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FOREWORD

The preliminary communication by R. B. Woodward and seventeen postdoctoral colleagues describing the total synthesis of chlorophyll *a* was published in 1960 [*J. Amer. Chem. Soc.*, 1960, **82**, 3800].

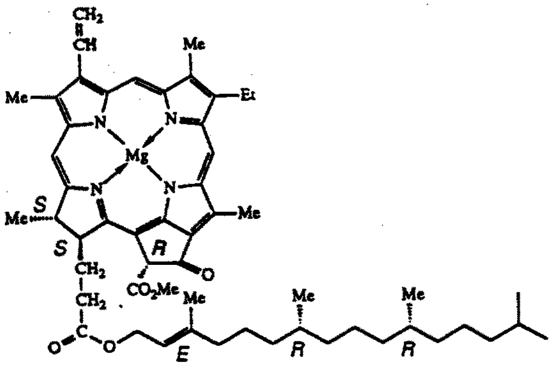
R. B. Woodward subsequently reported on the philosophy, the planning, and the successful execution of the total synthesis of chlorophyll *a* in two important lectures. His first lecture [*Pure Appl. Chem.*, 1961, **2**, 383] was given at the I.U.P.A.C. Meeting on "The Chemistry of Natural Products" which was held in Australia during August 1960. At the closing session, Sir Robert Robinson presented a summary of scientific achievements of the I.U.P.A.C. Symposium so it is particularly appropriate to recall his statement about the lecture by R. B. Woodward:

> We were greatly privileged to hear the lecture of Professor Woodward, in which he described, I believe for the first time, the outstanding achievement of the total synthesis of chlorophyll. Professor Woodward is not only a most brilliant synthetic organic chemist, who gives us metaphorical left hooks and right jabs in bewilderingly quick succession, but also an expositor able to convey a sense of the drama of the development to his audience. His lecture was thoroughly enjoyable, even thrilling, as an experience. No doubt in places he admitted to a little good fortune, though he also made it clear that it was expected. I was reminded of Benjamin Franklin's wise saying— "Luck is a bonus that accrues to industry". Well, Woodward and his team were surely industrious. This achievement of the synthesis of chlorophyll is a very good example of the kind of comment that one often sees, "what good is it?" Presumably the 'good thing', as Woodward has so admirably pointed out himself, is the new knowledge that is obtained; increased understanding of the chemistry of chlorophyll, and of how it is likely to behave in a variety of circumstances. We do not know where that new knowledge may lead us, but it is certainly a most important substance and, therefore, we must know everything we can about it. [R. Robinson, *Pure Appl. Chem.*, 1961, **2**, 631].

The second lecture on the total synthesis of chlorophyll was given by R. B. Woodward on 8th November 1960 at the Fourth Robert A. Welch Foundation Conference on Molecular Structure and Organic Reactions. What a conference! His co-speakers included R. Adams, A. C. Cope, V. Prelog, R. Huisgen, J. M. Robertson, D. H. R. Barton, and S. Winstein. His lecture contained the following introduction and conclusion:

> Chlorophyll *a*, the major green pigment of the plant world, is certainly the most widespread and conspicuous of organic natural products. Few can be unaware of its decorative function, and all are beneficiaries of its central role in transforming sunlight into substance and sustenance. Yet the fruitful chemical study of this green badge of life did not commence until fairly recent times. For chlorophyll *a* is a very reactive, sensitive, and complicated substance. Only when, early in this century, the genius of Willstätter applied itself to the problem were the first sure steps taken. That great investigator isolated the pigment—and its closely related frequent minor concomitant chlorophyll *b* as well—in the pure state, established correctly the empirical formula of the substance, and laid down a sound and extensive preliminary basis of transformation and degradation. These achievements can be measured against the fact that the isolation of chlorophyll in a state of purity is even now, after more than fifty years, no mean feat, and further that the empirical formula defined by Willstätter, repeatedly called into question by subsequent investigators, has stood the test of time. For some

