A molecule of this complexity, having nine centres of asymmetry and seven similar carboxylic functions of which only one is free—not to speak of a new ring system (the corrin ring) and the presence of a metal atom that (unlike the magnesium atom in chlorophyll) could not be expected to slip with ease into place—clearly called for some division of labour between the two laboratories and it was decided that the Harvard team should work on the left-hand (or 'western') part of the molecule, divided as shown by the dashed line, and that the Zürich team should tackle the right-hand part. The two pieces were then to be joined together.

Woodward's plan for the western part, with its six centres of asymmetry forming a continuous chain of carbon atoms, characteristically took into account all the peculiarities of its structure. He had fixed on the pyrrolinyl-pyrrolidone **129** as the desirable objective. In this, the group R is anything distinguishing that carbonyl function from the three methoxycarbonyl groups; but the group R′ has special requirements.

The plan also provided a starting point from which should be solved, as soon as possible, one of the hardest problems of the synthesis: the



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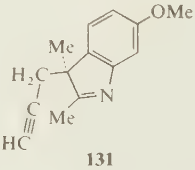

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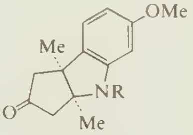


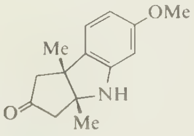
132 R = H

132a $R = C_6H_5\overset{\text{Me}}{C}HNHCO$

introduction of two contiguous quaternary centres of asymmetry. The synthesis started from 6-methoxy-2,3-dimethylindole (**130**), and readers will recognize here an echo from the strychnine synthesis.

Reaction between the iodomagnesium derivative of **130** and propargyl bromide gave the indolenine **131** in a smooth reaction. With boron trifluoride and mercuric oxide in methanol the indolenine, probably by way of an intermediate enol ether formed by addition of methanol to the triple bond, was cyclized to the tricyclic ketone **132**. The two small rings made generation of a *trans* junction most unfavourable and in the product the two contiguous quaternary centres had been set up, in their correct relative configuration.

Not every chemist would have decided at this point to resolve the ketone **132** into its two enantiomers. Even now, many a synthesis of a chiral natural product stops short of resolution: there is a widespread fear of the procedures as being too unpredictable and laborious. Woodward never had this fear and he applied to his choice of resolving agent (and of the particular stage at which he did the resolution) the same selective care that he used for chemical processes in general. In this case, he made a urea (**132a**) from the racemic substance **132** and optically active α-phenylethyl isocyanate. Only one diastereomer crystallized and the ketone **132**, in its optically pure form, was regenerated from the urea by pyrolysis. By use of both enantiomeric isocyanates, which are equally readily available, he made both enantiomers of the ketone **132** in quantity.



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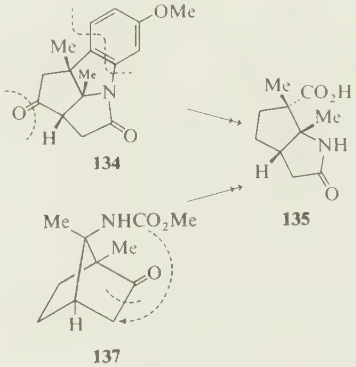

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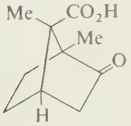
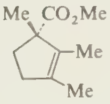


136

He already had it in mind to use the 'wrong' enantiomer as an expendable substance to try out reactions that might then be executed with the 'right' one; but first it was necessary to know right from wrong. This ambiguity was removed by a clever correlation of the laevorotatory tricyclic ketone with dextrorotatory camphor. This ketone (**133**) was converted, by chloroacetylation on nitrogen followed by an intramolecular alkylation using potassium *t*-butoxide as the enolizing base, to the tetracyclic ketone **134**. Conventional removal of the carbonyl group *via* a dithioketal and destruction of the aromatic ring by ozonolysis led to a bicyclic lactam (**135**) identical with a lactam made from the known keto-acid (**136**), derived from (+)-camphor, by a Curtius degradation of the carboxyl group and treatment of the resulting urethane (**137**) with potassium *t*-butoxide and then potassium hydroxide. Hence, the laevorotatory ketone was the 'wrong' enantiomer.

It is an additional feature of this early resolution that it permitted the use of optically active natural products to add pre-formed centres of asymmetry in the correct absolute configuration, thus avoiding formation of diastereomers. Methyl laurolenate (**138**) is available from (−)-camphor and it could be converted, *via* the corresponding aldehyde, into the acrylic acid (**139**). A later synthesis of the acid (**139**) from camphorquinone is one of the few pieces of the Harvard synthesis that have been published in detail (152, 176). In 16 steps from (−)-camphor, an overall yield of 17% was reported. The earlier synthesis was shorter but the overall yield was not specified. This small part of the main synthesis does, however, give some idea of the effort required to supply materials for further progress as the succession of steps became longer and steeper.



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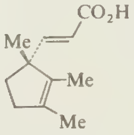

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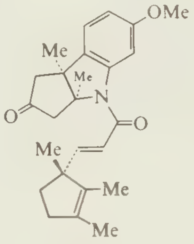

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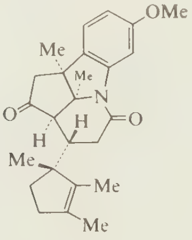
The two pieces, **132** and **139**, were now put together, the acid chloride from **139** acylating the indoline nitrogen of **132** to give the amide **140**. The expected Michael addition occurred under the influence of potassium *t*-butoxide and the pentacyclic lactam **141** was the product. The *trans* geometry of the double bond in **139**, and the relative inaccessibility of one side of the cyclopentanone ring in **132**, assured the stereochemistry as shown. At the time of the first progress report (154) over two hundred



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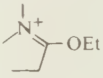

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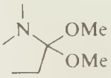

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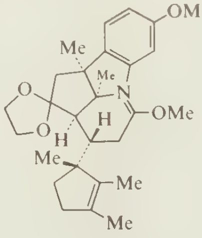
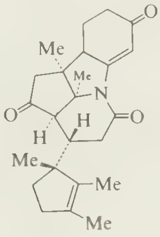


144

grams of this substance and of its enantiomer had been prepared—a task recalling the building of the Pyramids.

A Birch reduction on the aromatic ring was next proposed and it was necessary first to tie up both carbonyl groups in a non-reducible form. The keto group was first simply protected as a dioxolane, but the lactam had then to be converted into an immonium salt (partial structure **142**) and thence *via* an orthoamide (partial structure **143**) into a methoxy-enamine (**144**). This sequence marked the first use in this synthesis of Meerwein's reagent—triethyloxonium fluoroborate—for O-alkylation of the lactam to give the immonium salt **142**.

Birch reduction of the protected intermediate **144** proceeded normally and the unsaturated ketone **145** was formed after hydrolysis. The stereochemistry at the newly introduced centre of asymmetry could not be predicted and was, in fact, 'wrong' for vitamin B_{12}; but the synthesis had been designed with this contingency in mind. The master plan envisaged the introduction of the ring D nitrogen atom by way of a Beckmann rearrangement, and the ketone **145** was converted into the monoxime **146** *via* a dioxime which could be partially cleaved by nitrous acid. The oximino group in **146** was highly hindered, which explains perhaps its resistance to the oxidative steps which followed. The crowded environment of this group also left little doubt that the geometrical isomer formed was as shown—an important point, for otherwise the wrong group would have migrated in the Beckmann rearrangement.



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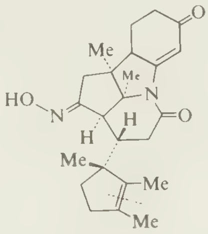

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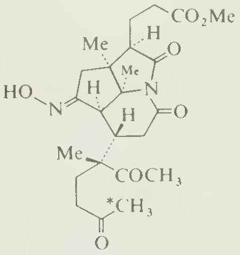
Ozone at −80°, followed by periodic acid and diazomethane, cleaved both double bonds and smoothly provided the intermediate **147**.



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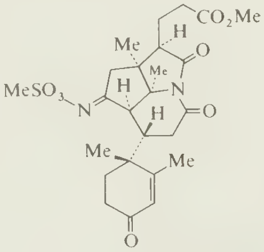

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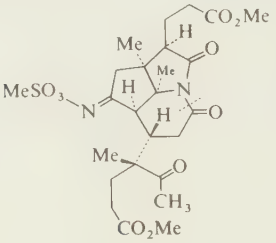
The convenience of using optically active camphor for preparing the intermediate **139** had the consequence that a superfluous methyl group (starred in **147**) had been carried through the synthesis to this point: it was now neatly eliminated. The intermediate **147** is a 1,5-diketone and could cyclize to a cyclohexenone in two different senses. Pyrrolidine acetate in methanol brought about cyclization to the desired cyclohexenone, isolated as the oxime mesylate **148**. This mode of cyclization probably depends on a strong preference for pyrrolidine enamine formation from the less hindered carbonyl group, and it is the opposite of what one would expect from the usual alkaline cyclization. This trick has been useful in several syntheses since that time. The cyclohexenone **148** was again cleaved by ozone and periodic acid; the product after esterification was the keto-ester **149**.



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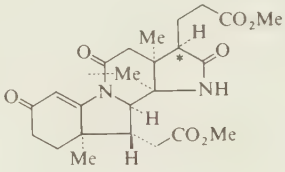
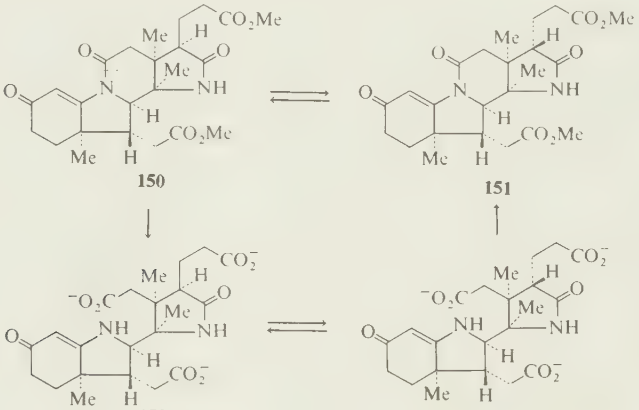


150

The chemistry so far had been relatively simple, with well-known reactions progressively shaping one part of the structure after another. In this way, a complex combination of potentially reactive groups had been assembled. Had the Beckmann rearrangement of the oxime mesylate **149** occurred easily, the subsequent course of the synthesis would probably have been different. In fact, 2 hours in methanol at 170 °C in the presence of a polystyrenesulphonic acid were required to effect rearrangement and several other changes occurred also. The N-acylpiperidone ring was opened by methanolysis and, more surprisingly in these acidic conditions, the δ-ketoester grouping was cyclized to a dihydroresorcinol, which promptly condensed to form a cyclic enamide with the piperidone nitrogen formed during rearrangement.

The product (**150**) was dubbed 'α-corrnorsterone' from its fancied resemblance to a B-norsteroid structure and its intended role as a precursor of corrins. One positive gain from its formation was that the future ring D had been closed correctly when there might have been alternative cyclizations. However, to continue the synthesis it was necessary to cleave the piperidone ring as shown (dashed line in **150**) and α-corrnorsterone proved so resistant to hydrolysis by alkali or acid that no way of opening this ring smoothly could at first be found.

The saving grace appeared in the form of a very minor by-product, called β-corrnorsterone. Its general properties and spectra were so similar to those of the α-isomer that it was considered to be a diastereomer (**151**) generated by a change at the only centre of asymmetry (starred in **150**) likely to be configurationally unstable. However, the finding that the piperidone ring in β-corrnorsterone was exceptionally easily cleaved by alkali was so surprising that this structural assignment was questioned. There was no mistake, however; in the puckered system generated by the relative stereochemistry of the ring-junctions in **150** and **151**, a change in the orientation of the propionic side-chain materially affects the access of nucleophilic reagents to the piperidone carbonyl group. In practice, it was found that heating of α-corrnorsterone for some time with a large excess of concentrated base gave a solution from which, by acidification and then treatment with diazomethane, β-corrnorsterone was obtained in almost 90% yield, together with about 6% of the α-isomer. Equilibration of **150** and **151** could also be effected (by methoxide ion in methanol) but the equilibrium constant was close to 1.



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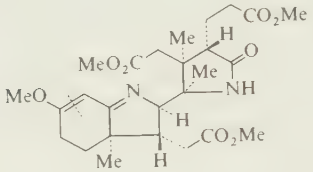
152

153

The explanation offered was that in concentrated base the piperidone ring in α-corrnorsterone did open and that the amino-acid **152** was then equilibrated with its stereoisomer **153**. The equilibrium would certainly favour **153**—the two anionic groups want to get out of each other's way—so that on acidification the β-isomer (**151**) was formed almost exclusively. A bromo-derivative of β-corrnorsterone was examined by single-crystal X-ray crystallography and the structure **151** for the parent substance was confirmed in every detail.

The piperidone ring in β-corrnorsterone proved labile to acids as well as to bases, and treatment with methanolic hydrogen chloride gave the imino-ester **154**, the concomitant O-methylation of the enaminone system preventing re-closure of the lactam ring. This secondary change was useful in another way, for ozonolysis at −80 °C followed by treatment with dimethyl sulphide gave the aldehyde **155**. Here, all the structural requirements of the initial objective (**129**) had been satisfied, with the exception that all four carboxyl groups were present as methyl esters.

The tetramethyl ester **155** was in fact used for continuation of the synthesis up to the point where the corrin ring was formed, and most of delicate procedures necessary were developed in that series. Later, a method for preserving the individuality of the propionic acid chain in the future ring D was devised. Instead of using methanol for the reaction that produced **154**, use of a mixture of methanol and a thiol (eventually, thiophenol was found best) gave the thioether-ester **156**. This ingenious combination of two reagents, each going to its appointed place, was the product of acute reasoning about the properties of a monothioketal from β-corrnorsterone and β-hydroxyethyl mercaptan. Treatment of that substance with acid generated an ultraviolet spectrum interpreted to mean that the oxthiolane ring in this derivative had opened by cleavage between carbon and oxygen rather than between carbon and sulphur! The product **156** on ozonolysis smoothly gave the thiolester-aldehyde **157** (this ozonolysis was where the phenyl group was superior to others).



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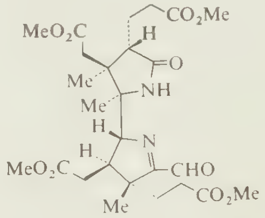

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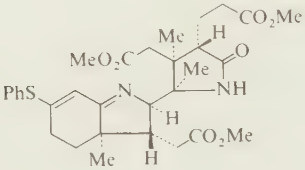

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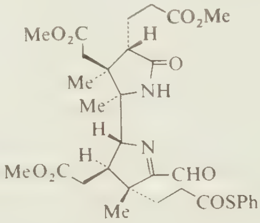
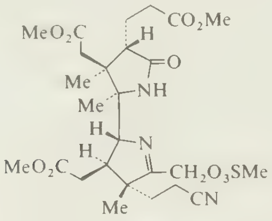


157

The thiolester **157** formed an amide on dissolution in liquid ammonia, the three methoxycarbonyl groups remaining intact. The aldehyde group in this amide was reduced by borohydride to a primary alcohol; then, the action of methanesulphonic anhydride in pyridine both mesylated the alcohol and dehydrated the amide, so that the product was the nitrile **158**. Displacement of methanesulphonate anion by bromide ion then gave the bromonitrile **159**, and this intermediate representing rings A and D of the vitamin, was destined to be coupled with the B/C precursor synthesized in Zürich. From this point onward, the two laboratories were working on the same problems.

The B/C precursor, nicknamed 'thiodextrolin', was put together by chemical processes very different from those described above. The fight for the bromonitrile **159** was typical Woodward. As ever, his goal was a particular synthesis. He revelled in complications and the solutions he found for his problems were particular not general solutions, drawn from his immense repertoire of chemical reactions. Eschenmoser has always been more interested in invention of new chemical reactions and his solution of the problem of the B/C precursor introduced a novelty that not only achieved its immediate end but also provided the method for stitching together the two halves of the corrin ring. Moreover, his studies of pyrrolidine and pyrroline derivatives, and of corrin synthesis in general, led him eventually to a simpler synthesis of vitamin B_{12}, based on the assembly of four such derivatives. Since this memoir is Woodward's I shall omit a description of the synthesis of 'thiodextrolin' (**160**), but one feature of the crystalline compound obtained must be mentioned: it turned out to be stereochemically inhomogeneous at one centre of asymmetry (circled in **160**). This was not, however, a deficiency which it was desirable then to correct, for the configurational lability at that centre would have produced similar mixtures at many subsequent stages.



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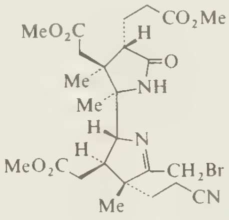
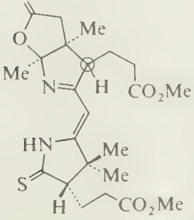


159

The thioamide group in **160** was appreciably acidic and it could be *S*-alkylated by the bromonitrile **158** in the presence of potassium *t*-butoxide



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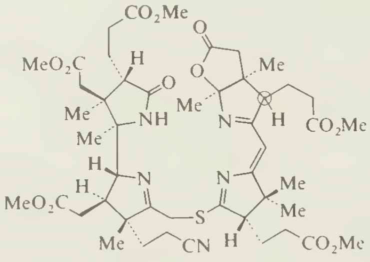
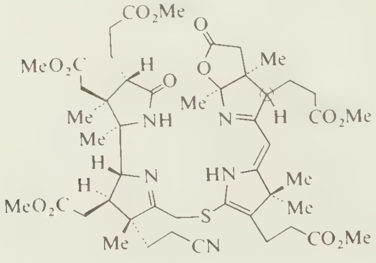


161

to give the thioether **161**. The intention then was to eliminate sulphur from this molecule, leaving one carbon-carbon bond where the two carbon-sulphur bonds had been. This scheme had already been successful in the synthesis of thiodextrolin, but its application in the more complex environment was one of the most difficult steps of the whole synthesis. The studies that eventually overcame these difficulties were made not with the nitrile **159** but with its methyl ester analogue (from **155**).

It should be recalled that the product **161** had behind it some sixty to seventy steps of synthesis. Even one experiment with a few milligrams of material required an enormous logistic effort. As if that were not enough, both reactants in the formation of **161** were sensitive substances. All operations had to be conducted in specially purified solvents with complete exclusion of oxygen, and this requirement persisted for most of the remaining stages in the synthesis. Further, the product itself was tautomerically unstable, being readily isomerized by acidic reagents to the relatively more stable **162**. In this change, of course, a centre of asymmetry was destroyed and for a very long time it proved impossible to proceed further with this isomer. Progress was indeed made with a third isomer obtained in certain conditions as a by-product of the isomerization, but the complexity, low overall yield, and difficulty in scale-up of the process were prohibitive. Eventually, a way was found to proceed. When the stable thioether (**162**, obtainable in quantitative yield from **161** by treatment in dichloromethane with a trace of trifluoroacetic acid) in sulpholane was heated for 20 hours at 60 °C with tris-(β-cyanoethyl)phosphine and trifluoroacetic acid in strictly defined proportions, the desired extrusion of sulphur was effected and the product, called cyanocorrigenolide (**163**), was formed smoothly. Here, of course, another centre of asymmetry was introduced non-specifically, and mixtures of epimers at the two circled centres were formed. That was the solution found at Harvard: the Zürich group used the primary intermediate **161** (in the methyl ester series) and converted it into **163** by a highly unusual mixture of reagents: triphenylphosphine : boron trifluoride : methylmercury isopropoxide.



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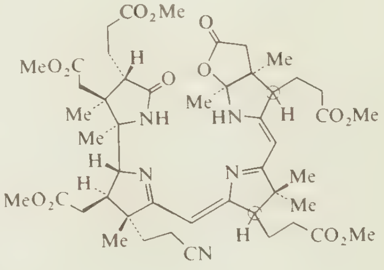
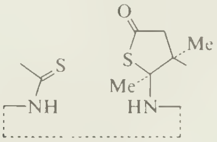
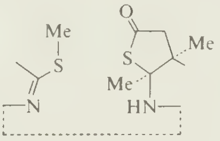


163

The second ring-closure to form the macrocyclic corrin system gave scarcely less trouble. Clearly, the γ-lactone ring attached to the future ring B would have to be opened at some stage; but if this opening was accompanied by elimination of the proton on the adjacent nitrogen atom a stable pyrrolenine structure was formed with which nothing useful could be done. The first step forward was taken with the preparation of the thioamide-thiolactone (**164**; only the relevant parts of the molecule are shown) from **163** by the action of phosphorus pentasulphide.

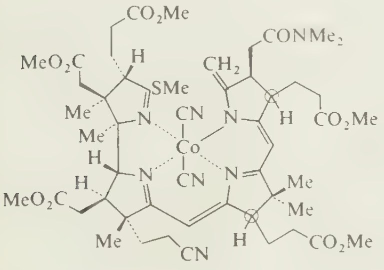


164



165

Trimethyloxonium fluoroborate S-methylated the thioamide group to give the imino-thioether **165**, and then, in an unique reaction, dimethylamine opened the thiolactone ring and left an exocyclic methylene group. This reaction, discovered at Zürich, was crucial. The product was treated directly with anhydrous cobalt chloride in tetrahydrofuran and was isolated as the dicyanocobalt complex **166**. This method of cobaltation was found after much experiment; in other conditions, all too frequently, the cobalt catalysed far-reaching destruction. In the complex **166** the cobalt atom was of course holding the two ends of the molecule close together in a configuration favourable for closure of the corrin ring; and in fact, treatment of **166** with basic reagents (diazabicyclononene for choice) gave cyclization to the full corrin **167**. An alternative cyclization starting from **164** and using an intermediate zinc complex had already been found at Zürich.



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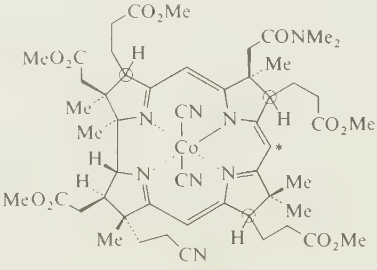
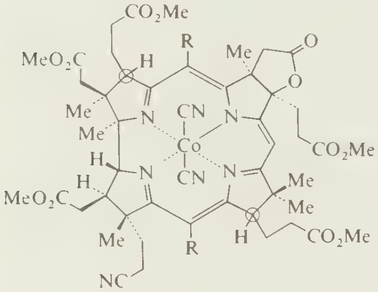
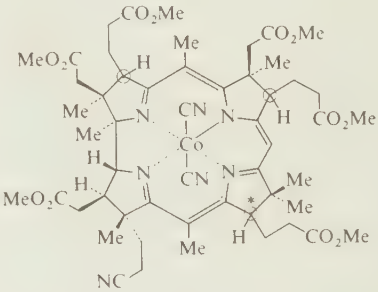


167

Note that in formation of **167** a third centre of asymmetry had been potentially labilized, so that the product could be, and was, a mixture of several diastereomers. This mixture might well have proved intractable but for the technique of high-pressure liquid chromatography. The strong absorption of visible light by the corrins made the observation of fractions an easy matter; but the mixture was not separated at this stage, again because of the possibility that the work would be undone in a later step. The product **167** differs from a cobyrinic acid derivative in lacking two methyl groups at the top and bottom *meso* positions. It was expected on the basis of earlier work that alkylation at these positions would be possible, but there is a third *meso* position (starred) that is also a candidate for alkylation. The next step was therefore an oxidation—by iodine in acetic acid—which converted the dimethylamide in ring B to a lactone (**168**). This device had the effect of crowding the environment of that third *meso* position by flanking it with two quaternary carbon atoms, and it was successful in inhibiting reaction there.



168 R = H
169 $R = CH_2Cl$
170 $R = PhSCH_2$

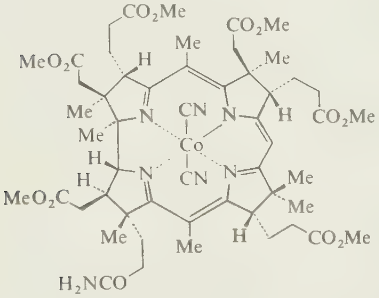


171

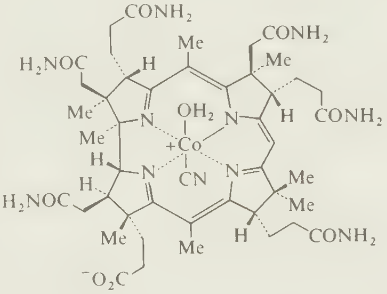
The alkylation process was a chloromethylation, effected by heating with benzyl chloromethyl ether, and it gave the bis-chloromethyl compound **169**. Methyl chloromethyl ether was thought to be a superior reagent for chloromethylation, but it was abandoned after the almost disastrous finding that it also converted the nitrile group into a sixth methoxycarbonyl. The chloromethyl compound was not isolated but converted by reaction with thiophenol to yield the bis-phenylthiomethyl ether derivative **170**. Treatment of this substance with Raney nickel not only generated the two required methyl groups but also reduced the lactone ring leaving, some stereochemical details apart, the full structure of a cobyrinic acid derivative. The product, after esterification of the carboxyl group liberated by reduction, had the structure **171**.

High pressure liquid-liquid chromatography then separated a fraction that had homogeneous and correct stereochemistry at all asymmetric centres except one (starred in **171**). It subsequently became possible to separate the two diastereomers in this fraction, but again this was not desirable since the asymmetric centre in question was labilized in the next step, the hydration of the nitrile group. It is a very surprising testimonial to the stability (in some ways!) of the corrin system that the reagent used for this hydration was cold concentrated sulphuric acid. In the product, the 'unnatural' (called *neo*) diastereomer predominated by nearly 3 : 1, but the two amides were separable by high pressure chromatography and the isomer of the 'natural' series (**172**) could be shown by direct comparison to be identical with a specimen prepared from vitamin B_{12} by degradation.

The two remaining steps necessary to complete the formal total synthesis of the vitamin were conversion of the amide to a carboxylic acid and of the six methoxycarbonyls to carboxamido groups. Nitrous deamination of the amide was troublesome, and Eschenmoser had already devised a most ingenious alternative method before it was discovered that nitrogen tetroxide in the presence of sodium acetate could, in special conditions, give the carboxylic acid in good yield without disturbing the rest of the molecule. Amidation also gave some trouble until it was found that a trace of ammonium chloride catalysed the ammonolysis and suppressed an unexpected dehydrogenation. Thus finally the synthesis of cobyric acid *a* (**173**), and with it the formal synthesis of vitamin B_{12}, was complete.



172



173

The quality of the effort needed for this extension of man's control over matter can quite fittingly be compared to the better known (and much more costly) feat of placing men on the moon; but no one who has not taken part in a long synthesis can appreciate the unremitting effort, care and skill required of the many bench-workers, or the necessary qualities of their directors: immense knowledge of chemistry, reaching the level of intuition; superb powers of planning and leadership; and—not least—mental resilience and refusal to be beaten. A dozen times they overcame difficulties that threatened to abort the whole synthesis.

Woodward was not content with cobyric acid, and in one of his last published lectures (195) he described the completion, using totally synthetic material, of the synthesis of the vitamin, by the path already traversed by others. There we see photomicrographs of the beautiful scarlet crystals, synthetic and natural, on a background of Woodward blue. Undoubtedly, it would have been better for the rest of us if he had spent the same effort in composing a dozen full papers on the synthesis of cobyric acid; but if he had not had this urge to make a vitamin programmed by human brains instead of by a string of desoxyribonucleic acid, he might not have found the force to push the cobyric acid synthesis through.

Generalizations

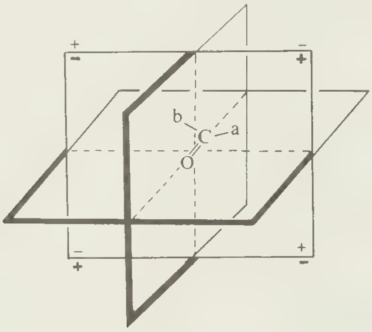
Woodward possessed to an unusual degree the power of making self-consistent patterns out of the information that he absorbed from the literature, from the work of colleagues, and from his own experiments. This power was manifested when he was only 23 years old in a series of four papers (11, 12, 15, 16) about the ultraviolet absorption spectra of αβ-unsaturated ketones and conjugated dienes. None of these papers contains a single original measurement; he got all the data from the literature. He showed that the exact position of the short-wave absorption maximum in the ketones was dependent on the extent of substitution on the double bond and he constructed a very simple additive formula for predicting the position of the maximum in any αβ-unsaturated ketone. Later, the formula was modified slightly to accommodate an observed difference between endocyclic and exocyclic double bonds; and he constructed an analogous formula for conjugated dienes. One paper (12) showed that a compound formulated previously as an αβ-unsaturated ketone, but having an absorption maximum at a much shorter wavelength than predicted, was an αβ-unsaturated acid.

Octant rule

The generalization about ultraviolet spectra was an acute empirical observation needing no theoretical background. Woodward's formulation of the octant rule, with Moffitt, Moscowitz, Klyne and Djerassi (109) showed deeper theoretical insight. Part of this, no doubt, was due to the young theoretician Moffitt, who became a good friend of Woodward and probably sharpened his intuitive feeling for molecular orbital theory; Moffitt died prematurely in 1958, before the paper was published.

The development of a practical spectropolarimeter to explore optical rotations into the ultraviolet was first exploited systematically by Djerassi, particularly in his exploration of the anomalous dispersion (Cotton effect) associated with absorption of light in the n→π* transition of the carbonyl group. A very large body of information was assembled on cyclic ketones where the structure, absolute configuration and (usually) preferred conformation were known. Some gave a positive Cotton effect (where dextrorotation increased abnormally and then fell sharply, as the wavelength diminished towards the absorption band) and some gave a negative effect (where laevorotation behaved in the same manner). It was clear from the data that the spatial disposition of groups in the neighbourhood of the carbonyl was influencing the sign of the Cotton effect, but Woodward's rationalizing genius seems to have been needed to produce a coherent explanation.

Space around the carbonyl group is divided into eight octants by three mutually perpendicular planes (**174**). The carbon and oxygen nuclei of the carbonyl group, and the two nuclei attached to the carbon, lie in one plane. The C═O bond lies in the second plane and is bisected by the third. These three planes correspond generally to nodal and symmetry planes of the orbitals involved in the transition. Now the assumption was made that if an atom in any octant had an effect inducing asymmetry (+ or −, in terms of the Cotton effect) in the processes of light absorption, an atom in the mirror-image position produced by reflection through any of these three planes would have an effect opposite in sign. This means in practice that if a sign (+ or −) is associated with any one octant, the signs of other octants follow uniquely. Only two distributions (**174** and its mirror-image) of sign are possible.



174

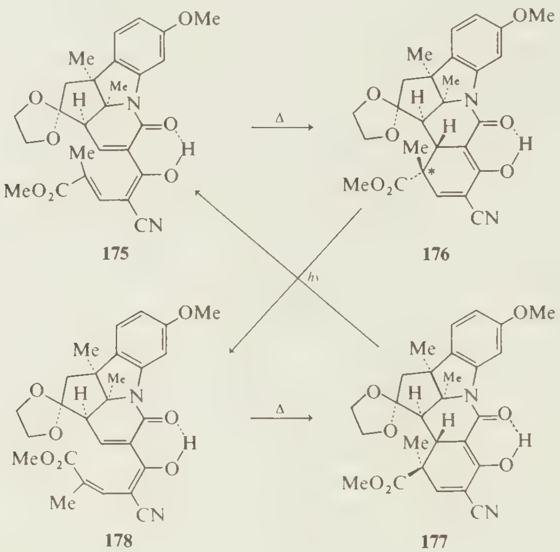
Accurate geometrical representations, based on observed bond lengths and angles, were made to assign substituents in a large number of ketones to their appropriate octants around the carbonyl group. Generally, only carbon and hydrogen atoms were present; and hydrogen atoms were ignored since it was expected that their contributions would be small and largely self-cancelling. Naturally, paired carbon atoms occupying adjacent octants were regarded as self-cancelling also.

Consistently, it was found that carbon atoms in the top left rear octant made a positive contribution to the Cotton effect, as in the diagram **174**. The contributions of carbon atoms in other octants were entirely compatible with the sign pattern of **174** and totally incompatible with its mirror-image alternative. In this way, the octant rule was established. Like all Woodward's generalizations it has stood the test of time; and theory has grown up around it.

Orbital symmetry

The principles of orbital symmetry conservation arose in a most interesting manner from Woodward's work on the synthesis of vitamin B_{12}. In the course of synthesizing the 'western half' of that molecule he had occasion to prepare the compound **175**. Readers will recognize in this a variant (it was a very ingenious variant) of the procedure finally adopted to add carbon atoms representing ring D to the portion (e.g. formula **132**) already synthesized.

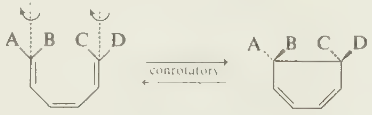
The substance **175** was made with the idea of executing an intramolecular Michael condensation of its complex anion, to give a product



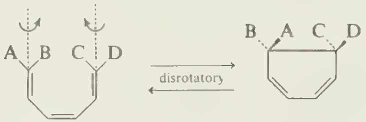
which would have, it was predicted, the structure **177**. The prediction was based on the usual considerations of the geometry of alternative transition-states. Cyclization of the anion could not be induced, but the cyano-enol itself (**175**) was rearranged thermally (on melting) to a mixture of the diastereomers **176** and **177**. It was shown that the appearance of this mixture was due to a preliminary partial conversion of **175** into the geometrical isomer **178** and that the thermal cyclizations were in fact stereospecific (**175**→**176** and **178**→**177**). Most strikingly, it was also found that the cyclization was reversed by irradiation, but in this, also stereospecific, process **176** gave **178** and **177** gave **175**.

For Woodward, the worrying thing about these results was that the thermal cyclizations were not what he had expected. Certainly, the new ring had been closed according to expectation on the convex side of the existing ring system, but the disposition of substituents at the starred centre of asymmetry (in **176** and **177**) was 'wrong', and the stereospecific photochemical ring-opening had no existing theoretical explanation. In the unpublished Chicago lecture mentioned earlier (p. 638) and in a Chemical Society lecture (148), Woodward described how from these contradictions the theory of the conservation of orbital symmetry was born.

Woodward's notation for the stereochemistry of such changes is simple. A conjugated polyene can be regarded as a planar molecule. When a single bond is formed between the terminal carbons, the substituents attached to both of them must move out of the plane. If this can be done by two rotations in the same sense, the process is conrotatory (**179**→**180**); and so of course is the reverse reaction. If the two rotations are in opposite senses (**179**→**181**) the process and its reversal are disrotatory. So the thermal changes **175**→**176** and **178**→**177** were disrotatory and the photochemical changes **176**→**178** and **177**→**175** were conrotatory.



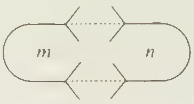
179 **180**



181

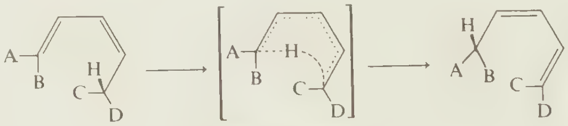
Woodward had at the back of his mind a case of thermal ring-opening observed by Vogel in the cyclobutene series. The process was highly stereospecific and unlike the hexatriene cyclizations it was conrotatory: yet another discord to harmonize! He said that the flash of enlightenment came to him in algebraic rather than geometric form; he remembered that the coefficients of the terminal terms in the expression representing the highest occupied molecular orbital in butadiene were of opposite sign, while those for hexatriene had the same sign. This soon led to the geometric idea that in cyclization of a *diene* the top face of one terminal atom should attack the bottom face of the other—a conrotatory process—while from a *triene* the new bond should grow between the top faces of both terminal atoms, in the disrotatory mode. Woodward soon recognized that he needed help in developing these ideas; and this was how the most fruitful collaboration with Roald Hoffmann began. Their first communication (131) enunciated the now famous Woodward–Hoffmann rules for electrocyclic reactions: in open-chain systems containing $4q$ π-electrons, a bonding interaction between the terminal atoms requires overlap between orbital envelopes on opposite faces of the system; in systems containing $4q+2$ π-electrons, the bonding interaction must be between orbital envelopes on the same face of the system. That is the rule for ground-state (thermal) processes; in the corresponding photochemical processes the symmetry of the excited orbitals is different and the stereochemical result is reversed. Theoretical calculations using an extended Hückel theory for the cases butadiene⇄cyclobutene and hexatriene⇄cyclohexadiene supported the initial hypothesis. The contribution of Woodward's young colleague—then a Junior Fellow, as he had been, of the Harvard Society of Fellows—in giving precision and scope to the theory was recognized in 1981 by a Nobel Prize.

The theory was soon extended to cycloadditions (133), in which polyenes with m and n π-electrons were added together (**182**): the Diels–Alder reaction is a familiar example of this ($m = 4$, $n = 2$). The molecular orbitals involved in the reaction were studied in a correlation diagram (a method independently used by H. C. Longuet-Higgins, F.R.S), classifying the energy levels with respect to the symmetry elements of the transition state. It was concluded that thermal cycloadditions (and their thermal reversals, as before) were favoured when $m+n = 4q+2$ and photochemical additions when $m+n = 4q$ where q is an integer. The initial paper (133) considered only *cis-cis* additions but later (150) the more general treatment was given.

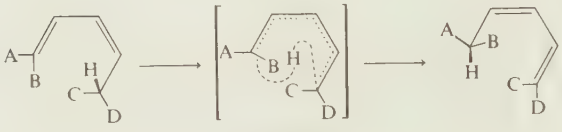


182

The third communication in this wonderful sequence (134) defined *sigmatropic* reactions: the migration of a σ-bond to a new position in a π-electron system by an uncatalysed intramolecular process. Stereochemically, this could happen *suprafacially* (when the migrating σ-bond is considered to stay on one face of the π system) or *antarafacially* (when it crosses from one face to the other). The two processes are illustrated (**183**, **184**) for a [1, 5] shift of hydrogen in a substituted butadiene. Here, the suprafacial change is favoured in a thermal reaction and the antarafacial change in a photochemical reaction. Selection rules for all types of sigmatropic reactions were formulated.



183 suprafacial



184 antarafacial

This is a brief outline of the conclusions of Woodward and Hoffmann, as originally formulated and surveyed (161–163). The summarizing paper in *Angewandte Chemie* (161, 162) is probably the most cited contribution to modern chemistry. The work gave molecular orbital theory a practical role in organic chemistry which hitherto it had lacked. It systematized an enormous body of chemical knowledge. Better still, it predicted new results at a time when experimental knowledge and technique were capable of verifying the predictions. Experimentalists and theorists alike were stimulated to test the predictions and the theory, and to make applications of their own. If Woodward had left no other legacy, this one discovery would assure his fame. But if he had not at the time been attempting an extremely difficult synthesis, pushing to the limit his powers of prediction, he would not have come upon the set of facts that seemed inexplicable. Eventually, the chemical literature might have provided enough material for a generalization, but it must have been a great satisfaction to him that the solution arose from his own experimental work and from the pattern of organic chemistry that he had woven in his own mind.

The authors of this memoir are grateful to many friends, colleagues and former students of R. B. Woodward for their help in its preparation both on personal and scientific aspects. In particular they are deeply indebted to Professor R. A. Bonnett, Professor Roald Hoffmann, Dr Jacques Gosteli, Professor W. D. Ollis and the late Professor F. Sondheimer for their assessment of the various aspects of Woodward's work in which they were involved and to Professor F. H. Westheimer, Professor Elkan R. Blout and Professor Paul Bartlett for much information on the early part of his career.

The photograph is by Fabian Bachrach.

Honours and appointments

During his lifetime R. B. Woodward held a number of appointments in addition to those at Harvard, and he received many medals and awards; the recipient of honorary degrees from a large number of universities and colleges he was also honorary member or fellow of learned societies and academies throughout the world. The most important of these are set out below.

Appointments

Harvard University: Postdoctoral Fellow 1937–1938; Member of the Society of Fellows 1938–40; Instructor in Chemistry 1941–44; Assistant Professor 1944–46; Associate Professor 1946–50; Professor 1950–53; Morris Loeb Professor of Chemistry 1953–60; Donner Professor of Science 1960–79.

Woodward Research Institute, Basle: Director 1963–79.

Member of Corporation, Massachusetts Institute of Technology 1966–71.

Member of Board of Governors, Weizmann Institute of Science 1968–79.

Member of Board of Directors Ciba-Geigy Ltd, Basle, 1970–79.
Alexander Todd Professor of Chemistry and Fellow of Christ's College, University of Cambridge 1973–74.

Honorary degrees

LL.D.	University of Glasgow, 1966.
Dr.tech.wiss.	Eidgenössische Technische Hochschule, 1967.
D.Sc.	Wesleyan University, 1945; University of Manchester, 1954; Bucknell University, 1955; University of New Brunswick, 1956; Yale University, 1956; Harvard University, 1957; University of Southern California, 1959; University of Chicago, 1961; New England College of Pharmacy, 1961; Colby College, 1963; University of Cambridge, 1964; Brandeis University, 1965; Stonehill College, 1966; University of Sheffield, 1966; Israel Institute of Technology (Haifa), 1966; Polytechnic Institute of Brooklyn, 1967; University of Western Ontario, 1968; Columbia University, 1969; Université de Louvain, 1970; Université Pierre et Marie Curie de Paris, 1975; University of St. Andrews, 1976; University of London, 1976.

Medals and awards

John Scott Medal (Franklin Institute and City of Philadelphia), 1945; Baekeland Medal (North Jersey Section of the American Chemical Society), 1955; Ledlie Prize (Harvard University), 1955; Research Corporation Award, 1955; Nichols Medal (New York Section of the American Chemical Society), 1956; Synthetic Organic Chemistry Award (American Chemical Society), 1957; Richards Medal (North-eastern Section of the American Chemical Society), 1958; Davy Medal (Royal Society), 1959; Roger Adams Medal (American Chemical Society), 1961; Pius XI Gold Medal (Pontifical Academy of Sciences), 1961; Scientific Achievement Medal (City College Chemistry Alumni Association), 1961; Priestley Medallion (Dickinson College), 1962; Stas Medal (Société Chimique de Belgique) 1962; Gold Medal for Creative Research in Synthetic Organic Chemistry (Synthetic Organic Chemical Manufacturers Association), 1962; National Medal of Science (United States of America), 1964; Kirkwood Medal (Yale Department of Chemistry and New Haven Section of the American Chemical Society), 1965; Nobel Prize in Chemistry (Royal Swedish Academy of Sciences), 1965; Willard Gibbs Medal (Chicago Section of the American Chemical Society), 1967; Lavoisier Medal (Société Chimique de France), 1968, The Order of the Rising Sun, Second Class (His Majesty the Emperor of Japan), 1970, Hanbury Memorial Medal (The Pharmaceutical Society of Great Britain), 1970; Pierre Bruylants Medal (Université de Louvain), 1970; Scientific Achievement Award (American Medical Association), 1971; Dr B. C. Law Gold Medal (Indian Association for the Cultivation of Science), 1972; Arthur C. Cope Award (American Chemical Society), 1973; Copley Medal (Royal Society), 1978.

Honorary membership of academies and learned societies

Member of the National Academy of Sciences; Fellow of the American Academy of Arts and Sciences; Honorary Member of the German Chemical Society; Honorary Fellow of the Chemical Society; Foreign Member of the Royal Society; Honorary Member of the Royal Irish Academy; Corresponding Member of the Austrian Academy of Sciences; Member of the American Philosophical Society; Honorary Member of the Belgian Chemical Society; Honorary Member of the Harvey Society of New York; Honorary Fellow of the Indian Academy of Sciences; Honorary Member of the Swiss Chemical Society; Member of the Deutsche Akademie der Naturforscher (Leopoldina); Foreign Member of the Accademia Nazionale dei Lincei; Honorary Fellow of the Weizmann Institute of Science; Honorary Member of the Pharmaceutical Society of Japan; Honorary Member of the Pharmaceutical Society of Great Britain; Honorary Fellow of the Indian Chemical Society; Honorary Life Member of the New York Academy of Sciences; Foreign Fellow of the Indian National Science Academy; Honorary Member of the Royal Institution of Great Britain; Foreign Member of the Academy of Sciences of the U.S.S.R.; Foreign Member of the Yugoslav Academy of Sciences and Arts; Honorary Member of Phi Lambda Upsilon (National Honorary Chemical Society); Honorary Fellow of the Royal Society of Edinburgh; Foreign Member of the Academy of Sciences of the Institute of France; Honorary Member of the Spanish Royal Society of Physics and Chemistry; Foreign Member of the Royal Academy of Sciences of Spain.