period after this solid foundation had been laid by Willstätter there was little activity until three new groups took the field late in the 1920's. Stoll, who had played a prominent role in the early studies as a collaborator of Willstätter, took up the work anew with Wiedemann, and made important contributions, as did Conant at Harvard. But by far the greatest contribution was made by Hans Fischer and his collaborators at Munich. Fresh from his dramatic conquest of the blood pigment, Fischer hurled his legions into the attack on chlorophyll, and, during a period of approximately fifteen years, built a monumental corpus of fact. As this chemical record, almost unique in its scope and depth, was constructed, the molecule was transformed and rent asunder in innumerable directions, and the fascination and intricacy of the chemistry of chlorophyll and its congeners was fully revealed. These massive contributions were crowned by the proposal, in 1940, of a structure which was complete except for stereochemical detail. Finally, in a series of elegant investigations completed only during the last few years, Linstead and his associates at Imperial College were able to solve the stereochemical problem and to provide definitive confirmatory detail in respect to the number and disposition of saturated carbon atoms within the nuclear framework. A half century of structural study had culminated in the complete formula for chlorophyll *a* (**101**).



101 Chlorophyll *a*

Our active interest in chlorophyll was initiated four years ago, in 1956. The first questions we asked were very general ones. The structural investigations had been carried out almost entirely during the twilight of the classical period of organic chemistry. Only the very simplest basic elements of theory played any role in the whole vast study. Neither was succor nor control sought in chemical principle, nor was any attempt made to place the often striking observations in any generalized framework. Would the conclusions from such a study stand scrutiny from the viewpoint of the present day? Was the structure proposed for chlorophyll correct? When we embarked upon the examination of these questions, we entered a chemical fairyland, replete with remarkable transformations which provide unusual opportunities for the testing and further development of principle, and we cannot but urge others to follow us in penetrating what must have seemed to many the monolithic wall of a finished body of chemistry. But this is not the place to outline those opportunities at length. Here we shall mention only a few major points, which brought us at first to view the proposed structure for chlorophyll with considerable skepticism, and whose resolution was of importance in our subsequent planning.

> The total synthesis of chlorophyll *a* described here constitutes final verification of the structure earlier deduced for the leaf pigment from analytical and degradative studies. Now that the synthetic and structural phase of our interest in chlorophyll has been brought to a successful conclusion, it is perhaps worth while to look back briefly in a very general way over the development of the investigation. We admit to taking special pleasure in the fact that our work evolved in such wise as to provide at its conclusion clear, unambiguous, entirely new evidence for every single detail in the structure of chlorin e_6. As all projects of such magnitude must be, this one was planned in a fairly elaborate way at the outset. The measure in which our initial plans were realized is very gratifying, but it is at least equally so that major elements of discovery, and increase in understanding through observation and experiment, were involved in our progress. We learned and established much about this important class of compounds which could not have been known, or at best could only have been dimly foreshadowed, before our work was carried out. This fascinating aspect of work in chlorophyll chemistry has by no means been exhausted—indeed, we feel that our studies have opened up many more avenues than they have traversed, and we do not hesitate to hazard the opinion that the area is one from which much increase in chemical knowledge and understanding is to be had in the future.
>
> It remains to thank with all the warmth at my command those who fought and enjoyed the battle with me. During the first year [1956/57] I had the good fortune to be associated with Drs. John M. Beaton, Gerhard Closs, Albert Langemann, and Zdenek Valenta. These men did much exploratory work, established the validity of our general approach to porphyrin synthesis, and made the observations which provided an important clue to the problem of passing the barrier between the porphyrins and the chlorins. Then their places were taken, during 1957/58, by Drs. William A. Ayer, John Hannah, and Fred P. Hauck. This second group did much to develop and improve the methods of synthesis of our dipyrrylmethane intermediates, performed Herculean preparative tasks, and brought much further understanding to our studies of chlorin formation. They in their turn were replaced [in 1958/59] by Drs. Raymond Bonnett, Hans Dutler, Shô Itô, Jürgen Sauer, and Heinrich Volz, whose victory it was to bring our orientationally directed porphyrin synthesis into being. Of this group, Dr. Dutler remained for half of the succeeding year, and was joined by Drs. Paul Buchschacher, Friedrich Bickelhaupt, Eugene Le Goff, Willy Leimgruber, and Walter Lwowski, who brought the work to its successful conclusion. It has been a great privilege to share with these men the pleasures and vicissitudes of a long and fascinating journey. [R. B. Woodward, *Proc. R. A. Welch Foundation Conf.*, 1961, 4, 99].