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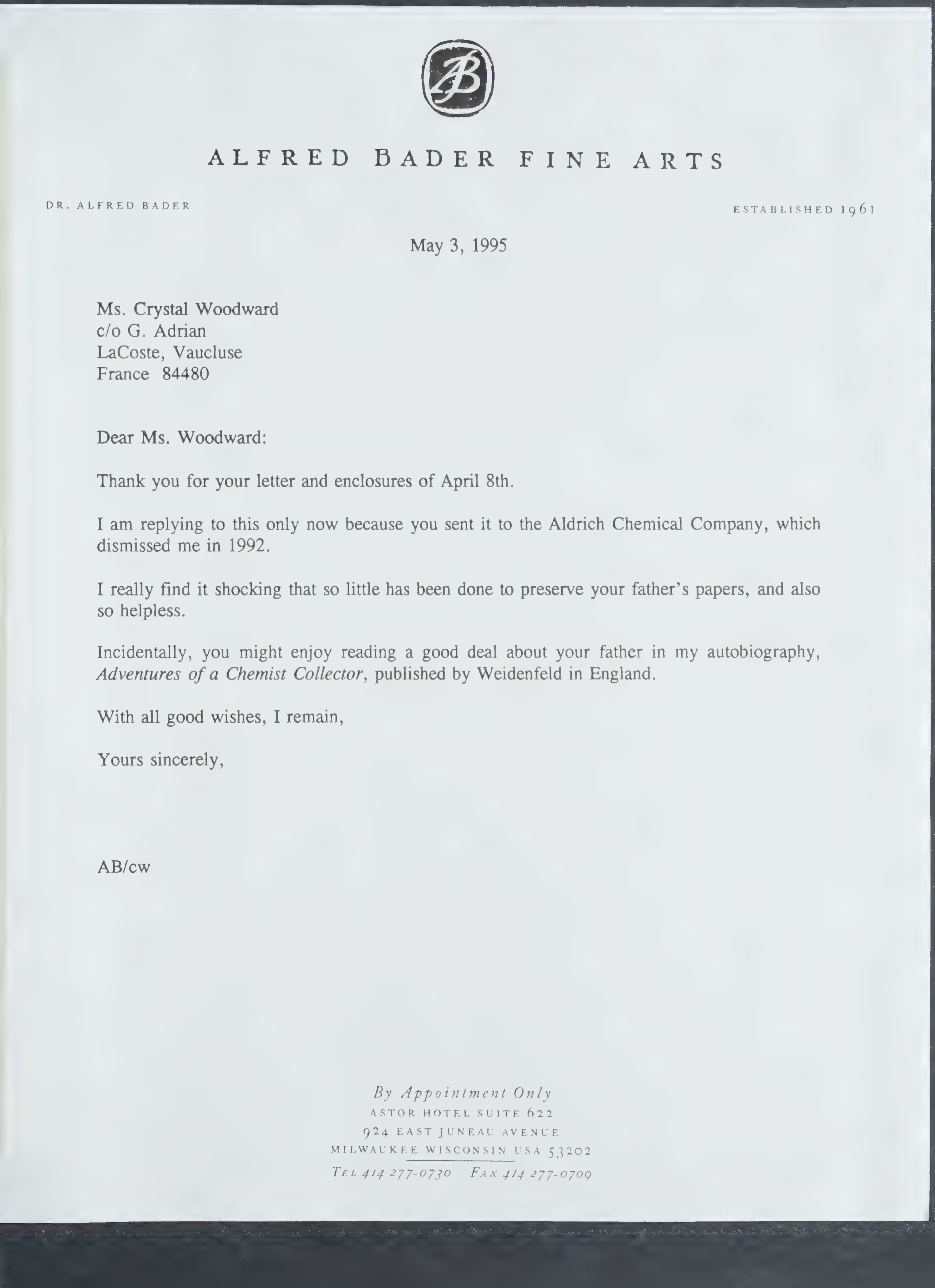

ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

May 3, 1995

Ms. Crystal Woodward
c/o G. Adrian
LaCoste, Vaucluse
France 84480

Dear Ms. Woodward:

Thank you for your letter and enclosures of April 8th.

I am replying to this only now because you sent it to the Aldrich Chemical Company, which dismissed me in 1992.

I really find it shocking that so little has been done to preserve your father's papers, and also so helpless.

Incidentally, you might enjoy reading a good deal about your father in my autobiography, *Adventures of a Chemist Collector*, published by Weidenfeld in England.

With all good wishes, I remain,

Yours sincerely,

AB/cw

By Appointment Only
ASTOR HOTEL SUITE 622
924 EAST JUNEAU AVENUE
MILWAUKEE WISCONSIN USA 53202
TEL 414 277-0730 FAX 414 277-0709

8 April 1995

Dear Dr Bader.

I shall be on my way back to France probably before Clark Elliott of the Harvard archives gets back to me about the latest preservation update. But since, I am enclosing the report which was written up 2 years ago. Because of the fact that the deacidification process available 2 years ago is no longer available, we have to re-think all of this... maybe only selecting items in small quantities to be deacidified. In any case, I wanted you to see [illegible]

Clark Elliott also is to get back to me as to whether Harvard can hold a fund for this work; he thinks it should be possible but had to check with the financial office. At that point then I would welcome contributions.

I've put off my departure to the 10th April.

I was glad to hear from you, and send best wishes

Sincerely

[illegible]

c/o [illegible]

Lacoste 84480 France

1605 BROADWAY • NEW YORK, NY 10019
TEL: 212/977-4000 • FAX: 212/333-7393

/

[Feb. 1993]

HARVARD UNIVERSITY ARCHIVES
CAMBRIDGE, MASSACHUSETTS 02138

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A Proposal for Archival Preservation and Improved Description and Access to the ROBERT B. WOODWARD PAPERS in the Harvard University Archives

Description of the Collection:

The Robert B. Woodward Papers in the Harvard University Archives cover the life and career of the Nobel Prize winning organic chemist from his childhood until his death in 1979. Included are personal and family papers, professional correspondence, reports, manuscripts, research notes and data, teaching materials (e.g., examinations, course outlines), photographs, files on graduate students and postdoctoral fellows, and other material. Overall the papers relate to Woodward's teaching and research activities, his personal life, awards, relations with professional groups and colleagues. There is a separate series of papers relating to the Woodward Research Institute (Basel, Switzerland).

The collection occupies about 90 linear feet of shelf space (in some 220 containers). The major part of it, however, is in three series collectively titled "Professional correspondence and other papers" that cover the years 1935-1979 (140 containers). The collection has been processed by the Harvard University Archives and a 60 page finding guide has been prepared that describes the collection and lists its content to the level of folder titles.

Problem Features:

The collection is on paper of greatly varying quality, as is typical of any such large twentieth-century accumulation. Especially problematic is the fact that many of Woodward's notes and drafts are on extremely poor and acidic paper and already have deteriorated. It was Woodward's practice, in his research, to sketch out chemical structures and these often are on the poorest quality paper. Research assessment and use of the collection is complicated by the fact that the drawings frequently are not identified by date or project, and the sequential relation of individual pages is not indicated. Following standard procedures, the Archives has maintained the papers in the order in which they were received.

Proposed Action:

Given the situation outlined above, and in light of Woodward's importance in the history of chemistry, the University Archives would like to undertake appropriate additional preservation measures for the collection, beyond those already accomplished as part of normal archival processing. The latter have included the substitution of acid-neutral for the original folders throughout the collection. At the same time, description and access to the collection will benefit from the advice of knowledgable and interested chemists and historians of chemistry who are able to visit the Archives and examine aspects of the papers. Several individuals have volunteered to do so, and others are expected in the future. The product of this activity will be the preparation by the examiners of written commentary and advice that subsequently can be made available to other researchers as a supplement to the existing finding prepared by the Archives' staff.

The project has three primary goals:

(1) To mass deacidify the entire collection in order to arrest further paper deterioration (90 linear feet);

(2) To identify brittle items liable to damage during use and to photocopy them, or to enclose them in mylar sleeves. (Mylar would be used chiefly for items that cannot be copied effectively --e.g., where the originals contain color. These items would be left in their original location in the collection. For items photocopied, the originals also would be retained but removed to a separate storage box to be made available to researchers only for special purposes);

(3) To facilitate examination (by knowledgable chemists and historians) of the chemical drawings and related notes in the collection that are largely unidentified at present. Much of this phase of the work will involve numbering folders and items within folders, in order to assure maintenance of the original sequence of material and to provide the examiners with page numbers that can be used as "index" references when preparing notes and comments on unidentified items.

Much of the work will be done by student or temporary staff under the supervision of the curators. The curatorial staff, in consultation with the Harvard University Library Preservation Office, will prepare evaluative and procedural guidelines.

Photocopies of several sample pages of the unidentified notes are enclosed as illustration of the nature of those parts of the collection.

Stages in the Work and Estimated Costs

Examine all folders and remove photographs and other non-paper items preparatory to deacidification; pack and otherwise prepare for shipment:
50 hours x $10.00 = $500

Mass deacidify, by Akzo Chemicals, Inc. (Deer Park, Texas). Approximate total of 200 archival document boxes in two shipments:
Deacidification = $10,000

Receipt and inspection of deacidified papers:
35 hours x $10.00 = $350

Locate and enumerate brittle paper and insufficiently identified research papers. (The following steps are listed separately, but ideally they would be done concurrently.)

Number all folders in collection and add numbers to folder list in collection finding guide. Estimated 1800 folders [9 folders x 200 boxes]:
50 hours x $10.00 = $500

Identify and flag brittle paper requiring photocopy or enclosure in mylar sleeves for use (preservation), and all folders containing chemical drawings and related research notes (description and access). These two categories of material largely overlap:
150 hours x $10.00 = $1,500

Number each sheet in all flagged folders (to establish the original sequence of sheets and for reference by chemist advisers):
Estimated 20,000 sheets / 300 per hour x $10.00 [rounded] = $700

Photocopy flagged brittle pages onto acid-free paper:
Estimated 11,000 pages x $0.30 = $3,300

Prepare folders, boxes, labels for original brittle pages after preservation photocopying, and annotate finding guide:
50 hours x $10.00 = $500

Enclosure of selected brittle pages in mylar sleeves:
Estimated cost of mylar sleeves:
1000 sleeves x $.84 = $840

Insertion of items in sleeves:
Approximately 1000 sheets / 30 per hour x $10.00 [rounded] = $350

Adjustments in number of containers and finding aid lists following addition of mylar sleeves:
20 hours x $10.00 = $200

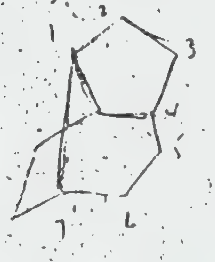
TOTAL = $18,740

ROBERT B. WOODWARD PAPERS HARVARD UNIVERSITY ARCHIVES

Call no. HUGFP 68.6: Professional correspondence
and other papers, 1935-1973.
Box 3, folder: [Notes D]

Note on attached photocopies:

The section of the Woodward Papers from which the attached sample pages were taken consists of several boxes of unlabeled material. In preparing the papers for use in the Archives (i.e., during archival processing), the materials were left in their original sequence and given the covering title of "Notes." Each folder of material was assigned a letter of the alphabet for purposes of identification and to maintain sequence. The attached pages are the entire content of folder "[Notes D]."



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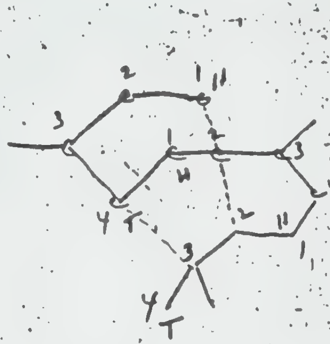

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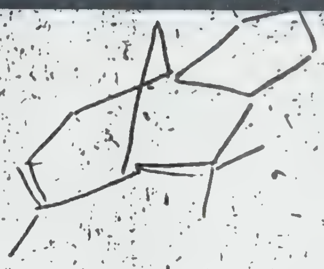

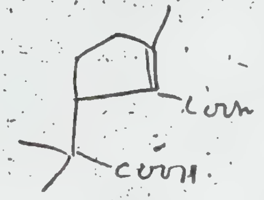

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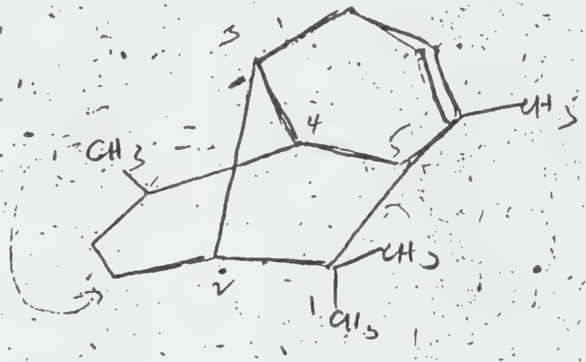

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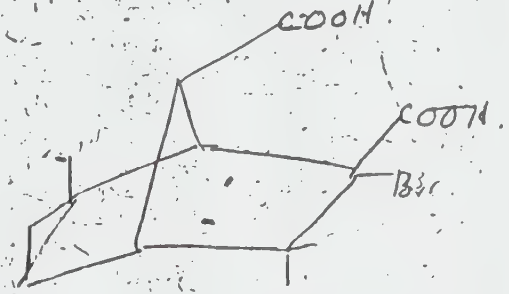

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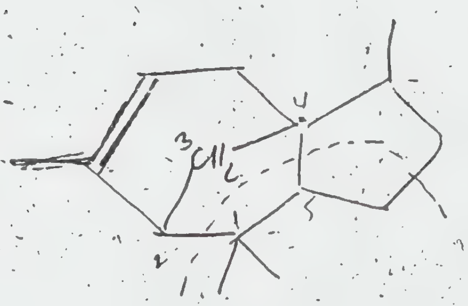

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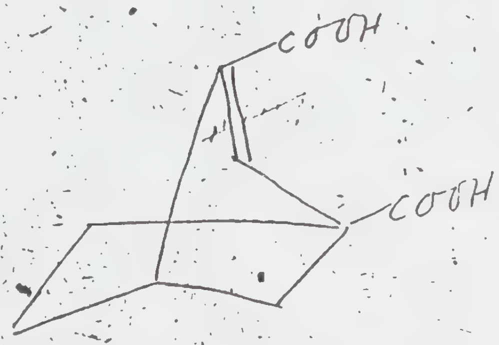

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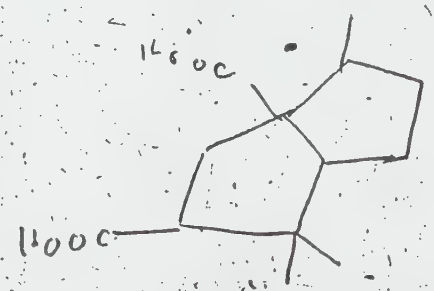

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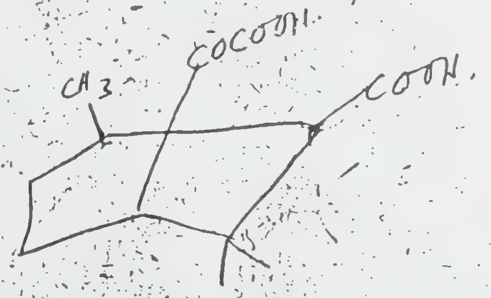

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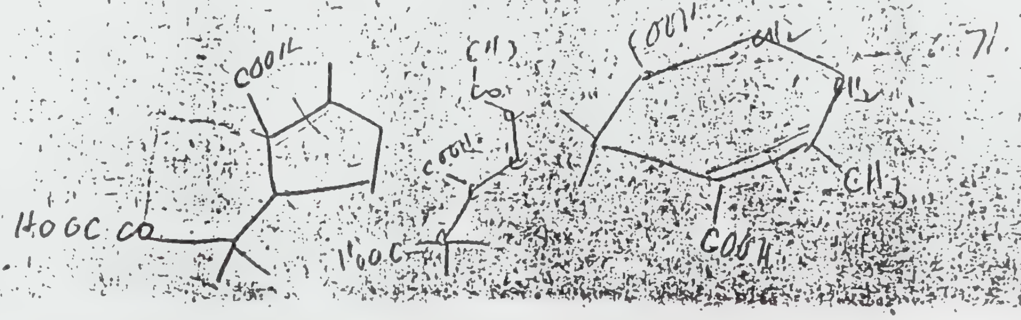

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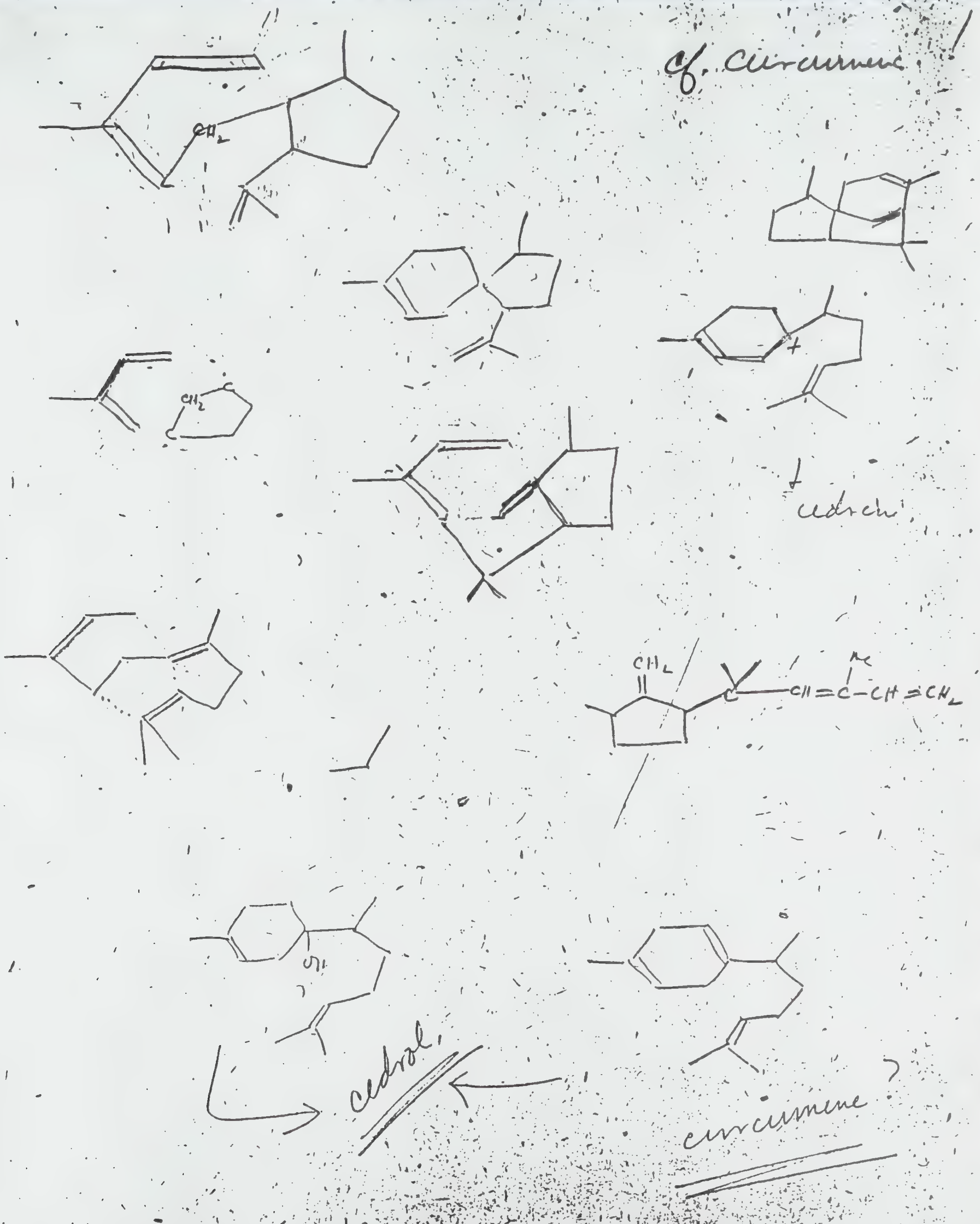
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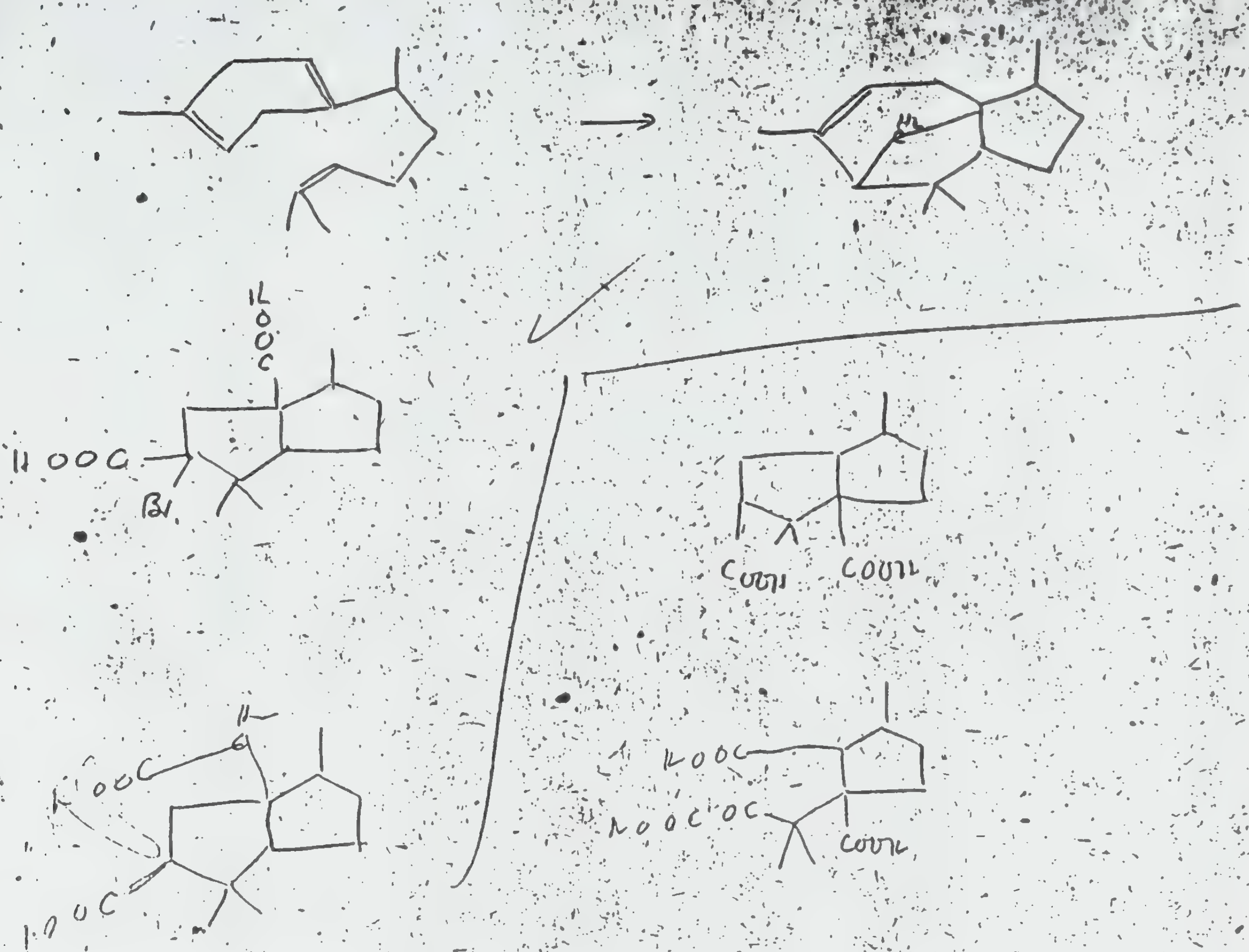
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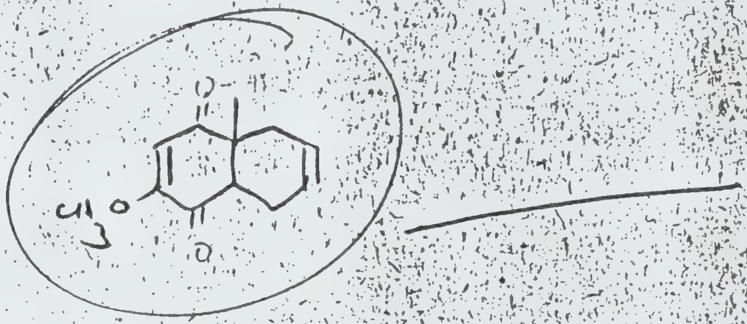
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ROBERT BURNS WOODWARD