R. B. Woodward had style. He had already established the wonderful tradition that he would select an appropriate method to announce to all members of his team the successful completion of a total synthesis. For example, on 19th April 1954, all members of the postdoctoral team associated with the total synthesis of strychnine [M. P. Cava, A. Hunger, H. U. Daeniker, W. D. Ollis, and K. Schenker] received the following cable: WE HAVE MET THE ENEMY AND THEY ARE OURS. WARMEST CONGRATULATIONS. R. B. Woodward. Commandant Beresina Group. Students of the history of Switzerland will enjoy this reference to the association of the Swiss, Hans Daeniker and Karl Schenker, with the concluding phase of the project. The successful execution of the total synthesis of chlorophyll was announced to all members of the postdoctoral team by the dispatch of a green leaf signed by R. B. Woodward accompanied by the famous red tick. The red tick was used by R. B. W. in his lectures to indicate that discussion of a particular matter was now concluded. The chlorophyll announcement was also signed by Paul Buchschacher, Friedrich Bickelhaupt, Eugene Le Goff, Willy Leimgruber, and Walter Lwowski, who completed the synthesis.

It is entirely appropriate that this full paper, which was written by Professor Raymond Bonnett, should include a photograph of the chlorophyll announcement which he received as a member of the postdoctoral team [1958–1959].

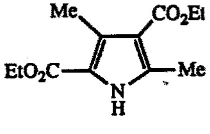
R. B. Woodward was elected a Foreign Member of the Royal Society in 1956. Lord Todd and Sir John Cornforth have provided a sensitive and detailed appreciation of R. B. Woodward's remarkable contributions to the development of modern organic chemistry. In their discussion of the total synthesis of chlorophyll, Todd and Cornforth made the following two comments:

> Woodward at first approached the structure with scepticism. Simple dihydroporphyrins [chlorins] are easily oxidized to porphyrins; chlorophyll is not.
>
> 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. [A. R. Todd and J. W. Cornforth, *Biographical Memoirs of Fellows of the Royal Society*, 1981, **27**, 629].

This situation has at last been rectified by the devoted efforts of Professor Raymond Bonnett. On the occasion of the Memorial Service for R. B. Woodward, which was held in the Harvard Memorial Church on 9th November 1979, a discussion took place between W. E. Doering, A. Eschenmoser, W. D. Ollis, V. Prelog, and A. R. Todd about the need to publish, as full papers, a number of R. B. Woodward's outstanding achievements in organic synthesis. Professor Raymond Bonnett was proposed as the obvious person to report the chlorophyll synthesis. The rest is history which has been recorded by R. Bonnett in his Prefatory Note.

Our debt to Professor Bonnett is shared by all members of the chlorophyll team. The commitment which was undertaken by Professor Bonnett required the transformation of the laboratory records of seventeen postdoctoral colleagues into a full paper. The result of all his hard work is this full paper which obviously meets the standards of the leader of the group, R. B. Woodward. The final product is a superb contribution to the chemical literature and would have been given enthusiastic approval by the senior author.

The Woodward synthesis of chlorophyll involves 46 steps. The elegance of the plan is demonstrated by the fact that Knorr's pyrrole **1** was used as the single precursor of the four pyrrole intermediates **11**, **16**, **20**, and **25** which provided the four pyrrolic residues in chlorophyll *a*. The quality of the experimental work is amply demonstrated by the following facts:



1

1 ⟶ **11**, 11 steps, 14% overall yield

1 → **3** → **16**, 5 additional steps, 52% overall yield

1 ⟶ **20**, 4 steps, 39% overall yield

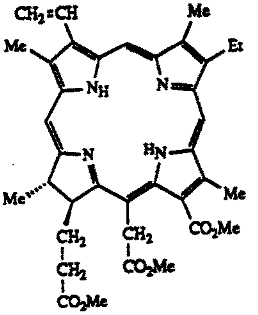
1 → **4** → **25**, 5 additional steps, 22% overall yield

These four intermediates [**11**, **16**, **20**, and **25**] were then used to produce the required dipyrrolic intermediates **26** and **31** by the following sequences:

11+**25**→**26**, 1 step
16+**20**→**31**, 5 steps

In a total synthesis of this complexity, every step is critical. However, one step which exemplifies brilliant conception and intensive experimental investigation was the regiospecific generation of the porphyrin **35** from the two dipyrrylmethanes **32** and **31**. **The regiospecific macrocyclisation [26+31 → 35, 4 steps] was achieved in 50% overall yield.** The porphyrin **35**, which was available by total synthesis in 50 g quantities, was then transformed by a sequence of 11 steps [**35**→**36**→**37**→**38**→**39**→**40**→**41** (resolution)→**42**→**43**→**44**→**45**→**46**] into chlorin e_6 trimethyl ester **46** which was identical in all respects with material of natural provenance. The final 11 of the 46 steps to chlorin e_6 trimethyl ester **46** are appealing examples which provide striking support for the following opinion:

> He was, however, a great believer in the experimental approach and, in his words, "it is well to remember that most arguments in favour of not trying an experiment are too flimsily based". If, in fact, the result of an experiment was not in accord with his expectation, he just modified his original plan and adopted his new plan adroitly and relentlessly. He did not believe that chemical reactions could be forced to work: he preferred to coax them to proceed in accord with his aspirations. [W. D. Ollis, *Chemistry in Britain*, 1980, **16**, 210].



46 Chlorin e_6 trimethyl ester

This completed the synthesis because the remaining steps, [i], [ii], and [iii] from chlorin e_6 trimethyl ester **46** to chlorophyll *a* [**101**] had already been traversed: [i] Dieckmann cyclisation, [ii] exchange of one methyl ester by a phytyl ester group, and [iii] introduction of magnesium.

The professionalism of the experimental investigation leading to the total synthesis of chlorophyll *a* [**101**] is impressive. These results were obtained before chromatographic methods [TLC and HPLC] and modern physical methods including NMR spectroscopy and low- and high-resolution mass spectrometry were routinely available. R. B. Woodward's insistence that all intermediates should, if possible, be crystallised and properly characterised by elemental analysis is salutary. The loving care which he displayed towards new organic compounds in their crystalline state is admirably illustrated by the concluding remarks in his 1965 Harvey Lecture:

> One aspect of work of this kind hardly shows through a dry account of the sort I have presented here and deserves explicit mention. Each of the intermediates along our progression to the colchicine molecule is a beautifully crystalline substance, an entirely new form of matter, persuaded into being in response to the challenge of an often remote objective. It is delightful to work with such things, and the delight which

> the experimenter experiences in his manipulation contributes in no small measure to the skill required to create them. [R. B. Woodward, *Harvey Lectures*, 1965, 31, Academic Press, New York].

Since the completion of the total synthesis of chlorophyll *a* by R. B. Woodward in 1960, tremendous progress has been made towards the definition of the complex sequences of photochemical reactions, chemical reactions, and electron transfer processes which operate during natural photosynthesis. Photosynthesis is surely the most important chemical transformation which takes place on Earth: it is estimated that 2×10^{11} tonnes of carbon dioxide per annum are converted by photosynthesis into biomass [D. C. Phillips, *Chemistry in Britain*, 1988, **24**, 1182]. These biomass products constitute direct input to the food chain for all animal life and eventually yield all the conventional fossil fuels which now meet 82% [1989 figures, excluding the centrally planned economies] of primary energy consumed on the planet Earth. Very important progress towards the current understanding of the central role of the chlorophylls at the photosynthetic reaction centres was recognised by the award of the 1988 Nobel Prize in Chemistry to Deisenhofer, Huber, and Michel.

Organic chemists owe a great debt to Professor Raymond Bonnett for his commitment in producing this full paper. The seventeen-man chlorophyll team must have enjoyed their association with R. B. Woodward as a chemist and as a raconteur. It is therefore appropriate that we conclude this Foreword by a story reported by Professor Gilbert Stork:

> One anecdote, perhaps, sums up the view he had of his rightful place in the world: A new guard at Harvard University had just told Woodward that his [blue] car could not be left where he had placed it. "Why is that?" said Woodward. "Your name is not on the list", said the guard. "It isn't?" said Woodward, turning back toward the guard without stopping, "well... put it there!". One thing is certain, Woodward's place in chemical history is permanently reserved. [G. Stork, *Nature*, 1980, **284**, 383].

We shall be pleased to consider the offer of similar facilities to any former members of the Woodward Research Group who may wish to produce full papers describing their researches which have not yet been published.

D. H. R. BARTON W. D. OLLIS