1917–1979

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ROBERT BURNS WOODWARD
April 10, 1917–July 8, 1979

ROBERT BURNS WOODWARD
A Remembrance

Speakers
Elkan R. Blout
Lord Todd
Vladimir Prelog
Frank H. Westheimer

Friday, November 9, 1979
at four o'clock

Harvard Memorial Church
Harvard Yard

Remarks by Professor Elkan R. Blout
School of Public Health and Medical School
Harvard University

Honored Guests, Colleagues, Friends:

We assemble here today to remember and to speak of Robert Burns Woodward. How do we eulogize a man of such prodigious talents and accomplishments — one who had received almost every possible award, recognition, and honor for contributions to chemistry?

These special recognitions began early. At his *alma mater*, Massachusetts Institute of Technology, the faculty discerned his uniqueness, both as an undergraduate and a graduate student, and awarded him the Ph.D degree in 1937 when he was only twenty years of age. As many of you know, Bob came to Harvard as a Junior Fellow and subsequently was appointed full Professor of Chemistry at the then astonishingly young age of 33. Seven years later Harvard further recognized the exceptional abilities and achievements of this man by bestowing on him an honorary doctoral degree — an indication of esteem that Harvard does not give casually to members of its faculties!

His scientific work grew from an early interest in the art of chemical synthesis: but Woodward was not a synthetic organic chemist in the classical sense — although he was a superb one! His aim was not synthesis for its own sake: rather, it was *understanding* the processes by which both nature and man can construct complicated compounds — compounds that allow life to exist, and compounds that can be used to improve the quality of life. This theme ran through all his research — and it was this vein that the fortunate graduate student, postdoctoral fellow, or colleague was able to tap when he was associated with RBW.

Bob Woodward was also a "practical" man. Although some of the scientific problems on which he worked had no obvious utility, many of his long-term goals were to combine pure science with practicality. This attribute, along with his obvious intellectual abilities, led several of the most prominent industrial organizations to seek him out. At the time of his death, Bob had been a scientific consultant and adviser to Polaroid Corporation for almost forty years. He had also been associated with Ciba-Geigy Corporation for nearly twenty-five years, becoming director of a research institute that bore his name and also a member of the board of directors. In addition, he lent his talents to several other important organizations in the "real" world.

The speakers who follow will tell you some of the scientific achievements that have led Woodward to be recognized as the greatest organic chemist of modern times — and perhaps of all time. I will, therefore, confine my further remarks to consideration of the attributes that made this remarkable scientist also a remarkable man for his friends, family, and colleagues.

What words can one use to describe succinctly the qualities of this man? First and foremost, he had *brain power*, in the analytical and scientific senses, and also in much more. Certainly this was his most easily recognized quality. But it was also rewarding to find that the possessor of such superior powers had a real warmth, friendliness, and helpfulness for his fellow scientists and friends.

Also, Bob had "style". In his work this personal stamp could be seen in the way he chose chemical problems, analyzed them, planned syntheses, and ultimately presented the results of his work. All who have been privileged to hear him lecture recognized the style in which he presented complicated thoughts logically, clearly, and dramatically. In addition, those of us who also knew him as a friend recognize that he had "style" in his demeanor, in the way he dressed, and in all aspects of the way he lived. He was truly a man to whom quality and style were important in life.

What else did Bob believe in? He believed in individuality, in the worth of individuals, and in the value of intellectual achievement. He worked hard himself, and was not ashamed to admit it. One of his favorite aphorisms was "thinking is very hard work, but it is worth the trouble". This passion for thinking carried over to almost all aspects of his life. He was fond of all types of puzzles and games, as well as challenges in Science. His interest in mathematics and probability was lifelong. In fact, he was a founding member and devoted participant in a monthly sporting event — euphemistically called a "probability session" — which started in the basement of the Converse Lab in the early 40's and continued to this year in several private residences, including Bob's, in the Boston area.

One of Bob Woodward's most widely appreciated abilities — both scientific and social — was his sense of the dramatic and of the importance of timing. Those who have heard him lecture — especially in the last few years — need no proof that this man with the quiet, forceful voice, and the conservative blue tie and suit, provided his audiences with the most exciting scientific-intellectual dramas of our time.

How else can we describe this man — that he was a perfectionist?; that he was an Anglophile?; that he was a bibliophile? His perfectionism was clearly indicated in his science, and also in the demands that he placed on himself. Perhaps this can best be illustrated by the fact that Bob knew both French and German very well and read both languages easily, but was unwilling to speak in either because he felt he was not perfect in their use! One can also see perfectionism — perhaps a platonic search for the ideal — in his fascination with geometrical objects, spatial forms, and the roles of symmetry and asymmetry in molecules and in life. His sense of spatial relationships was truly remarkable, and it allowed him to visualize molecules in ways that contributed to his chemical investigations. Indeed, his fascination with spatial and geometrical relationships led him to consider the possibility of a career in architecture at an early stage in his life.

I have said that Bob was an Anglophile, and that was clear from his pronunciation, enunciation, and his many visits to academic institutions in Great Britain. As an English friend said to me recently, "He had a supreme command of the English language, was a perfect gentleman, and was 'more English than the English'. He loved ceremonies and enjoyed the pomp and circumstance of royal occasions."

I have noted that Bob was also a bibliophile. He not only read extensively in science, but he enjoyed most kinds of reading—averaging a book a day for most of his life. Also, he had the most highly developed visual memory of any scientist I have known. Because he spent much time in solitary pursuits such as reading, many people felt that Bob was a lonely man. A better description would be that Bob was a very private person. He shared his deep emotions with very few; but make no mistake, he had deep emotions, he had strong feelings, and he was truly artistic, romantic, and sentimental! Some people regarded Bob Woodward as a difficult and demanding person, but those who knew him recognized clearly that his demands were greatest on himself. He had the ability to concentrate absolutely, and this ability served him well in his solitary pursuit of visible and invisible goals.

In truth, Robert Burns Woodward was very much a man of preeminent style, of the highest quality, and of true greatness! We miss him today, and we shall always miss him.

Remarks by Lord Todd
Christ's College, Cambridge, England

To become legends in their own lifetime is a distinction achieved by very few men; but it was achieved by Robert Burns Woodward whose memory we are met this day to honour. Precocity is not synonymous with genius, although they are often found together as they surely were in his case. Born and reared in Boston, a city which remained dear to him all his life, Bob Woodward enrolled at the Massachusetts Institute of Technology to study chemistry when only 16 years of age and four years later he obtained his doctorate. Such precocity is not unique but it is very rare. The only comparable case I know is that of William Thompson, Lord Kelvin, who matriculated in the University of Glasgow at the age of 14. Bob Woodward's phenomenal achievement has certainly not been equalled this century and it must have given many headaches to both faculty and administration, for people who do not fit smoothly into standard patterns are not popular in any institution. Immediately after graduation he had a brief spell at the University of Illinois before coming to Harvard as a postdoctoral fellow in 1937. Soon made a member of the Harvard Faculty he remained in this University which he loved until his untimely death; many were the attempts made by other institutions to have him join them, but all failed in face of his loyalty to Harvard. His original research publications, begun as a trickle while he was yet an undergraduate, rapidly swelled to a flood which continued unabated till his death. By then the number had swollen to something like 200 — a remarkable output when one remembers that he was a perfectionist who left unpublished much work which lesser mortals would have been proud to display; it is to be hoped that his unpublished results will in one way or another be made available to succeeding generations. For Bob was a veritable giant among chemists and his influence on the science and its practitioners — already great — will undoubtedly grow further with the passage of time.

In the past four years I have lost two very dear friends in Robert Robinson and Bob Woodward. In years they were two generations apart but both of them stood scientifically head and shoulders above any other chemist I have known, and I have known many. As human beings they were both complex and very different from one another but in their science their interests were similar; each of them had two main topics which he pursued throughout his career — the structure and synthesis of natural products and the theoretical basis of organic chemical reactions. Which man was the greater is for others to debate if they wish — for me it is enough that I was privileged to know them both and I am proud to have enjoyed their friendship.

This is not the occasion for a detailed discussion of Bob Woodward's scientific contributions but it is noteworthy that the twin interests I have mentioned are clearly evident from the subjects of six of his earliest papers published before he was twenty-five years of age. All his theoretical contributions rest on established experimental fact; to him chemistry was above all an experimental science and he had no time for theories which did not rest on experiment. Although myself no theorist, it was Bob's early work on the structural interpretation of ultraviolet absorption spectra in 1941 that first drew my attention to him, and, despite our lack of personal contact until after the war, it really marks the starting point of our long association. From 1947 onwards we not only corresponded more or less continuously but also visited one another and travelled together to chemical gatherings all over the world; indeed in the 1950's and 60's we were involved in so many symposia that we felt at times rather like a travelling vaudeville act. And so we came to know one another well — as indeed befits men who have together explored the jungles of New York, London, Malaysia and even Papua-New Guinea!

One of the most striking features of Bob Woodward was the way in which he could transmit his passion for organic chemistry and his enthusiasm to young chemists of all races. They idolised him and would listen to him lecture literally for hours on end. I do not know nor have I ever known any other scientist who could so hold an audience; young chemists and many not so young were spellbound by him as by an evangelist or a political demagogue. He was, of course, a brilliant lecturer and withal no mean actor; his timing was always perfect and the famous little box containing his own set of coloured crayons, his special blackboard duster, his methodical and meticulous drawing of formulae (which at once slowed the pace and aided understanding) and his apparently extempore lectures were all carefully calculated to focus the attention of the audience and at the same time to conceal the immense amount of hard work he put into lecture preparation. This effort to conceal from others the amount of work he put into his science — for he was a prodigious worker with an equally prodigious memory — was one of his characteristics and one which, I fear, not all of his students and would-be disciples fully appreciated. It was, of course, a part of the image he presented to the world — that of a man indifferent to the buffetings and constraints of everyday life whose astonishing insight into problems rested on genius alone. To those who did not know him this characteristic pose made him seem at times insensitive and even arrogant. But they were wrong! Behind this facade was the real Bob — a loyal and generous friend.

It may seem strange that he should have presented this facade to the world for he had no need to do so although perhaps it served to protect him from fools and sycophants for whom he had no time. His passion was chemistry and he was well aware of his ability; but he also had a consuming ambition and a burning desire to excel in all that he did. Essentially a sensitive and even in some respects a shy person I believe he dreaded exposure of himself and his feelings to hasty and perhaps ill-judged criticism; so he built a protective fence around himself. I have said that he was sensitive and even at times shy; but his was a complex character for he could also be a gay companion and the life and soul of a party. Although devoted to his science he was widely read and his views on political and social matters were always at once definite and well-informed. Bob had a strong sense of humor — the pawky humor of the Scot which he derived from his Scottish ancestry — which appeared prominently in his letters to friends. I treasure my large file of personal correspondence with him over the years for in it his sense of fun keeps surfacing again and again.

Men like Bob Woodward with a single-minded devotion to their science and a burning desire to excel are hardly likely to be ideal family men much though they need companionship; this may explain the domestic difficulties which led to his living alone during his latter years. But he loved and was proud of his children whom he continued to see and to help right to the end. I confess that it was his passion to excel in all he did that at times disturbed me greatly especially during the last few years when his loneliness was increasingly evident. For with advancing years even his ability to excel would have declined and the blow to him would have been heavy — even devastating. As his friend I mourn his all too early loss; mourn it indeed perhaps more than I can properly express. And yet to depart this life suddenly and while still at the height of his powers is almost certainly what he himself would have wished.

And so it has come to pass. Bob Woodward has gone from us — gone as he would have wished and, I confess, as I too would have wished. Gone with a reputation untarnished as the greatest chemist of his generation. "A wise man shall inherit glory among his people and his name shall be perpetual." So it is written in the scriptures and so let it be with Bob. He is gone but he has left with each of us a memory to treasure and our lives are all a little brighter for having known him.

Remarks by Professor Vladimir Prelog
Laboratorium für Organische Chemie
Eidgenössische Technische Hochschule
Zürich, Switzerland

Robert Burns Woodward — Bob, as all his friends called him — was certainly an American and a Harvardian. He told me once that Cambridge, Massachusetts was the only place where he could live and work permanently. But, remembering Hermann Hesse's words "My homeland is where the pathways of my friends cross" one might say that Bob also had other homelands and that one of them was Switzerland. I would like to say a few words about how Switzerland came to be his second homeland.

Bob, who was at the time associate professor at Harvard, first visited Switzerland in 1948 as American Swiss Foundation lecturer. He delivered in Zürich two lectures, on May 31st about the chemistry of santonin and on June 2nd on the structure of strychnine. The head of our laboratory, my predecessor, Leopold Ruzicka, introduced him to the audience as a "chemischer Wunderknabe", a chemical boy prodigy. Ruzicka, who had a very good instinct for excellence, recognized immediately Bob's genius. This unconditional acceptance and recognition by a Nobel-Prize winner and renowned chemist evidently meant very much to Bob, who at that time was not fully accepted by the American chemical establishment. He never forgot it.

During the first visit we spent many hours together discussing chemistry, chemists and many other subjects. That was the beginning of a life-long friendship, and I cannot imagine a better and more loyal friend than Bob. Since 1948 we met innumerable times and our encounters were for me always sources of enlightenment, stimulation, and pleasure. I remember that in the course of our first meeting in my office I said to Bob "You smoke too much" and repeated that every time we met. If I would omit my warning, he would consider that as a lack of concern and remind me, saying "Today you didn't tell me that I smoke too much."

We discussed with Ruzicka many times the possibility of creating for Bob a chair at the Federal Institute of Technology in Zürich. Bob always said that he would consider an offer from Zürich very seriously. However, after much soul searching, we realized that our school was not able to offer him a position which would give him as much freedom as he already had at Harvard.

Searching for another chance to bind Bob more tightly to Switzerland, I found an ally in the Ciba Company and especially in the head of its pharmaceutical department, Albert Wettstein. He persuaded the president of the Company, Robert Käppeli, to offer Bob a facility for working in Basel on problems of his choice in an institute, supported financially and technically by Ciba.

After some hesitation caused by the necessity to settle previous obligations, Bob accepted the offer, and the Woodward Institute in Basel became a reality. With a few permanent staff members and a couple of temporary coworkers, in 1963 he started his successful activity in Basel. Karl Heusler, Ivan Ernest and Jacques Gosteli in chronological order functioned as his deputies. The most important achievements of the Institute were: the synthesis of cephalosporin, the Woodwardian approach to prostaglandins and the synthesis of highly active cephem derivatives.

In its last meeting before the merger with Geigy, on October 20, 1970, the board of directors of Ciba nominated Bob a member, and by that he became a member of the board of Ciba-Geigy. This made his connection with Switzerland even tighter, because he had to attend meetings of the board several times a year. Before the sessions we used to meet for breakfast to discuss whatever was on our minds. I still find it hard to accept that this can never happen again.

Bob's frequent visits to his second homeland had important consequences for organic chemistry at the ETH. We benefited from his lectures, delivered sometimes "off Broadway" before he presented them to an international congress or symposium. His lectures were not merely reports about "recent advances in the chemistry of natural products" but were often milestones in the development of organic chemistry. Attending international meetings I often heard them twice and that enabled me to enjoy fully not only their content but also their inimitable, though often imitated, formal perfection.

By his work and personality Bob attracted dozens of coworkers from Switzerland, proportionally more than from any other country. Their experimental skill, diligence and perseverance contributed to the success of his work, and he often acknowledged that. Especially well known is the group which performed the last steps of the strychnine synthesis, which used to refer to itself as the Beresina group after the famous Swiss rearguard, which was sacrificed to make possible the retreat of Napoleon's army from Russia.

Last but not least, the cooperation of laboratories at Harvard and ETH should be mentioned. When we found that both laboratories were working on the structure of veratrum alkaloids, Bob, Oskar Jeger and myself combined our efforts. With the help of Derek Barton the structure of the key compound of this group, cevine, was quickly elucidated. Another product of such cooperation was a paper on the correlation of a sesquiterpene with steroids; Oskar Jeger and Duilio Arigoni (at that time 25!) are the coauthors.

When Albert Eschenmoser disclosed to Ruzicka that he had started the synthesis of Vitamin B_{12} in cooperation with Bob, the old gentleman warned him that this would end in a disaster. Ruzicka's prediction was wrong, because he underestimated the high professional and personal qualities of both cooperative competitors. They achieved their objective, which was described by a German colleague as the Mount Everest of synthetic aims, by stimulating and emulating each other in an unprecedented way.

Unfortunately Bob was not left time to write down himself the full account of his part, but it is good to know that a phalanx of his friends is going to edit and publish the whole work, an endeavour which even Bob called a "formidable task".

Bob delivered his last lecture in Zürich on March 5 of this year. It was moving to witness his painstaking care in describing all details of already known steps in the conversion of cobyric acid to vitamin B_{12}. Some of us believe that his message was: "Chemistry is an experimental science and we should make every effort to secure its experimental fundaments.'' Let us never forget it.

Remarks by Professor Frank H. Westheimer
Department of Chemistry, Harvard University

Robert Burns Woodward will be remembered, along with August Kekulé and Emil Fischer, as one of the great organic chemists of all time. We mourn him as friend, colleague, and teacher; we fully recognize his loss to Harvard, to chemistry, and to science. What he accomplished during his spectacular career was no less than the rationalization — the intellectualization — of the process by which organic chemists achieve syntheses of complex vital molecules.

An analysis of the last one hundred years in science will help us to put his achievements in perspective. During the second half of the nineteenth century, the structural and stereochemical theory of organic chemistry — one of the most magnificent intellectual generalizations of mankind — was developed, principally by Kekulé, Butlerov, Cooper, Pasteur, van't Hoff and Le Bel. The applications of their theory, achieved through long, painstaking, systematic work at the laboratory bench led, principally in Germany, to great practical advances of organic chemistry; these included the syntheses of innumerable dyestuffs and pharmaceuticals, and the determination of the structures of sugars, alkaloids, steroids, and of the components of nucleic acids and of proteins. In the first half of this century, a few English and American scientists turned their attention to more theoretical aspects of organic chemistry, and particularly to reaction mechanisms. Yet most leading practitioners paid scant attention to the struggling new area of physical-organic chemistry; they were delighted with and captivated by their success in the assignment of structures and in syntheses based on classical theory. But nothing fails like success; the older generation of organic chemists stuck so close to their flasks that they failed to recognize the revolution implicit in the application of reaction mechanisms to synthesis, a revolution that permitted the determination of structures and the preparation of materials so complicated as to be wildly beyond the capabilities and perhaps even the imagination of the leaders in nineteenth century chemistry.

That revolution in methodology was sparked by Woodward. In totally remaking the strategy for synthesis, he not only incorporated mechanistic thinking into practical work, but he also capitalized fully on the potential of the burgeoning electronic instrumentation for which chemistry is indebted to physics. Through these major shifts in strategy he showed how to assign structures to compounds such as strychnine, to understand biogenesis such as that of the steroids and to carry out fabulous syntheses of complex natural products with only a fraction of the man-years previously needed for much simpler tasks. He illustrated the power of his methods with the syntheses of quinine, cholesterol, chlorophyll, strychnine, reserpine, vitamin B_{12} and a host of less well known but important natural products. At the time of his premature death, his research group was well on the way to the preparation of erythromycin. In all of these researches, he demonstrated how to maintain precise control of the stereochemistry — the arrangement of atoms in space — for each and every step. Although Woodward is famous for these specific syntheses, his intellectual synthesis was a much greater achievement. He formed a coherent methodology for planning and carrying out the synthesis of intricate biologically active molecules.

For many years, the seven-foot high jump was a major objective in track. Then that height was scaled, and it turned out that many athletes could do it. So it was with Woodward's work; after he had shown how to utilize theory and advanced instrumentation in planning and executing syntheses, many skilled chemists, all over the world, found that they, too, could do wonders by emulating him. In particular, his many students and post-doctoral fellows, who now occupy some of the most prestigious chairs in chemistry throughout the world, carry his methods forward with verve and imagination.

But even scientists who mastered his methods could not match his style. For there is an elegance about Woodward's work — his chemistry, his lectures, his publications — that was natural to him, and as unique as the product itself. This statement does not refer to his idiosyncracies, although sometimes they have been confused with his intrinsic style: his twin daiquiries, his dozens of identical blue wool ties, his many identical blue suits, the blue of his office walls, the blue paint his graduate students applied to the parking space reserved for his blue Mercedes. His real style was most clearly expressed in the syntheses themselves, in the ways he found to put molecules together, ways that somehow feel right — each step neatly designed to prepare for the next, a kind of art that combined inevitability with surprise, as in great classical music. The style was there, too, in his lectures. These often lasted for three or four hours; his Thursday night seminars began at about 8:30 and continued, with probably the best and most penetrating discussions of organic chemistry ever heard anywhere, far into the night — and into the early morning. Although the large lecture halls needed for large audiences finally forced him to use slides, he much preferred a blackboard and chalk. A lecture on a particular synthesis would begin in the upper left hand corner of the board and end in the lower right, with the entire surface filled with artistic formulas, the essentials highlighted in color, and the whole looking ready to be photographed for publication. And the style was evident in his writing; though precision came first, he did not shrink from flamboyance. One paper on total synthesis began "Strychnine! The fearsome properties of this notorious substance attracted the attention of XVI century Europe. . . ." and continued a while in that vein.

In addition to sparking the revolution in synthesis, Woodward, together with Roald Hoffmann, made the most significant contribution to the theory of organic chemistry of recent decades: the set of rules known as the conservation of orbital symmetry. These rules have illuminated much previously obscure chemistry of olefins, and have stimulated a vast expansion of organic chemistry that has occupied the profession for the past fifteen years.

Though one cannot convey a true picture of such a complicated individual in a few words, something must nevertheless be said of his sense of fun: he was not just a man of towering intellect enlivened by eccentricities. Among his pleasures was that of innocent practical jokes, jokes that the "victims" treasured and enjoyed as much as he, jokes that frequently depended on his accurate perception of the reactions of his friends. One example comes from the opening of the Conant Laboratory in 1959, long before Pope Paul VI relaxed the dietary restrictions of the Catholic Church. The Department had arranged a reception in the new laboratory, to be followed by a dinner at the Faculty Club for President Conant, President Pusey, McGeorge Bundy, and many distinguished chemists from Harvard and elsewhere. The wife of the Chairman had planned the dinner with loving attention to detail — recipes, silver, flowers, candelabra. At the reception before the dinner, Woodward approached this lady, and asked what was on the menu. Learning that it included filet mignon, he remarked, solicitously, "I hope you remembered to order fish for those individuals who aren't permitted to eat meat on Fridays." The Chairman's wife panicked, and turned white; her knees trembled, as she stammered, "Good Lord, Bob, I never thought of it. What shall I do?" "Well," he reassured her, "don't worry. It will be all right . . . . today's Tuesday."

We shall miss him.

HARVARD UNIVERSITY

DEPARTMENT OF CHEMISTRY

12 Oxford Street
Cambridge, Massachusetts 02138
U.S.A.

5 August 1982

Dr. Alfred Bader, Chairman
Aldrich Chemical Company
P. O. Box 355
Milwaukee WI 53201

Dear Al:

I am sorry to miss you, but I have taken off a few days to spend with my daughter in Maine.

I had wanted to alert you to the possibility that Professor Ray Bonnett of Queen Mary College may be in touch with you about certain samples in the RBW collection relating to the synthesis of chlorophyll.

He is undertaking to prepare the chlorophyll work for publication and already knows that RBW had noted certain compounds as needing better IR spectra. If the samples are not ordered and listed in the computer by the time you hear from Bonnett, perhaps you could make some other arrangement for giving him access to the relevant samples.

With warmest regards, I am

Yours sincerely,

Bill

William Doering
Mallinckrodt Professor
of Organic Chemistry

WED/s

cc: Professor Ray BONNETT

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ACH

CHF Exhibits on the Road: 1994

Our traveling exhibits are becoming widely known, and reservations need to be made early. The only cost is that of return shipping. Write to Exhibits at the Chemical Heritage Foundation.

Exhibit itineraries for 1994 are as follows:

Polymers and People
1–15 October: Arco, Monaca, PA

Structures of Life
29 May–2 June: Canadian Chemical Conference, Winnipeg, Manitoba, Canada
15–31 October: University of Missouri, Columbia, MO
5–30 November: Las Cruces Natural History Museum, Las Cruces, NM

RBW

Woodward and the Art of Organic Synthesis
15 May–30 June: Joint Meeting of the ACS Great Lakes Region and Central Region, University of Michigan, Ann Arbor, MI
24 July–7 August: ACS Division of Chemical Education 13th Biennial Conference, Bucknell University, Lewisburg, PA
27 September–3 October, Department of Chemistry, SUNY Stony Brook, Stony Brook, NY
15–31 October: University of Missouri, Columbia, MO
7–30 November, East Stroudsburg University, East Stroudsburg, PA

Dear Dr. Bader,

I was in the U.S. in October, and towards the end of the month I went to see Bill Robinson at the Fogg, thus to learn that you had been in Cambridge not long before. I was sorry not to have known, so as to have been able to see and talk to you.

What brought me to the U.S. now, was a project which some people called "the International Management group" (or, Trans World International) are doing, to make a television series called "The Nobel Legacy". For the chemistry segment, they've chosen to focus on my father. They wanted to interview me, and, having read my chapter ("Art and Elegance in the Synthesis of Organic compounds; R.B. Woodward") to have me highlight some points from that chapter. As they had heard about my concern with the problem of my father's papers — and the need to do de-acidification work on them —, they decided to do the filming in the Harvard Archives. A later filming will take place this weekend at Harvard, with a numb of chemists who will go over scientific points and recount some stories from R.B.W.'s life and work. I'm sorry not to be at this second occasion; I had to get back to Europe for a meeting.

I had gone to Mr Robinson for 2 reasons. One, I wondered if the Fogg might be inte-ed in acquiring one of my drawings (I'm a Radcliffe alumna); and, two, I wanted to ask if they might have some ideas as to whether and how an exhibit could be organized, to show some of my father's chemical drawings, — and, possibly, alongside that some of my art works from my Visual Language series. I thought it could be interest to do this in conjunction with the Beckman Ctr.'s Exhibit's being at Harvard, next April 15 to May 7. This would both illustrate the art aspect of my father's work, and ser to publicize the need for preservation of the papers, as people would see the exquisite molecular drawings and see how some of the manila pages are already flaking around the edges.

It was only when I mentioned this 2nd point, about R.B.W., that Mr Robinson remembered having met me years ago, with you. In any case, he seemed, unfortunate to have no interest in the idea of exhibitting the Woodward papers. As for the chemist dept. people with whom I talked, Jim Davis and Alan Long as well as Dudley Hershbac they have decided that the place for the Beckman Exhibit is the Mallinkrodt Lobby. The security there is not sufficient, however, for me to envisage showing any of RBW's origina drawings (or my art works) there; and, my thought of having another, additional exhibition location for those is in part due to the hope that a location in one of the Harvard museums or libraries would give the Woodward material more visibility: not many non-chemists will go into Mallinkrodt, whereas people do go into the Fogg or Houghton and could from there be directed to Mallinkrodt. Anyway, I haven't yet found a solution, and from this distance it may be difficult.

On the same idea, I would still like to put together a book, such as we talked abo over lunch in Philadelphia, including reproductions of some RBW drawings, and some of my Visual Language art works. I'd be interested to hear if you have any further thoughts about this idea. Perhaps it could be combined with a project of asking whether previous post-docs of Woodward, and other chemists, would be interest, to make a contribution to a fund for preservation of Woodward's papers. I recal with gratitude your offer to seed such a fund; and I think that in the near future, I should go ahead and set up the fund. Somehow, I shall try to get information sent to me here on how to do that, on how to make it tax-exempt, etc. The more we wait, the more fragile — and unsavable — the papers will be. Sometime after the C&ENews article of May 4, 1992, — which covered the Beckman Exhibit and included a note about my quest for funds and advice about preserving the papers, I heard from Dr Jim Whitesell, now in Texas and a previous RBW postdoc; he wanted to get involved in helping on the funding project. He sent a proposal to the A.C.S., and yet they rejected it, saying that they didn't want to set a precedent by funding preservation of papers; I didn't find their grounds for rejection very sound, but in any case, that was one hope gone. And Whitesell has been too busy on a textbook project to do anything since.

I recall you telling me that you and your wife were going to be working on some projects in Eastern Europe. I would be glad to hear from you; and to hear how those projects are going, — and, also, to hear more about your on-going interest in art. On my way back to France, I had to stop in Antwerp for a meeting, and got to see some beautiful things there, for example, I especially liked the Mayer van den Bergh museum.

my Best wishes to you.

Sincerly,

crystalwoodward

CRYSTAL WOODWARD
c/o G. Adrian
LACOSTE 84710 (Vaucluse)
France

[Tel 90. 75 81 65]

ALFRED BADER FINE ARTS

DR. ALFRED BADER

ESTABLISHED 1961

March 29, 1994

Miss Crystal Woodward
c/o G. Adrian
LaCoste, Vaucluse
84710 France

Dear Crystal,

I have kept hoping that something would materialize about your efforts to have your father's papers preserved. All I can say is that the librarian in charge of this at Harvard cannot know what a towering figure your father was. Perhaps my letter to Arnold Thackray, copy enclosed, will make him think of this problem once again.

Enclosed please also find a rough draft of what I wrote about the symposium in Philadelphia. If you see any mistakes, please let me know.

All good wishes.

Sincerely,

Enclosures

By Appointment Only
ASTOR HOTEL SUITE 622
924 EAST JUNEAU AVENUE
MILWAUKEE WISCONSIN USA 53202
TEL 414 277-0730 FAX 414 277-0709

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

March 28, 1994

Dr. Arnold Thackray
Beckman Center for History of Chemistry
3401 Walnut Street
Philadelphia, Pennsylvania 19104

Dear Arnold:

I haven't heard from you for a long time and hope you are well.

I am just finishing my autobiography and that, of course, includes the story of your wonderful Woodward Exhibit. Will it be travelling, and if so, what is the schedule?

A number of chemists around the world have asked me whether I could send them your publication No. 9, and I have sent what few I had. If you have quite a few more, could you please send six more copies?

Do you know what is happening about Crystal Woodward's efforts to have her father's notes preserved? I promised to provide seed money of $2000 through the Beckman Center or through Harvard University. What is certain is that the papers should be preserved.

What can you tell me about the editor of the Bulletin for the History of Chemistry, William Jensen? Let me relate a most singular experience with him.

You may recall that I have been giving lectures on Josef Loschmidt, and you may actually have heard one of them in Philadelphia. Last year, Professor Noe and I published an article on Loschmidt in Chemistry in Britain, and I enclose a copy as well as copy of a response from Professor Alan J. Rocke at Case Western in Cleveland. Since then, I have had some long discussions with Professor Rocke, and discovered, I believe, that we are not really so very far apart.

Chemistry in Britain sent me a most singular letter from Professor William Jensen, copy enclosed, in which Professor Jensen accused the paper of "tepid academic yellow journalism," and unfortunately Chemistry in Britain did not print it. I sent

a long letter with lots of explanatory material to Professor Jensen, and enclose copy. He did not reply. I did see him very briefly before giving paper on Loschmidt at the Chicago A.C.S. meeting and invited him to come to my talk, but he didn't have time for that, either. This seems like a very odd way for a historian to act.

Recently I have had the good fortune of being able to acquire a good deal of correspondence between Anschütz and Alexander Crum-Brown in their quest for Couper. It is really amazing how hard Anschütz worked to bring both Couper and Loschmidt to the attention of chemists.

Now that my autobiography is almost finished, I look forward to delving more into the history of chemistry.

My annual contribution to the Chemical Heritage Foundation is enclosed.

All good wishes, also from Isabel.

Sincerely,

Enclosures

FAX FROM

DR. ALFRED R. BADER
Suite 622
924 East Juneau Avenue
Milwaukee, Wisconsin 53202
Telephone 414-277-0730
Fax No. 414-277-0709

July 13, 1993

To: Ms. Carol Lynn Alpert
The Nobel Legacy
International Management Group - FAX 617 964 0533

When I spoke to Dr. Bader recently, he told me he has written to you, and you may now have his letter. He also stated he would be happy to talk to you after his return on July 26th. Also, he will be in the Boston area round the 15th of October.

Cordially,

Marilyn

Marilyn Hassmann

THE NOBEL LEGACY

18 June 1993

Dr. Alfred Bader
c/o M.B. Glynn (Kindly Forward)
Fax: 011-44-424-730-668

Dear Dr. Bader,

I'd like to request your assistance with a television project concerning Robert Burns Woodward. We are planning to do a story about him as part of the first season of "The Nobel Legacy," a new television series for PBS about Nobel Prize winning scientists and their work. "The Nobel Legacy" will be comprised of three television specials, one each for the fields of chemistry, physics, and medicine. The specials will each present characteristic modes of thought and historic turning points in each scientific discipline in a dramatically compelling and lively manner. They will also address the significance of pure scientific research to our everyday lives. The programs are being produced for broadcast on PBS and international venues in the fall of 1994.

The first year's chemistry program is including a retrospective on the life and work of Robert Burns Woodward. I understand that you knew Woodward well and supplied chemicals he needed for his work. I'm wondering whether you would be willing to talk with me about your experiences with Woodward. If so, please give me a call or let me know when I can call you during the next week or two.

Sincerely,

CAlpert

Carol Lynn Alpert
Co-Producer

cc: Marilyn, Alfred Bader Fine Arts
Fax 414-277-0709

Called again 7/7 has not heard from you

617 964 0533

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fax 617 964 [illegible]532

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THE NOBEL LEGACY

BET 1, 2
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[illegible]

Dr. [illegible] Bader
c/o [illegible]
[illegible]

Dear Dr. [illegible]:

I'd like to request your assistance with a television project concerning Robert Burns Woodward. We are planning to do a story about him as part of the first season of "The Nobel Legacy," a new television series for PBS about Nobel Prize winning scientists and their work. "The Nobel Legacy" will be comprised of three television specials, one each for the fields of chemistry, physics, and medicine. The specials will also present the extraordinary modes of thought and historic turning points in each scientific discipline in a dramatically compelling and lively manner. They will also address the implications of basic scientific research in our everyday lives. The programs are being produced for broadcast on PBS and international venues in the fall of [illegible].

The first year's chemistry program will be taking a retrospective on the life and work of Robert Burns Woodward. I understand that you knew Woodward well and supplied chemicals he needed for his work. I'm wondering whether you would be willing to talk with me about your experiences with Woodward. If so, please give me a call or let me know when I can call you during the next week or two.

Sincerely,

[illegible]
Co-Producer

cc: [illegible]
Fax [illegible]

617 964 0533

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

January 5, 1993

Dr. Charles Price III
The Quadrangle, # C301
3300 Darby Road
Haverford, Pennsylvania 19041

Dear Charlie:

Thank you so much for your letter of December 18th and sharing with me Crystal Woodward's moving letter of October 12th.

There is no doubt in my mind that Bob Woodward's papers should be preserved as they are among the most important chemical documents of this century. Harvard is a responsible institution, surely not particularly lacking in funds.

During the Woodward Symposium, which Isabel and I remember with such pleasure, we promised the Beckman Center a contribution of $2,000 if others could also be induced to provide funds to help for the safe-keeping of the papers. Unfortunately, I am not now in a position to do further fund raising.

I notice from Crystal's letter that there must be quite a few papers not of interest to the Harvard Archives. Surely those should go to the Beckman Center.

As you will see from the enclosed, I plan to be at Harvard on May 17th and will then stress the importance of preserving the Woodward papers.

All good wishes for 1993.

Sincerely,

c: C. Woodward

Dr. & Mrs. Charles C. Price III
The Quadrangle, # C301
3300 Darby Road
Haverford, PA 19041

18 Dec 1992

Dear Alfred.

Enclosed is a letter from Crystal Woodward appealing for help to preserve the intriguing and important voluminous notes of Bob Woodward.

I am up to my ears in fund raising activities for the Chem. Heritage Foundation and the World Federalist Association and just can not see my way clear to help. Is there any way you could help in this project of hers?

Best wishes!
Sincerely
Charles

Oct. 12, 1992

Dear Dr. Price,

I enjoyed meeting you, in April, at the Opening of the Woodward Exhibit in Philadelphia. I was glad to hear your affirmation that an issue such as the preservation of R.B. Woodward's papers is a concern, — or, is in a way the very type of matter which is the responsibility of the Beckman Center.

Since April, I have been able to get a rough estimate from Harvard on costs of preservation, though all this is tentative as various preservation methods would probably be engaged: I urge de-acidification, and it seems that techniques are being narrowed down as to which would make the most sense and be the most suited for the kind of papers concerned. I also got a few responses from the *C&En News* article's note about this matter; thus, one chemist* has done a sample-look at some of the chemical drawings of R.B.W, and reported back to Clark Elliott at the Harvard Archives that yes, indeed, these papers deserve to be preserved.**

I requested to Dr. Benfey that a note about this matter be included in the Washington ACS Meeting's Host-

---

* Dr. David Taub

-ing of the Exhibit, and he replied to me that this could be done. However, apparently this cannot be done for subsequent hostings, - though I would like to raise the question as to whether it *could* be. From the distance of France, it is difficult for me to reach channels of communication, whereas the Beckman Center, and the Travelling Exhibit, have a structure in place for the dissemination of this information. And, where the Beckman Newsletter has carried a note on this, and is to include a longer report next Spring (on the contents of the RBW papers at Harvard), that may be read mainly by historians of chemistry; as the Exhibit travels to places such as Merck, Ely Lilly, Harvard and so on, a note included there would be a good way to inform chemists and others.

Some two and more years ago, when communicating with the Beckman Ctr. and Harvard rē permission to use photographs for the Exhibit, I explained that, in granting permission I would very much appreciate that the Beckman Ctr. consider a way whereby the Exhibit could include a note — a small mention at least — as to the issue rē the need for preservation. Of course, now having received some responses from chemists, and heard the variety of ideas proposed, I see how such a small message needs in fact to give more information, - for ex-

ample. we must inform people <u>how</u> <u>many</u> pages are in need of preservation. Yet this is dependent on whether one envisages preserving the whole collection, or just the chemical drawings, or just a selection of the chemical drawings, and so on. My sense is that it would be a mistake to preserve <u>only</u> a selection of the drawings, and I was glad when Dr. Taub agreed with this.

Clark Elliott has prepared a several-page long "Notes and Questions for Chemists", in response to my telling him that chemists were volunteering to do some work on a more indepth cataloguing of the Woodward papers. Harvard's Cataloguing and Finding guide are basically completed now; but this does <u>not</u> <u>in detail</u> give the contents of the papers, for the cataloguing was done by non-chemists, unfamiliar with the "language" of chemical diagrams enough to decipher them.

So, work is on-going as to refining our vision of just <u>what</u> the preservation situation is. Nonetheless, I still think it would be helpful to adjoin an informing note to the Beckman Ctr. Woodward Exhibit as it travels. For me to arrange that from here is very difficult; for example, it took 4 months before I could finally obtain the name of the contact person for the Exhibit at Harvard, and it required expensive overseas calls on my part.

- and, at that, all I could ascertain - only last week - was that the Exhibit's time at Harvard has been moved from Oct. 28 to sometime next spring.

Dr Benfey requested that I prepare a report on the situation of the Woodward Papers at Harvard, for next Spring's Newsletter. I am going to suggest to Dr. Benfey that he might take a look at Clark Elliott's "Notes and Questions for chemists", and, possibly as well, at the now available finding guide to the papers. For the report I sent 2 months ago emphasized the preservation issue (partly in anticipation of the ACS Meeting in Washington) and gave too little as to the contents of the papers.

Another matter I shall bring up with Dr. Benfey, is that there are some boxes of material from my father's files which Harvard has looked at but will not need to include in the Archive Collection; this goes back to the family, or, to a destination we deem suitable. I am considering whether some of this might be of interest to the Beckman Ctr., and hope to be in communication with my brother on this. Unfortunately, my distance from Cambridge adds delay to these considerations, and to writing up a list-of-contents from which a next step could be taken.

This is, in brief, an update on the matters we discussed at last April's luncheon. Your interest there, added to by the

kindness of Mrs. Price and her enthusiastic response to my presentation of the Art and Chemistry topic, gave me the sense that you could find this update interesting. Any response from you would be welcome, particularly on points around which I have raised questions.

One further point is that of funding for preservation of the papers. As Harvard will not provide the funding, it must come from elsewhere. I haven't experience in fund-raising, and would appreciate any suggestions or guidelines. I infer that the Beckman Ctr. does not see itself as a fund-raiser, but might it have a way of being somehow one of a possible network of information relayers, – without drawing too much on the schedules of otherwise already busy persons?

With my Best wishes to you for a pleasant Autumn,

Sincerely,

crystal woodward

CRYSTAL WOODWARD (PhD)
c/o G. Adrian
LACOSTE, Vaucluse
84710
France
Tel. (33) 90·75 81 65
Fax. at Institute 33) 90·75 92 43

** Taub wrote: "[Woodward's] unpublished files are a unique legacy. They should be preserved for future generations—and should be examined knowledgeably and completely...."

Enclosed: a page of Clark Elliott's summary re the RBW. papers.

from Clark Elliott

draft

copy

ROBERT WOODWARD PAPERS
Notes and Questions for Chemists

The Robert B. Woodward Papers in the Harvard University Archives cover Woodward's life and career from his childhood to his death in 1979. Included are personal and family papers, professional correspondence, reports, manuscripts, research notes and data, teaching materials (e.g., examinations, course outlines), photographs, files on graduate students and postdoctoral fellows, and other material. Overall the papers relate to Woodward's teaching and research activities, his personal life, awards, relations with professional groups and colleagues. There is a separate series of papers relating to the Woodward Research Institute (Basel, Switzerland). The bulk of the collection is in the three series titled "Professional correspondence and other papers" (constituting 140 of some 220 containers in the collection). Within these particular groupings, materials generally are arranged alphabetically by the names of individuals or organizations, subjects, and names of chemical substances. Copies of the description and folder lists for these parts of the collection can be provided upon request.

Many of Woodward's notes and drafts are on poor quality paper and already have deteriorated. It was Woodward's practice, in his research, to sketch out chemical structures and these often are on the poorest quality paper. Some of these are separate groups of papers and largely unlabeled, while others are included in labeled folders along with related material such as handwritten drafts or typescripts of manuscripts, and correspondence. Research assessment and use of the collection is complicated greatly by the fact that the drawings frequently are not identified by date or project, and the sequential relation of individual pages is not indicated. The Archives has maintained the papers in the order in which they were received.

Given the situation outlined above, and in light of Woodward's importance in the history of chemistry, the University Archives would benefit from the advice of knowledgable and interested chemists and historians of chemistry who are able to visit the Archives and examine even small sections of the papers. Our initial concerns are along the lines of the following questions. Several sample pages of unidentified notes are enclosed as illustration (but no claim is made that they are representative, such a determination being part of the uncertainty relating to the collection).

[etc -- 30 pgs]
with specific questions etc

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

November 6, 1992

Professor C. Marvin Lang
Department of Chemistry
Univeristy of Wisonsin
Stevens Point, Wisconsin 54481

Dear Marvin:

What a bit of luck that you are the Chairman of the A.C.S. Public Affairs Committee.

I don't quite understand Ernest Eliel's pessimism about getting Bob Woodward onto an American postage stamp. Surely he was the greatest organic chemist of the world in this century.

Do you have the booklet published in his honor by the Beckman Center for the Woodward festivities last April? Is there anything that I can do to help? Would letters to our two U.S. Senators help?

All good wishes.

Sincerely,

Enclosure

American Chemical Society

OFFICE OF THE PRESIDENT

Ernest L. Eliel
President-Elect, 1991
President, 1992
Immediate Past President, 1993

Department of Chemistry CB #3290
University of North Carolina
Chapel Hill, NC 27599-3290
Phone (919) 962-6198
Fax (919) 962-2388

October 27, 1992

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, WI 53211

Dear Alfred:

Thank you for your letter of October 21. The matter of a Woodward stamp was discussed in the Public Affairs and Public Relations Committee of the ACS Board of Directors some months ago. It happens that Marvin Lang, the chairman of this committee, is an ardent philatelist who also knows about the rules of getting people on stamps. I understand it is an extraordinarily difficult process, unlikely to succeed. You may wish to get in touch with him directly.

Best regards.

Sincerely yours,

Ernest L. Eliel

ELE/sp

cc: Dr. C. Marvin Lang
Department of Chemistry
University of Wisconsin-Stevens Point
Stevens Point, WI 54481
(715) 346-3609 or 346-2888

Dr. Alfred Bader
2961 North Shepard Avenue
Milwaukee, Wisconsin 53211

September 17, 1992

Miss Crystal Woodward
c/o G. Adrian
LaCoste 84710
France

Dear Crystal:

Your kind and detailed letter of May 14 arrived in Milwaukee while we were on a very long trip to Europe. Please forgive the delay.

It was such a pleasure to be at your father's symposium, and I do hope you will be successful in having your father's documents preserved.

Isabel and I are just off on a lecture tour to Spain, but shortly after our return at the end of this month, I will speak to Arnold Thackray about how we might help.

Best personal regards,

c: Dr. A. Thackray

item. If I had money, I'd put something together like my slide show and [illegible] Phila-
delphia, i.e., my father's papers being juxtaposed with landscape photos and [illegible]

May 14, 1992

Dear Dr Bader,

I was very glad to have the chance to see you, and Mrs Bader, at the Symposium and Opening of the Woodward Exhibit. I prolonged my visit in the U.S. a bit longer, and was glad to hear that the Harvard Archives Director, Clark Elliott, has scheduled a meeting with the preservation librarian Carolyn [illegible], for May 20. Before leaving, I looked at the RBW collection, not as much time as I would have liked but enough to get an idea of how the cataloguing has been done. I hope that the preservation librarian will be in favor of de-acidifying the large number of pages of my father's [illegible] drawings. I appreciate your interest in them, and will be in touch concerning [illegible] next steps, including those of funding.

I gather that the ACS is planning to make a book on my father, and that they may include some of the talks from the Symposium. I wonder if my talk, or at least part of it, could be included: the aspect of my father's work which I spoke about, the artistic quality, is not explored by other authors, and yet deserves to be included.

Your talk on April 13 was very interesting. I mentioned it to a friend, Professor Howard Gruber, cognitive psychologist with a special interest in creativity; his approach is to do in-depth study of the processes and notebooks of individuals. He was the co-editor of the book in which I published my chapter "Art and Elegance in the Synthesis of Organic Compounds" about my father. He was very interested to hear of your talk as he has also been making a case study of the whole Kekulé story. He may have written to you by now; if not he would like to receive a copy of your talk, if possible, and could send you a paper he has on the topic. His address is [illegible] [illegible], New York, NY.

On the topic of [illegible] people with experience working [illegible], I have gotten a few responses to the notice in C&En News, from people who would be interested in helping out. [illegible] cataloguing of my father's papers at this point. I am not sure what should be the procedure. In-depth cataloguing in itself is not necessary, it would be helpful to [illegible] necessary, if for example Harvard says they can only do a small number of the acidifying (actually, if they say that I'll make a move to change their decision) but in any case, might some selection of materials be needed, for the de-acidifying? It would also be necessary toward the idea I spoke to you about – of making a book of reproductions of a good selection of Woodward's hand drawn pages, with some accompanying text. From my looking through the papers in 1979-80, I know of many pages which would be wonderful to see in good reproduction. Whether those persons responding to the C&En notice would be appropriate for that work, I won't know until I [illegible] with them further. But should I mention that additional project to them now, I wonder. My thought is that perhaps a limited edition could be envisaged on the other [illegible] more large scale. The ^raw^ pages reproduced even without text would be an interesting item. If I had money, I'd put something together like my [illegible] and [illegible] [illegible] [illegible], of my father's papers being juxtaposed with landscape photos and forms of

2) my own work in that particular "visual magazine" approach I evolved [illegible] [illegible] [illegible] in getting a sense of the art of [illegible] chemistry. I think my father would like [illegible] a more imaginative project i.e., would not insist that one must [illegible] a strictly chemical [illegible] of [illegible]. But I wouldn't by myself know how to go about the funding, nor the [illegible] and distribution of such a book.

Within the more strictly chemical domain, [illegible] may be that [illegible], [illegible] my [illegible] host at lunch on April 13, that is, chemists [illegible] [illegible] speaking on [illegible] papers about [illegible] papers and their in-depth content. In any case, I'm interested in any further thoughts you may have, on all of these [illegible] [illegible] [illegible] [illegible] and [illegible].

Thank you also for sending me the exchange of letters concerning a postage stamp [illegible]. Is there further news on this project? [illegible] [illegible] [illegible] [illegible]. [illegible] it would be of interest, it occurred to me later to [illegible] the design of such a stamp if they decided to [illegible] an artist! As you know, perhaps, my manuscript on my father was called "[illegible] first", and it would be fitting to have the stamp [illegible] [illegible] [illegible] [illegible].

Do you know where and for how long the [illegible] [illegible] will be [illegible] [illegible] [illegible] report, in conjunction with the ACS Meeting there?

With all best wishes. [illegible] to hear from you soon.

[illegible],
[illegible]

[illegible]
[illegible] St [illegible], 84210,
France
[illegible] Institute [illegible]
tel 90 75 52 24 [illegible]

ps. liked very much the piece "[illegible] with [illegible]," by [illegible]. It captures some [illegible] very well.
Let me know if you are passing through [illegible] this summer

Dr [illegible]
[illegible]
[illegible]
[illegible]

PAR AVION,
Air Mail

Dr. Alfred Bader
Chairman Emeritus

December 31, 1991

Dr. Peter J. T. Morris
Edelstein International Fellow
Beckman Center for History of Chemistry
3401 Walnut Street
Philadelphia, Pennsylvania 19104 6228

Dear Dr. Morris:

A long trip to Europe has delayed my responding to your interesting letter of November 27.

It seems to me that the papers which you have picked are certainly among the most important. However, you must remember that I am not a Woodward student, but rather was just his personal friend. He helped me a great deal while I was working for Fieser in the 40's, and at that time Prof. Fieser was travelling so much that I saw him very little, but of RB a great deal.

The members of the advisory committee, particularly Professors Hoffmann, Eschenmoser and Ollis, may well be able to point to some additional important papers.

All good wishes.

Sincerely,

Alfred Bader

SIGMA-ALDRICH
P.O. Box 355 Milwaukee Wisconsin 53201 USA Telephone (414) 273-3850 Cable Aldrichem TWX 910-262-3052 Telex 26-843

the Beckman Center for the History of Chemistry
AMERICAN CHEMICAL SOCIETY • UNIVERSITY OF PENNSYLVANIA •
AMERICAN INSTITUTE OF CHEMICAL ENGINEERS

The Arnold and Mabel Beckman Center for the History of Chemistry
3401 Walnut Street • Philadelphia, PA • 19104-6228 • USA
Telephone: (215) 898-4896 • Telefax: (215) 898-3327

Director: Arnold Thackray

27 November 1991 12-2-91

Dr. Alfred Bader, Chairman
Sigma-Aldrich
P. O. Box 355
Milwaukee, WI 53201

Dear Dr. Bader:

Please let me introduce myself, and seek your help as a member of the Advisory Committee to the R. B. Woodward 75th Anniversary Celebration travelling exhibit. I am the Edelstein International Fellow in the History of Chemistry for 1991-2. As a major part of my activities at the Beckman Center, through the end of January, I am editing a collection of R. B. Woodward's most significant papers. The aim is to publish these next year as part of the symposium volume.

In order to assist the process of editing, I would be most grateful if you could look over the enclosed provisional list of selected papers and give me your comments. Doubtlessly, there are important papers which have been inadvertently omitted. Conversely, I may have chosen papers that are relatively insignificant. You may wish to make comments about the key points of the papers listed.

Thank you for your time and interest. Please let me hear from you promptly if you have comments and suggestions at this stage.

I look forward to hearing from you and working with you on this celebration of R. B. Woodward's life and work.

Sincerely yours,

Peter Morris

Peter J. T. Morris
Edelstein International Fellow

PJTM/ec

Draft List of RBW's Most Significant Papers

Syntheses

Quinine (1944): Journal of the American Chemical Society 67 (1945) 860
Cholesterol/Cortisone (1951): Journal of the American Chemical Society 74 (1952) 4223
Strychnine (1954): Tetrahedron 19 (1963) 247
Resperine (1956): Tetrahedron 2 (1958) 1
Chlorophyll (1960): Pure & Applied Chemistry 2 (1961) 383
Cephalosporin C (1966): Nobel Prize Lecture
Vitamin B_{12} (1973): Pure & Applied Chemistry 17 (1968) 519
Pure & Applied Chemistry 25 (1971) 283
Pure & Applied Chemistry 33 (1973) 145

Generalizations

Octant Rule: Journal of the American Chemical Society 83 (1961) 4013
Woodward-Hoffmann Rules: Journal of the American Chemical Society 87 (1965) 395
Journal of the American Chemical Society 87 (1965) 2046
Angewandte Chemie International Edition 81 (1969) 797

Philosophy

"Synthesis," in A.R. Todd, Perspectives in Organic Chemistry (1956), 155

P.J.T. Morris, 11/18/91

With Compliments

11-19-91

Alfred,

Nice to know we have a fan club!

Arnold

the Beckman Center for the History of Chemistry

3401 Walnut Street • Philadelphia, PA 19104-6228
Telephone 215/898-4896 • Telefax 215/898-3756

HANS BICKEL
Mühlesteig 4
CH-4102 Binningen
Switzerland

4 November 1991

The Beckman Center for
the History of Chemistry
attn.: Mary Ellen Bowden
3401 Walnut Street
PHILADELPHIA, PA
19104-6228 . U S A

"R.B. Woodward and the Art of Organic Synthesis"

Dear Mrs. Bowden,

Thank you for your letter with enclosures of October 17, which reached me only now returning back from holidays.

I have read with interest -and with some nostalgic feelings- the very short section devoted to the synthesis of reserpine within your forthcoming brochure on R.B.'s synthetic work. It highlights indeed one of the most essential parts of the reserpine work. I have nothing to add to your text nor to criticize it. However, I might suggest that you slightly change Figure 7 - 8.9, as indicated with red ink on the attached copy; this for the benefit of a better understanding of the text.

I wish you all success with your fifth travelling exhibit. I highly appreciate your activities intending to attract young women and men to the science of chemistry. Indeed we much need such activities also in my country.

Sincerely yours

H.Bickel

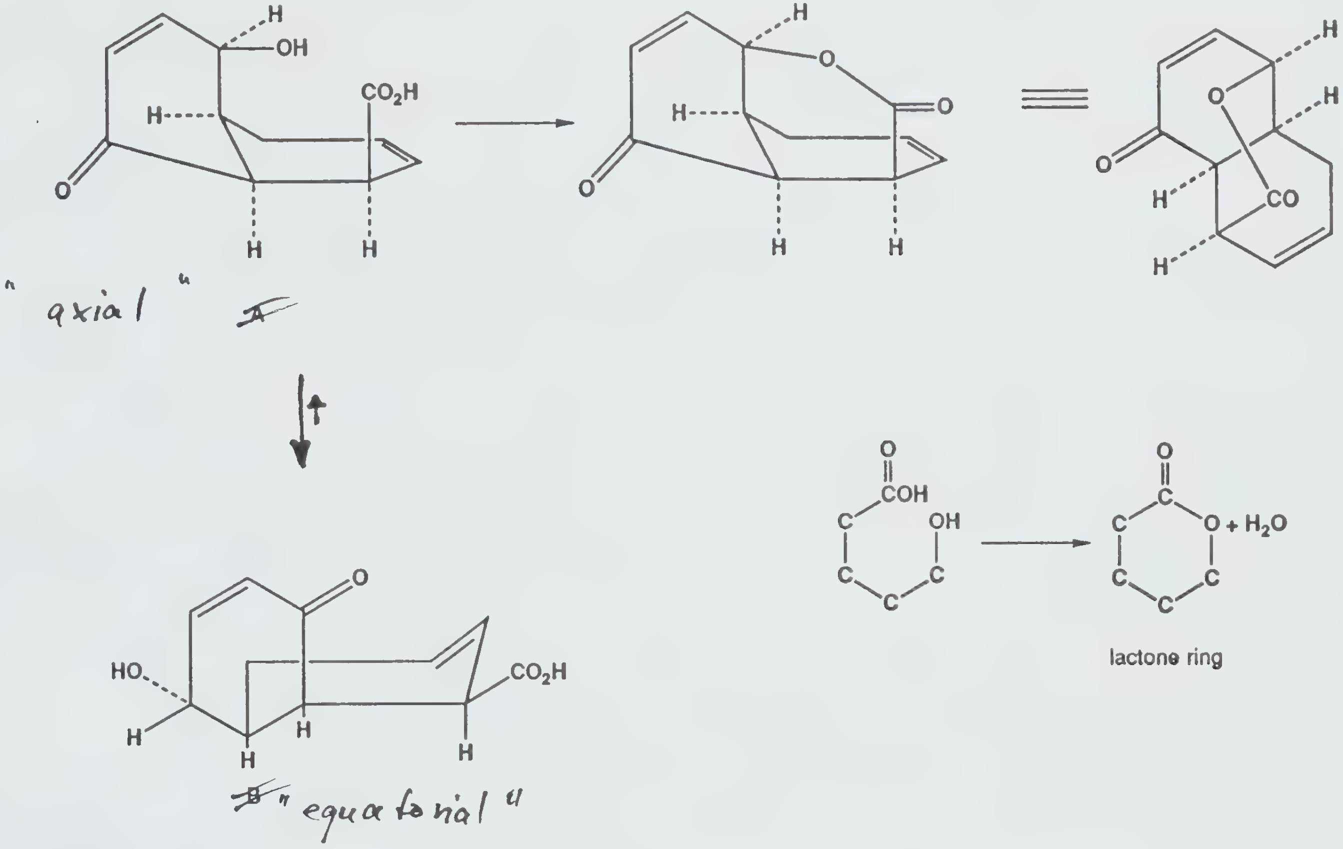

FIG ~~7~~ 8.9 - Beckman 8/27/91 11:11 AM

cc Alfred Bader
Roald Hoffmann

From Arnold – "Fyi"

PAUL ARTHUR, JR.
11 BRANDYWINE BOULEVARD
EDGEWOOD HILLS
WILMINGTON, DEL. 19809

Theodor Benfey
Natur Fr Cn

As possibly one of the last remaining fellow students of R B Woodward under Dr J F Norris at MIT in 1935-7 there are some untold stories about RBW that show how he was regarded by advisors and fellow students.

Walsh (in next lab) corked dead fish in the condensers to lend an aroma to RBW

lab,

Emerson felt like violence rampant and imminent when RBW undercut his Current Journal presentation by sequestering a newly-arrived journal with corrections.

Roger Adams + Speed Marvel finally prevailed on RBW not to publish a paper saying Willställer(?) never made cyclooctatetraene (only impure styrene.)

It should be made clear that RBW when doing one step in a 23 step sequence always claimed total credit.

So long
Paul [illegible] Jr

PAUL ARTHUR, JR.
11 BRANDYWINE BOULEVARD
EDGEWOOD HILLS
WILMINGTON, DEL. 19809

P.S.

RBW, with his eidetic memory, passed the Chem Eng test by borrowing notes ~~fro~~ on classes he never attended the night before the exam.

His thesis was OK'd by JF Norris who graciously agreed to sponsor RBW when all other profs refused, even though the key step in his attempted steroid synthesis ~~failed~~

Chemists Helping Chemists in Research and Industry

aldrich chemical company, inc.

Dr. Alfred R. Bader
President

January 21, 1981

Professor Jeremy Knowles
Chairman
Department of Chemistry
Harvard University
Cambridge, Massachusetts 02138

M.H.
File
Woodward

Dear Jeremy:

After our long telephone conversation yesterday, please allow me to share with you my concern and frustration about the Woodward collection of research samples.

I can certainly understand the students' upset, but I don't think that you should blame your legal department for the mixup. The sole cause is poor communication within the department, particularly to Professor Woodward's students and associates. But of that I had no inkling last Friday morning. Mrs. Jervey and Dr. Ciappenelli pointed out to me that there were a number of cigar boxes, clearly labeled with blue dots, which the students had put aside and wanted to keep. These we left. Professor Dolphin had marked some bottles of interest to him. These we left. A member of the Society of Fellows of Harvard--a man as obviously competent as likeable (but whose name I didn't catch) who I assumed is a member of the Woodward group, spent two hours with Barry Young and me selecting the compounds and packing them. Thus, I had every reason to believe that every student had had ample opportunity to keep whatever was of interest to him. Dr. Ciappenelli told me that after the last Woodward student had graduated, by the summer of 1982, Aldrich could pick up the samples now left behind.

Miss Woodward was interested in any samples of "historic" interest. We found a large bottle of synthetic quinine (her father's first great accomplishment), and that she took. I promised her that if I found any

P.O. Box 355, Milwaukee, Wisconsin 53201 USA, Telephone (414) 273-3850, Cable Aldrichem TWX 910-262-3052, Telex 26-843

synthetic strychnine, B_{12}, cortisone, etc., I would put it aside, and she should decide what had best be done with these--Harvard or the A. C. S. Museum of Chemistry (now just in the planning stage) might be a good place.

Of course, we also have the Chemistry Department's written authorization to take the samples. Incidentally, there are in the collection picked up 363 individual bottles outside the cigar boxes and 261 cigar boxes which we taped in Cambridge and which have not been opened.

You told me yesterday that Dr. Ciappenelli could not confirm that Harvard has sold Aldrich the collection, because Harvard may not have clear title to it. If you will read my "telex" carefully, you will see that I understand that. All that Harvard did was to sell Aldrich its rights, whatever they may be. Miss Woodward sold us the estate's rights. I realized, of course, that there was a question of title, and so I purchased the rights from both.

The students have asked, "Why the haste in picking up the collection?" Surely you realize that there was no haste in the decision. Professor von Doering had discussed the acquisition of the collection with me for the last two years, you and Dr. Ciappenelli last year. There was haste in the actual pickup, but only because I had been told that I had to finalize with Miss Woodward while she was still in this country, in January, and the only day I could free myself was last Friday, and I had an afternoon plane to catch to attend an A. C. S. committee meeting on TSCA in Washington. Of course, we wanted to take the samples in our car so that no one at Harvard would have the very difficult task of packing and shipping the samples.

Both you and Dr. Ciappenelli have said, "let's go back to square one, to last Thursday." This we cannot do. Aldrich has purchased the collection, whether from Harvard or the estate or both. If we haven't done so, somewhere along the line someone is bound to say, "Bader had no business to take the samples" and that is so close to stealing that the difference will become fuzzy. This concern is very real: when I asked Dr. Ciappenelli what was behind the students' concern, he told me that for all he knows someone may suspect him of having $10,000 of my money in his pocket!

These facts are clear to me:

(1) The collection belongs to Aldrich.

(2) The students should have every opportunity to use the collection to complete their research.

(3) Once that research is completed, Aldrich has the best means to make the collection available to research chemists around the world.

I have heard a great deal since Saturday about the students being upset, and I understand that. But do you understand how upset I am? Dr. Ciappenelli talked to David Harvey, Miss Saito, Mrs. Jules and my wife on Saturday, and when he then reached me in Cleveland that afternoon, he was unbelievably excited. I slept little on Saturday and Sunday nights, worrying.

You must realize that the Harvard students involved will be the leaders in the world of chemistry twenty years from now, and I do not want to live with the worry that any of them may think that Aldrich or Bader have done something wrong.

Naturally, I prefer that the collection return to Converse, under the condition outlined in the "telex". If we cannot do that, then we should consider moving it to our library of rare chemicals, but not disposing of any of it until the last Woodward student has graduated, and informing each student that any of the samples which they may reasonably require are theirs for the asking, of course without charge.

Please help me by sharing this with the students and any faculty member who is interested. By all means make copies and distribute these to the Woodward group.

Dr. Ciappenelli suggested that I come to Harvard later in the year to talk on "Chemistry and Art" and to have a bull session with graduate students to discuss problems faced by a chemical company such as Aldrich. I would love to come, but would then also like to have an opportunity to meet with the Woodward group to answer all questions they may have about how our library of rare chemicals will handle the collection.

This is one of the longest letters I have ever written. But then I cannot recall any Aldrich problem that has concerned me so much. For the first time ever I almost wished I were not a Harvard graduate, and had not considered Professor Woodward my good friend. Then I wouldn't care so much.

Sincerely,

Alfred Bader

Alfred Bader

AB:mmh

cc: Dr. Donald Ciappenelli
Miss Crystal Woodward
c/o Mrs. Katherine Jervey

HARVARD UNIVERSITY

DEPARTMENT OF CHEMISTRY

12 Oxford Street
Cambridge, Massachusetts 02138
U.S.A.

February 11, 1981

Dr. A. Bader, President
Sigma-Aldrich Corporation
940 W. St. Paul Avenue
Milwaukee, Wisconsin 53233

Dear Al:

As I said to you on the telephone on Friday, I am happy to report that everyone here is very much calmer about the samples from the RBW collection. I am sorry that we should have suffered this misunderstanding, and I want you to be assured that we are grateful that--by your concern and generosity--the RBW samples will ultimately find their way into your 'rare chemicals' collection, and contribute to the research efforts of the chemical community. I may have been rather too much of a mother hen to the Woodward orphans (though I shall not, of course, lessen my concern for their professional futures), and it is now clear that the samples that you took to New Jersey are unlikely to be needed by the remaining students as they complete their research projects. I therefore hope that you will keep them within Aldrich, and both I and the students are happy with your kind offer to make any of them available, should there be a research need arising in the work of an existing RBW student. When the group has finally evaporated the remaining samples in the collection will come to you. [The only possible perturbation on this might be a short time extension--mentioned to me by Yoshi--in the case of the B_{12} and erythromycin samples only. If Yoshi felt that he wanted the erythromycin samples, or Albert Eschenmoser the B_{12} samples, just while the manuscripts on these syntheses were being prepared for publication, I hope we might arrange that. With luck, it won't be necessary, since I should not want you to trouble with too many trips on account of the remaining samples.]

I was brought up with the phrase 'storm in a teacup' which is a rather smaller perturbation than a 'tempest in a teapot', I think. I hope that even that, has now blown away, and that the next time we see you here, we can again concern ourselves with the healthiness and excitement of chemistry.

With my best wishes and thanks.

Jeremy

Jeremy R. Knowles
Professor of Chemistry
and Chairman

JRK/cac

P.S. I enclose a copy of your Telex draft, amended to allow for the samples in New Jersey remaining with you. Do let me know if it is all right, and I'll send it.

DRAFT

Dear Dr. Bader:

This is to express our appreciation of your generous offer to send back to Harvard, any of the Woodward collection of chemicals, in the event that any of the remaining Woodward students has an explicit need for it in his research.

We want to assure you that your willingness to permit the return of any of these chemicals to Harvard for the purpose indicated above in no way alters the fact that the collection is now the property of the Aldrich Chemical Company, Inc. You can also be sure that this gesture on your part is appreciated by Professor Woodward's students and associates and the privilege of selecting samples of chemicals of interest to each of them will not be abused.

You have discussed the acquisition of these samples with us during the last two years and you acquired them by arrangements worked out with Harvard University and Miss Woodward with appropriate consideration to each, to serve the objective of carefully preparing and making these chemicals available to research chemists through the Aldrich Library of Rare Chemicals. This certainly is in keeping with our desire to make these compounds as widely useful as possible.

We recognize that, after the Woodward students have finished their research projects, the remainder of the sample collection would come to Aldrich (excepting only the possibility of a slight delay in the B_{12} and erythromycin samples, if those were needed during the preparation of these syntheses for publication).

Yours sincerely,

c.c. B [illegible]

HARVARD UNIVERSITY

DEPARTMENT OF CHEMISTRY

12 Oxford Street
Cambridge, Massachusetts 02138
U.S.A.

February 11, 1981

Aldrich Chemical Company, Inc.
940 W. St. Paul Avenue
Milwaukee, Wisconsin 53233

Attention: Dr. Alfred Bader

Dear Al,

I must apologize for not having written sooner but believe me it wasn't that I didn't enjoy seeing you just as much as ever. I also want to again thank you for your generosity in giving the department the stock certificate, which I am sure you know can always be used to its fullest. There is every reason to believe that Harvard will keep this one as they have those in the past. It was also comforting to know that our Woodward chemical sample thing has gently settled down.

When you were here, Barry Young also took our list of outstanding purchase orders and a reply was received from Eleanor Dalton on estimated delivery dates. On those that have a long lead time we have notified the person who placed the order asking them if they are willing to or can wait.

Thanks again. Best regards.

Sincerely,

Warren

W. R. Stockwood

WRS:d

Chemists Helping Chemists in Research and Industry

aldrich chemical company, inc.

Dr. Alfred R. Bader
President

February 6, 1981

Dr. Steven Benner
Department of Chemistry
Harvard University
Cambridge, Massachusetts 02138

Dear Dr. Benner:

Has it ever happened to you that you have met a man whom you liked a great deal, and who helped you a lot, but you were just too rushed and too busy to get to know him?

That is exactly what happened to me when I met you on Friday, January 16. You helped Barry and me a great deal packing the Woodward samples, yet I was too busy even to catch your name, or to thank you adequately.

I do hope that when next I come to Harvard I will have a chance to thank you personally and leisurely.

You may have realized that I had been distressed when I learned that some of the Woodward students were upset at what appeared to them to be a hasty removal of the Woodward samples. My letter to Professor Knowles, copy enclosed, will be self-explanatory. I was happy to learn from Professor Knowles today that the students have calmed down, and of course we shall keep the collection intact until the last Woodward student has graduated. Aft~~h~~er that, I believe that the collection will help a great many chemists.

Again, many thanks for all your help.

Sincerely,

Alfred Bader
AB:mmh
Enclosure

P O Box 355, Milwaukee, Wisconsin 53201 USA, Telephone (414) 273-3850, Cable Aldrichem TWX 910-262-3052, Telex 26-843

® *Chemists Helping Chemists in Research and Industry*

aldrich chemical company, inc.

Dr. Alfred R. Bader
President

January 19, 1981

Miss Crystal Woodward
c/o Dr. Donald Ciappenelli
Manager of Laboratories
Department of Chemistry
Harvard University
Cambridge, Massachusetts 02138

Dear Crystal:

You must have realized how very much I enjoyed meeting you last Friday morning and our lunch with Dr. Robinson. What a happy coincidence that we are both interested in chemistry and art!

As promised, please find enclosed Aldrich's check for the samples, made out to your father's estate.

I am sure that you were chagrined and disburbed by the upset in the Department because of the samples leaving. As you know, it had been my clear understanding that all of your father's students and associates had been notified well in advance that Aldrich would be adding the samples to its Library of Rare Chemicals. In fact, Dr. Ciappenelli and Mrs. Jervey pointed out to me that a number of boxes had been selected and clearly marked to remain at Harvard until the last of your father's students had completed his research. That, of course, was entirely acceptable to me, and those boxes were left behind. None of us had any idea that not all of the students had been notified, and you will be able to imagine my concern when I received Dr. Ciappenelli's phone call while traveling on Saturday.

You know and I know, but apparently the students didn't know, that there were only two reasons for the haste. I had been told some weeks ago that you would be in this country only through this month. I could come to Cambridge only on Friday and wanted to avoid anyone at Harvard having the rather considerable chore of packing and then shipping these chemicals.

P.O. Box 355, Milwaukee, Wisconsin 53201 USA, Telephone (414) 273-3850, Cable Aldrichem TWX 910-262-3052, Telex 26-843

Miss Crystal Woodward
January 19, 1981
Page Two

Hence, I asked Barry Young, our Eastern Sales Manager, to drive from New Jersey to Cambridge, to help us with the packing. I very much wanted to join you and Dr. Robinson for lunch and then had to catch a flight to Washington to attend an American ChemicalSociety committee meeting. Hence, we had to work rather hurriedly, without the slightest inkling that this would upset anyone.

Naturally, I agreed to the return of the collection to Harvard with the clear understanding that your father's students and associates will be fully informed of the facts.

I am convinced that the incorporation of your father's samples into our Library of Rare Chemicals will really help many chemists throughout the world.

I very much hope before long we will have a chance to meet again and talk about our many mutual interests.

Best personal regards,

Alfred Bader
AB:mmh
Enclosure
cc: Dr. Donald Ciappenelli
Professor Jeremy Knowles

Working with R. B. Woodward

by
Professor Dr. Helmut Vorbrüggen

Working with R. B. Woodward

Professor Dr. Helmut Vorbrüggen
Research Laboratories
Schering AG
1000 Berlin 65
Germany

Before I left Stanford in April 1963 to join the Woodward Institute (established within the Ciba Corporation in Basel, Switzerland in June 1963), a senior professor in the chemistry department tried to explain to me the singular phenomenon of Robert Burns Woodward, whom I had once heard lecturing at Stanford in 1961, but whom I had never met.

The Stanford professor pointed out that R.B. Woodward, whom all of us called R.B., was a problem to many, if not to most, of his colleagues in organic chemistry. If they happened to be in Boston and dropped by R.B.'s office at Harvard for a friendly chat, they sometimes mentioned a chemical problem, which had been occupying their minds. R.B. looked at the problem and, apparently quite often, presented a convincing solution within a few minutes. This had the result that these colleagues, after they left R.B., were hopping mad with themselves, wishing they had continued pondering their problem for some additional days or weeks to find the solution all by themselves.

I was naturally quite impressed by this story, which also explained to me why R.B. appeared not to be popular among some of his colleagues in the U.S., as well as abroad, and I wondered how he would be as a scientist and human being.

Later on, mostly during lunch or dinner, we sometimes tested R.B. with a chemical or intellectual problem, which he invariably solved practically on the spot. And, although he always kept a certain distance, as a person he turned out to be very kind and friendly.

R.B. came from Boston to the Woodward Institute five to six times a year. Between these week-long visits, communication was maintained by frequent phone calls and weekly reports. In June 1963, we discussed at length and in detail the synthetic pathways, perfectly planned by R.B., for the eventual conversion of L-cysteine into cephalosporin C. This particular week turned out to be fascinating, although at the same time an ordeal. In R.B.'s beautiful wood-panelled office in the Woodward Institute, the ventilation system did not work as yet, and we suffered from R.B.'s nearly constant smoking of about 100 cigarettes a day. In the newly established order at the beautiful round table, I was placed to his right as the senior post-doc and had to inhale quite a lot of his U.S.-brand Benson and Hedges cigarettes, the only brand he smoked. About one year later, his week's supply of cigarettes was stolen while changing planes at Heathrow for Basel. Thus R.B. had to make do for a whole week in Basel with other cigarettes. He tried and disliked the European brand of Benson and Hedges, Camel, Marlboro, and several others. All of us will remember the disgusted expression on his face whenever he tried a new substitute! That particular week without his favorite U.S. Benson and Hedges turned out to be a difficult one for all of us! While smoking, R.B. once burned a small hole into the perfect smooth surface of the round table, and I sensed that each time he noticed the scar on the table he was annoyed with himself.

R.B. once explained that he had tried to give up smoking altogether in 1962, apparently after the U.S. Surgeon General's strong indictment of smoking. However, he could not live, sleep, and, most importantly, work anymore. So, he decided after about six terrible weeks to take up smoking again just to be able to work and live, however much shorter his life might be. When he had not smoked for a time his fingers often started to tremble, but after one puff of his cigarette, his hands steadied and he drew one of his perfect and artistic structural formulas at the blackboard. I still wonder how much he must have suffered from our, particularly my, clumsy and awkward drawings at the blackboard. Once during dinner he took a paper napkin and drew a perfect structural formula of dodecahedrane, a molecule which had occupied his mind for years.

R.B. was usually quiet and relaxed,

and always seemed to have time to delve into any problem, if necessary in exhaustive detail. He once discussed with us for two days the ^{1}H-NMR spectra of substituted thiazolidine rings to find out whether adjacent ester- and hydroxy- or amino-substitutents were *syn-* or *anti*-substituted.

Working so far away from Harvard, we enjoyed a great deal of freedom in our work and were thus given the chance to try whatever we thought might succeed. During one of R.B.'s bimonthly visits to Basel, I suggested reacting *tert*-butanol with phosgene in the presence of pyridine at -78 °C in CH$_2$Cl$_2$ to prepare in situ the labile *tert*-butoxycarbonyl chloride for the introduction of the BOC-group into the thiazolidinecarboxylic acid by what R.B. called "internal delivery". He looked skeptical but then proclaimed: "Never prevent anybody from doing an experiment," and we were never reprimanded for doing any exotic nitrene-, radical-, or photochemistry to substitute the *S*-methylene group in our substituted thiazolidine!

R.B. liked new reagents and called them "magic bullets" if they, and only they, made a new reaction sequence possible. When the first crystals of the crucial bicyclic ß-lactam became available, R.B. spent nearly an hour looking at them through the fancy stereomicroscope, the Institute had specially aquired, to ascertain whether these crystals were suited for single-crystal x-ray crystallographic studies which were carried out within weeks by Z.A. Gougoutas at Harvard.

Our dinners, usually at a good restaurant in Basel, in particular Mrs. Casanova's restaurant, Neubad, nearly always took two hours and so we did not return to the Woodward Institute before 10 p.m. to start our evening session at 10:30, which sometimes lasted until after midnight. In one such session in 1965, at which A. Eschenmoser was a guest, R.B. presented the brand new Woodward-Hoffmann Rules. This discussion lasted until about 1 a.m., particularly strenous for A. Eschenmoser who had an hour and a half's drive to Zürich, to lecture at the E.T.H. at 8 a.m. that morning. We were all getting very tired but R.B. could have continued all night. He needed so little sleep and had so much time for his work and planning. This might partly explain why he rarely seemed to be in a hurry.

It was during these rather tranquil dinners that we got to know R.B. quite well. He had had his food, his favourite dessert, Coupe Denmark (he just loved to pour the hot chocolate sauce on the vanilla ice cream), and one or two highballs. He enjoyed sitting there drinking and smoking with his closest co-workers. Although he was an excellent performer in his lectures, like an actor, and loved these "shows" for which he meticulously prepared, he was really quite shy and only relaxed with people he knew. He was very entertaining, loved to tease us, told us amusing stories, and commented on life and politics.

He scorned all sports and called skiing a "criminal activity"—the more so since he knew that W. Oppolzer and I were avid skiers. One trying week in February 1965 when the whole synthetic scheme for the synthesis of cephalosporin C seemed to be in jeopardy, we had been discussing rather interesting alternative approaches and finally on Saturday afternoon at 5:30 p.m. R.B. dismissed us with, "I have no further plans for tonight," and added, "Tomorrow I will be in the Institute for informal discussions." On Sunday morning there was perfect winter weather with bright sunshine, and W. Oppolzer and I decided to drive with our wives and a Swiss friend to the Hasenhorn in the Black Forest to ski for a whole glorious day. On Monday we heard from another colleague, who had worked all Sunday in the Institute, that R.B. had not turned up at all. We were sun-tanned and tried to suppress gloating about the wonderful day on skis during lunch. During our time, R.A. Olofson, a former co-worker of R.B.'s who had become an assistant professor at Harvard, was persuaded by his colleagues at the chemistry department to join them and try skiing. Rumour has it that before he had even started to ski, he had fallen down and broken his ankle. When R.B. returned from a trip, he encountered one of Roy Olofson's graduate students from Harvard, who told him about Roy's misadventure and that he was sitting upstairs in his office, his foot in a cast. R.B. commented, "I went up to see him, and I am afraid he could not bear my sympathy."

One of his favorite stories was about a special official event at Harvard at which the retired faculty members participated in their gowns. "The old law professors, the old professors of medicine marched in (this went on for quite a time) and finally, there came in a group on crutches and wheelchairs"—R.B. then made an effective pause—"the physical education faculty." As he told this, he wore his particularly sardonic grin.

The story of his winter visit to the USSR got better and better each time R.B. remembered it. Several invited prominent guests had arrived somewhat late at the Moscow airport where nobody was expecting them that late anymore and tried to persuade the official at the Intourist agency to provide transportation to their hotel in Moscow. But the official was absolutely indifferent; he was reading Dumas's *The Count of Montecristo*, and claimed he could not help. Then R.B. told him, "O.K, if we cannot get into the city, when does the next plane depart for London or New York? We want to leave Moscow as soon as possible!" The official was startled, suddenly realizing that these foreigners, who would rather leave than

be stuck at the airport, must be some sort of V.I.P.s. He went into frantic action, made phone calls, and R.B. and his colleagues eventually got transportation in a semi-open military jeep to the city. The stay at the hotel was another story, but I have forgotten the details about his room and the adventures at the restaurant for breakfast and dinner.

Sometime in 1961 or 1962 R.B. was awarded the Papal Medal of Science in Rome. On his return to Logan Airport in Boston, the custom's official (naturally of Irish descent) asked R.B. whether he had anything to declare; R.B. said no, but then remembered, "Oh yes, I have a Papal Gold Medal with me." To the skeptical reply, "Sir, you are kidding," R.B. produced the beautiful case with the golden medal, on which R.B.'s name was engraved, identical to his name on his passport. The officer froze and saluted R.B., who moved on and claimed that the official was still standing to attention as he was leaving the customs hall!

R.B. loved to exaggerate to make a point or shock people. In 1956 he was invited to present a lecture at the occasion of the 100th aniversary of the French Chemical Society, but the French stipulated that he should deliver his lecture in French, a language he knew quite well, but not fluently. R.B. would never do or write anything if it were not masterful. He was offended that the French wanted him to do something he could not do perfectly. After having told this, he paused—and we anticipated that he would say something outrageous to express his indignation—he ended with, "1856, the decline of French chemistry started!" We all laughed since we knew that R.B. had always had a very high regard for French chemistry, especially their pioneering contributions to metallo-organic chemistry. If the German Chemical Society had dared to ask R.B. to give a lecture in German (which he also knew quite well), his comment would have been similar.

R.B. was quite interested in politics. In 1964/1965, he was reading a book about current U.S. party politics, and I remember that we once discussed the primary race in California between Goldwater and Rockefeller. He was skeptical about my proclaiming Southern California very conservative, a view partly based on the fact that the liberal magazine "The Reporter" was forbidden at quite a number of educational institutions in Southern California. But R.B. would not bet with us as he did not want to run the risk of losing a bet.

One of my colleagues, who was quite a good chessplayer, said that R.B. would never play with him nor any other co-worker—he did not want to lose—although R.B. himself was certainly also an excellent chessplayer.

To be the leading organic chemist in the world for so many years meant also a tremendous pressure to excel on all occasions and at all times, and to publish only the most original work.

R.B. was quite perceptive. Once during lunch, he remarked emphatically, "Before one makes a decision, one has to know all the facts." One of us had received a letter from his future employer, in which the question of his future status was vaguely left open, and remarked, "It is sometimes not possible to know all the facts; I got a letter today which leaves me puzzled." After lunch R.B. suddenly came into his lab and asked, "You wanted to discuss a letter with me?" When he was shown the letter, he read it, then shook his head and remarked, "You are right", and left.

R.B. used to tease me that I was too sensitive to drafts and to an open window behind my back just like another postdoc, who had worked for him at Harvard. He told us that he had been hardened as a boy, that in Boston he used to sleep in a bed between two open windows and sometimes in winter there was snow on his bed in the morning.

R.B. was fiercely loyal to his former co-workers and it would have been rather unwise to criticize any of them; only he was permitted to make one of his sometimes outrageous remarks. We once obtained an experimental procedure from a co-worker at Harvard in which a rather stable substituted benzyl chloride was recrystallized from methanol. When one of us commented that he would never recrystallize a compound with a potentially reactive halogen from an alcohol instead of from hexane or toluene, R.B. remarked, "He (the co-worker at Harvard) has a technique like a renaissance bandit." We all laughed, but realized that this joke was also a sign of R.B.'s affection. He used to tease us with the "achievements" of other co-workers at Harvard. Thus, he praised an English postdoc, who, in R.B.'s words, prepared a compound in the morning, recrystallized and dried it, and sent it off for analysis the same afternoon—a rational way of working we should follow too! But at the same time he appreciated, or at least tolerated, a fierce competion among his young and very ambitious co-workers, who wanted to please and impress him. This meant that there were sometimes transgressions into the field of a colleague and unpleasant jealousy and intrigue.

After I had left the Woodward Institute, these incidents caused me to write to R.B., "To work for you brings out the best in many (co-workers) but sometimes also the worst." Nowadays, after all my own experiences with ambitious co-workers and the publishing of scientific papers, I tend to view these instances of "human frailties" (R.B.'s expression) with much more lenience.

R.B. was absolutely a man of his word. If one needed a decision or permission from him one had only to call him. He would always remember what he had said or promised. This was better than expecting him to write a letter, which had to be perfectly worded, demanding quite an effort. When I sent

him a tiny book with a German translation of Jerzy Lec's aphorisms on the occasion of his 60th birthday, he replied, "I found my German occasionally taxed." R.B. would remember everything and anything—the good and the bad—including any unfortunate remark one might have made. He always knew who had had this or that idea, or made that suggestion and would later emphasize, "This was your idea".

For many years, organic chemists all over the world, and in particular R.B.'s co-workers and friends, had been waiting for him to receive the Nobel prize. Thus, we were happy to learn in October 1965 that he had finally been awarded the Nobel prize. We phoned him at Harvard to congratulate him. When my turn came to talk to him on the phone, after I had congratulated him, I said that we assumed he would rather speak in his Nobel lecture about something completely new, and asked him whether he would take the whole group to Stockholm if we finished our total synthesis of cephalosporin C in time. R.B. hesitated—he had obviously been drinking quite a lot of champagne—but then came his answer, which was a promise and a putdown, "Helmut, if you need this additional incentive, certainly."

Needless to say, we finished our synthesis, already in its last critical stages, before December 1965. R.B. gave his Nobel lecture on our work[1], and we all enjoyed our week in Stockholm very much. We participated in all the events, the Nobel prize award ceremony, the lecture, and, last but not least, the very elegant ball in the blue hall of the Town Hall—neatly dressed in our rented tailcoats. We also met R.B.'s second wife, his daughter and young son, who looked so much like R.B.! But all of us realized that we were also in Stockholm as representatives of all the former co-workers who had done all the work for which R.B. had received his Nobel prize!

When I left the Woodward Institute in March 1966, I had finally succeeded in raising the yield of the aforementioned bicyclic ß-lactam intermediate from 35% to ca. 70%. R.B. ordered a few bottles of champagne to be opened and called from Harvard to say goodbye to me and teased me, "Helmut, you are leaving the Institute on a path of glory." There were quite a number of occasions R.B. celebrated by drinking champagne—he just loved to open the bottles and shoot the corks against the ceiling. During these moments he was like a mischievous little boy.

As a person, R.B. was extremely sensitive and vulnerable. At the end of one of his bimonthly visits to Basel, he commented on the rather poor quality of the Swiss chalk and then exclaimed, "I leave you my chalk." He took his special chalk box with the initials R.B. and, in one of his grand gestures, tipped the opened box over and emptied its contents on the aforementioned round table. I found this a bit exaggerated and made the superfluous remark, "Most of them are broken anyhow." R.B.'s lips tightened, and I saw that he was offended—but I later forgot about the whole thing. At the end of his next visit to Basel, two months later, R.B. repeated the whole ceremony, and all the pieces of chalk were perfect! It occurred to me, then and later, that R.B. was in many ways absolutely defenseless. His own sarcasm and irony were only a shield to hide his sensitive self.

Years later he complained to me that, like everybody else, he was forced now to write detailed grant applications instead of automatically getting grants for his fundamental synthetic studies in the field of natural products. R.B. considered this an unnecessary and somewhat humiliating bureaucratic harassment!

But there were also the dark and pessimistic sides to R.B. The only movies he mentioned having seen with his daughters were "Divorce Italian Style" and "How to Murder Your Wife". On one of his visits to Basel we saw quite a good performance of Albee's "Who's afraid of Virginia Woolf." We talked about this during dinner, but R.B. did not like the play at all. Years later, a former colleague of R.B. at Harvard commented to me, "R.B. could not like this play; it hits too close to home!"

In later years, I often had the impression that he was getting more and more lonely and isolated. The final and fatal illness of Dody, his energetic and charming secretary, appeared to be one of the last tragedies in his life. Since I had been working for a number of years with nucleic acids, R.B. called me from Basel to inquire whether there was any progress in cancer chemotherapy and hope for Dody, but there was none.

Remembering R.B. from a few later brief visits to Harvard, an evening he took me out for dinner to Joseph's restaurant in Boston and the festive 60th birthday reception at the Woodward Institute in Basel, I feel that in spite of all his great achievements, all the awards and recognitions in his life, there was something sad and tragic about him.

He was admired by many of his colleagues and peers, and sometimes also envied and feared, yet he will be remembered with affection by most, if not all, of his former co-workers who will recall the intellectual excitement around R.B., his creative ingenuity, his ability to look at problems from all angles, and last but not least, the human warmth and benign irony of this extraordinary personality, one of the greatest scientists of this century.

Reference:

1) Woodward, R.B. *Angew. Chemie* **1966**, *78*, 557. Woodward, R.B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Amer. Chem. Soc.* **1966**, *88*, 852.

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Working with R. B. Woodward

by
Professor Dr. Helmut Vorbrüggen

Working with R. B. Woodward

Professor Dr. Helmut Vorbrüggen
Research Laboratories
Schering AG
1000 Berlin 65
Germany

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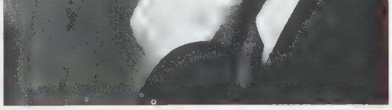
The Stanford professor pointed out that R.B. Woodward, whom all of us called R.B., was a problem to many, if not to most, of his colleagues in organic chemistry. If they happened to be in Boston and dropped by R.B.'s office at Harvard for a friendly chat, they sometimes mentioned a chemical problem, which had been occupying their minds. R.B. looked at the problem and, apparently quite often, presented a convincing solution within a few minutes. This had the result that these colleagues, after they left R.B., were hopping mad with themselves, wishing they had continued pondering their problem for some additional days or weeks to find the solution all by themselves.

I was naturally quite impressed by this story, which also explained to me why R.B. appeared not to be popular among some of his colleagues in the U.S., as well as abroad, and I wondered how he would be as a scientist and human being.

Later on, mostly during lunch or dinner, we sometimes tested R.B. with a chemical or intellectual problem, which he invariably solved practically on the spot. And, although he always kept a certain distance, as a person he turned out to be very kind and friendly.

R.B. came from Boston to the Woodward Institute five to six times a year. Between these week-long visits, communication was maintained by frequent phone calls and weekly reports. In June 1963, we discussed at length and in detail the synthetic pathways, perfectly planned by R.B., for the eventual conversion of L-cysteine into cephalosporin C. This particular week turned out to be fascinating, although at the same time an ordeal. In R.B.'s beautiful wood-panelled office in the Woodward Institute, the ventilation system did not work as yet, and we suffered from R.B.'s nearly constant smoking of about 100 cigarettes a day. In the newly established order at the beautiful round table, I was placed to his right as the senior post-doc and had to inhale quite a lot of his U.S.-brand Benson and Hedges cigarettes, the only brand he smoked. About one year later, his week's supply of cigarettes was stolen while changing planes at Heathrow for Basel. Thus R.B. had to make do for a whole week in Basel with other cigarettes. He tried and disliked the European brand of Benson and Hedges, Camel, Marlboro, and several others. All of us will remember the disgusted expression on his face whenever he tried a new substitute! That particular week without his favorite U.S. Benson and Hedges turned out to be a difficult one for all of us! While smoking, R.B. once burned a small hole into the perfect smooth surface of the round table, and I sensed that each time he noticed the scar on the table he was annoyed with himself.

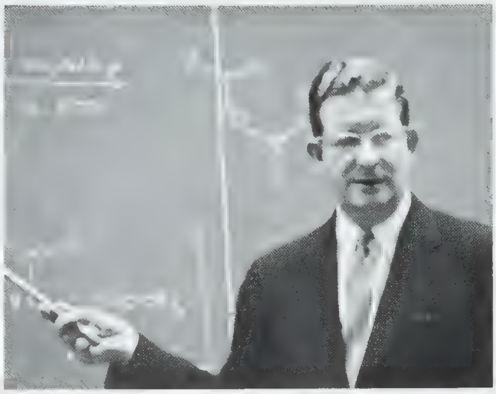


R.B. once explained that he had tried to give up smoking altogether in 1962, apparently after the U.S. Surgeon General's strong indictment of smoking. However, he could not live, sleep, and, most importantly, work anymore. So, he decided after about six terrible weeks to take up smoking again just to be able to work and live, however much shorter his life might be. When he had not smoked for a time his fingers often started to tremble, but after one puff of his cigarette, his hands steadied and he drew one of his perfect and artistic structural formulas at the blackboard. I still wonder how much he must have suffered from our, particularly my, clumsy and awkward drawings at the blackboard. Once during dinner he took a paper napkin and drew a perfect structural formula of dodecahedrane, a molecule which had occupied his mind for years.

R.B. was usually quiet and relaxed,

and always seemed to have time to delve into any problem, if necessary in exhaustive detail. He once discussed with us for two days the ^{1}H-NMR spectra of substituted thiazolidine rings to find out whether adjacent ester- and hydroxy- or amino-substitutents were *syn*- or *anti*-substituted.

Working so far away from Harvard, we enjoyed a great deal of freedom in our work and were thus given the chance to try whatever we thought might succeed. During one of R.B.'s bimonthly visits to Basel, I suggested reacting *tert*-butanol with phosgene in the presence of pyridine at -78 °C in CH_2Cl_2 to prepare in situ the labile *tert*-butoxycarbonyl chloride for the introduction of the BOC-group into the thiazolidinecarboxylic acid by what R.B. called "internal delivery". He looked skeptical but then proclaimed: "Never prevent anybody from doing an experiment," and we were never reprimanded for doing any exotic nitrene-, radical-, or photochemistry to substitute the *S*-methylene group in our substituted thiazolidine!



R.B. liked new reagents and called them "magic bullets" if they, and only they, made a new reaction sequence possible. When the first crystals of the crucial bicyclic ß-lactam became available, R.B. spent nearly an hour looking at them through the fancy stereomicroscope, the Institute had specially aquired, to ascertain whether these crystals were suited for single-crystal x-ray crystallographic studies which were carried out within weeks by Z.A. Gougoutas at Harvard.

Our dinners, usually at a good restaurant in Basel, in particular Mrs. Casanova's restaurant, Neubad, nearly always took two hours and so we did not return to the Woodward Institute before 10 p.m. to start our evening session at 10:30, which sometimes lasted until after midnight. In one such session in 1965, at which A. Eschenmoser was a guest, R.B. presented the brand new Woodward-Hoffmann Rules. This discussion lasted until about 1 a.m., particularly strenous for A. Eschenmoser who had an hour and a half's drive to Zürich, to lecture at the E.T.H. at 8 a.m. that morning. We were all getting very tired but R.B. could have continued all night. He needed so little sleep and had so much time for his work and planning. This might partly explain why he rarely seemed to be in a hurry.

It was during these rather tranquil dinners that we got to know R.B. quite well. He had had his food, his favourite dessert, Coupe Denmark (he just loved to pour the hot chocolate sauce on the vanilla ice cream), and one or two highballs. He enjoyed sitting there drinking and smoking with his closest co-workers. Although he was an excellent performer in his lectures, like an actor, and loved these "shows" for which he meticulously prepared, he was really quite shy and only relaxed with people he knew. He was very entertaining, loved to tease us, told us amusing stories, and commented on life and politics.

He scorned all sports and called skiing a "criminal activity"—the more so since he knew that W. Oppolzer and I were avid skiers. One trying week in February 1965 when the whole synthetic scheme for the synthesis of cephalosporin C seemed to be in jeopardy, we had been discussing rather interesting alternative approaches and finally on Saturday afternoon at 5:30 p.m. R.B. dismissed us with, "I have no further plans for tonight," and added, "Tomorrow I will be in the Institute for informal discussions." On Sunday morning there was perfect winter weather with bright sunshine, and W. Oppolzer and I decided to drive with our wives and a Swiss friend to the Hasenhorn in the Black Forest to ski for a whole glorious day. On Monday we heard from another colleague, who had worked all Sunday in the Institute, that R.B. had not turned up at all. We were sun-tanned and tried to suppress gloating about the wonderful day on skis during lunch. During our time, R.A. Olofson, a former co-worker of R.B.'s who had become an assistant professor at Harvard, was persuaded by his colleagues at the chemistry department to join them and try skiing. Rumour has it that before he had even started to ski, he had fallen down and broken his ankle. When R.B. returned from a trip, he encountered one of Roy Olofson's graduate students from Harvard, who told him about Roy's misadventure and that he was sitting upstairs in his office, his foot in a cast. R.B. commented, "I went up to see him, and I am afraid he could not bear my sympathy."

One of his favorite stories was about a special official event at Harvard at which the retired faculty members participated in their gowns. "The old law professors, the old professors of medicine marched in (this went on for quite a time) and finally, there came in a group on crutches and wheelchairs"—R.B. then made an effective pause—"the physical education faculty." As he told this, he wore his particularly sardonic grin.

The story of his winter visit to the USSR got better and better each time R.B. remembered it. Several invited prominent guests had arrived somewhat late at the Moscow airport where nobody was expecting them that late anymore and tried to persuade the official at the Intourist agency to provide transportation to their hotel in Moscow. But the official was absolutely indifferent; he was reading Dumas's *The Count of Montecristo*, and claimed he could not help. Then R.B. told him, "O.K, if we cannot get into the city, when does the next plane depart for London or New York? We want to leave Moscow as soon as possible!" The official was startled, suddenly realizing that these foreigners, who would rather leave than be stuck at the airport, must be some sort of V.I.P.s. He went into frantic action, made phone calls, and R.B. and his colleagues eventually got transportation in a semi-open military jeep to the city. The stay at the hotel was another story, but I have forgotten the details about his room and the adventures at the restaurant for breakfast and dinner.

Sometime in 1961 or 1962 R.B. was awarded the Papal Medal of Science in Rome. On his return to Logan Airport in Boston, the custom's official (naturally of Irish descent) asked R.B. whether he had anything to declare; R.B. said no, but then remembered, "Oh yes, I have a Papal Gold Medal with me." To the skeptical reply, "Sir, you are kidding," R.B. produced the beautiful case with the golden medal, on which R.B.'s name was engraved, identical to his name on his passport. The officer froze and saluted R.B., who moved on and claimed that the official was still standing to attention as he was leaving the customs hall!

R.B. loved to exaggerate to make a point or shock people. In 1956 he was invited to present a lecture at the occasion of the 100th aniversary of the French Chemical Society, but the French stipulated that he should deliver his lecture in French, a language he knew quite well, but not fluently. R.B. would never do or write anything if it were not masterful. He was offended that the French wanted him to do something he could not do perfectly. After having told this, he paused—and we anticipated that he would say something outrageous to express his indignation—he ended with, "1856, the decline of French chemistry started!" We all laughed since we knew that R.B. had always had a very high regard for French chemistry, especially their pioneering contributions to metallo-organic chemistry. If the German Chemical Society had dared to ask R.B. to give a lecture in German (which he also knew quite well), his comment would have been similar.

R.B. was quite interested in politics. In 1964/1965, he was reading a book about current U.S. party politics, and I remember that we once discussed the primary race in California between Goldwater and Rockefeller. He was skeptical about my proclaiming Southern California very conservative, a view partly based on the fact that the liberal magazine "The Reporter" was forbidden at quite a number of educational institutions in Southern California. But R.B. would not bet with us as he did not want to run the risk of losing a bet.

One of my colleagues, who was quite a good chessplayer, said that R.B. would never play with him nor any other co-worker—he did not want to lose—although R.B. himself was certainly also an excellent chessplayer.

To be the leading organic chemist in the world for so many years meant also a tremendous pressure to excel on all occasions and at all times, and to publish only the most original work.

R.B. was quite perceptive. Once during lunch, he remarked emphatically, "Before one makes a decision, one has to know all the facts." One of us had received a letter from his future employer, in which the question of his future status was vaguely left open, and remarked, "It is sometimes not possible to know all the facts; I got a letter today which leaves me puzzled." After lunch R.B. suddenly came into his lab and asked, "You wanted to discuss a letter with me?" When he was shown the letter, he read it, then shook his head and remarked, "You are right", and left.

R.B. used to tease me that I was too sensitive to drafts and to an open window behind my back just like another postdoc, who had worked for him at Harvard. He told us that he had been hardened as a boy, that in Boston he used to sleep in a bed between two open windows and sometimes in winter there was snow on his bed in the morning.

R.B. was fiercely loyal to his former co-workers and it would have been rather unwise to criticize any of them; only he was permitted to make one of his sometimes outrageous remarks. We once obtained an experimental procedure from a co-worker at Harvard in which a rather stable substituted benzyl chloride was recrystallized from methanol. When one of us commented that he would never recrystallize a compound with a potentially reactive halogen from an alcohol instead of from hexane or toluene, R.B. remarked, "He (the co-worker at Harvard) has a technique like a renaissance bandit." We all laughed, but realized that this joke was also a sign of R.B.'s affection. He used to tease us with the "achievements" of other co-workers at Harvard. Thus, he praised an English postdoc, who, in R.B.'s words, prepared a compound in the morning, recrystallized and dried it, and sent it off for analysis the same afternoon—a rational way of working we should follow too! But at the same time he appreciated, or at least tolerated, a fierce competion among his young and very ambitious co-workers, who wanted to please and impress him. This meant that there were sometimes transgressions into the field of a colleague and unpleasant jealousy and intrigue.

After I had left the Woodward Institute, these incidents caused me to write to R.B., "To work for you brings out the best in many (co-workers) but sometimes also the worst." Nowadays, after all my own experiences with ambitious co-workers and the publishing of scientific papers, I tend to view these instances of "human frailties" (R.B.'s expression) with much more lenience.

R.B. was absolutely a man of his word. If one needed a decision or permission from him one had only to call him. He would always remember what he had said or promised. This was better than expecting him to write a letter, which had to be perfectly worded, demanding quite an effort. When I sent

him a tiny book with a German translation of Jerzy Lec's aphorisms on the occasion of his 60th birthday, he replied, "I found my German occasionally taxed." R.B. would remember everything and anything—the good and the bad—including any unfortunate remark one might have made. He always knew who had had this or that idea, or made that suggestion and would later emphasize, "This was your idea".

For many years, organic chemists all over the world, and in particular R.B.'s co-workers and friends, had been waiting for him to receive the Nobel prize. Thus, we were happy to learn in October 1965 that he had finally been awarded the Nobel prize. We phoned him at Harvard to congratulate him. When my turn came to talk to him on the phone, after I had congratulated him, I said that we assumed he would rather speak in his Nobel lecture about something completely new, and asked him whether he would take the whole group to Stockholm if we finished our total synthesis of cephalosporin C in time. R.B. hesitated—he had obviously been drinking quite a lot of champagne—but then came his answer, which was a promise and a putdown, "Helmut, if you need this additional incentive, certainly."

Needless to say, we finished our synthesis, already in its last critical stages, before December 1965. R.B. gave his Nobel lecture on our work[1], and we all enjoyed our week in Stockholm very much. We participated in all the events, the Nobel prize award ceremony, the lecture, and, last but not least, the very elegant ball in the blue hall of the Town Hall—neatly dressed in our rented tailcoats. We also met R.B.'s second wife, his daughter and young son, who looked so much like R.B.! But all of us realized that we were also in Stockholm as representatives of all the former co-workers who had done all the work for which R.B. had received his Nobel prize!

When I left the Woodward Institute in March 1966, I had finally succeeded in raising the yield of the aforementioned bicyclic ß-lactam intermediate from 35% to ca. 70%. R.B. ordered a few bottles of champagne to be opened and called from Harvard to say goodbye to me and teased me, "Helmut, you are leaving the Institute on a path of glory." There were quite a number of occasions R.B. celebrated by drinking champagne—he just loved to open the bottles and shoot the corks against the ceiling. During these moments he was like a mischievous little boy.

As a person, R.B. was extremely sensitive and vulnerable. At the end of one of his bimonthly visits to Basel, he commented on the rather poor quality of the Swiss chalk and then exclaimed, "I leave you my chalk." He took his special chalk box with the initials R.B. and, in one of his grand gestures, tipped the opened box over and emptied its contents on the aforementioned round table. I found this a bit exaggerated and made the superfluous remark, "Most of them are broken anyhow." R.B.'s lips tightened, and I saw that he was offended—but I later forgot about the whole thing. At the end of his next visit to Basel, two months later, R.B. repeated the whole ceremony, and all the pieces of chalk were perfect! It occurred to me, then and later, that R.B. was in many ways absolutely defenseless. His own sarcasm and irony were only a shield to hide his sensitive self.

Years later he complained to me that, like everybody else, he was forced now to write detailed grant applications instead of automatically getting grants for his fundamental synthetic studies in the field of natural products. R.B. considered this an unnecessary and somewhat humiliating bureaucratic harassment!

But there were also the dark and pessimistic sides to R.B. The only movies he mentioned having seen with his daughters were "Divorce Italian Style" and "How to Murder Your Wife". On one of his visits to Basel we saw quite a good performance of Albee's "Who's afraid of Virginia Woolf." We talked about this during dinner, but R.B. did not like the play at all. Years later, a former colleague of R.B. at Harvard commented to me, "R.B. could not like this play; it hits too close to home!"

In later years, I often had the impression that he was getting more and more lonely and isolated. The final and fatal illness of Dody, his energetic and charming secretary, appeared to be one of the last tragedies in his life. Since I had been working for a number of years with nucleic acids, R.B. called me from Basel to inquire whether there was any progress in cancer chemotherapy and hope for Dody, but there was none.

Remembering R.B. from a few later brief visits to Harvard, an evening he took me out for dinner to Joseph's restaurant in Boston and the festive 60th birthday reception at the Woodward Institute in Basel, I feel that in spite of all his great achievements, all the awards and recognitions in his life, there was something sad and tragic about him.

He was admired by many of his colleagues and peers, and sometimes also envied and feared, yet he will be remembered with affection by most, if not all, of his former co-workers who will recall the intellectual excitement around R.B., his creative ingenuity, his ability to look at problems from all angles, and last but not least, the human warmth and benign irony of this extraordinary personality, one of the greatest scientists of this century.

Reference:

1) Woodward, R.B. *Angew. Chemie* **1966**, *78*, 557. Woodward, R.B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Amer. Chem. Soc.* **1966**, *88*, 852.

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