

THE TOTAL SYNTHESIS OF CHLOROPHYLL*

R. B. WOODWARD

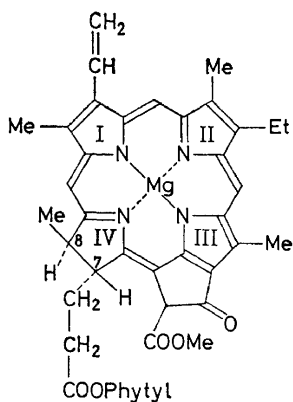
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Chlorophyll *a*, the major green pigment of the plant world, is certainly the most widespread and conspicuous of organic natural products. Few can be unaware of its decorative function, and all are beneficiaries of its central role in transforming 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 1920s. Stoll, who had played a prominent rôle in the early studies as a collaborator of Willstätter, took up the work anew, and made important contributions, as did Conant in the United States. 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 of the number and disposition of saturated carbon atoms within the nuclear framework. Half a century of structural study had culminated in the complete formula (I) for chlorophyll *a*^{1, 2}.

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

* A brief communication recording the results on which this lecture is based has appeared in *J. Am. Chem. Soc.*, **82**, 3800 (1960).

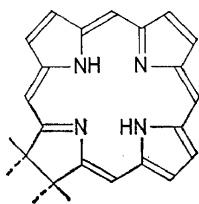
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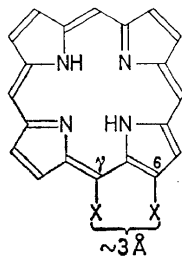
(I)

elements of theory played any role in the whole vast study. Neither was succour or 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 scepticism, and whose resolution was of importance in our subsequent planning.

Let us first consider an unusual feature of the structure (I), namely, the saturated carbon atoms at positions 7 and 8, with the attached, so-called "extra", hydrogen atoms which give chlorophyll its position as a member of the general class of green substances known as chlorins (II). Chlorins in turn are derivatives of the simpler, more electronically symmetrical, fully aromatic red porphyrins (III). It is well known that simple chlorins, as might be expected, are readily oxidizable to porphyrins. Not so chlorophyll itself, and many of the chlorins derived from the plant pigment. Surprisingly,



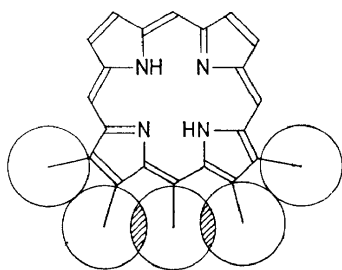
(II)



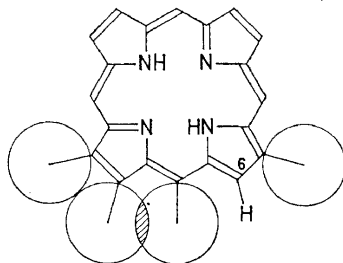
(III)

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these substances are deprived of the extra hydrogen atoms only with considerable difficulty. A second point which claimed our attention was the presence in the structure (I) of the carbocyclic 5-membered ring fused to the pyrroloid ring III of the nucleus. While no direct measurements have been made of the atomic parameters of any porphyrin or chlorin, it is possible to surmise with some confidence that groups attached at the 6- and γ -positions of those nuclei will be at a remove of some 3 Å (see III). Consequently, the formation of a bond which joins substituents in those positions must involve considerable distortion, with much resultant strain. The presence of strained systems within the molecules of substances of natural origin need not, of course, present an occasion for surprise, and indeed chlorophyll undergoes very ready changes which are interpreted as involving the opening of the carbocyclic ring. But the ring can be closed again with much ease, particularly so in the porphyrin series. Finally, mention may be made of the fact that porphyrins and chlorins containing substituents at the γ -position, and a carboxyl group at C-6, lose carbon dioxide with ease, while, by contrast, the γ -unsubstituted analogues are resistant to decarboxylation. All of these observations baffled us for some time, until they received a very simple rationalization in terms of the principle that two things cannot take up the same space at the same time. Thus, the lower periphery of porphyrins derived from chlorophyll is heavily laden with substituents—so much so that there is not room for all of them without considerable distortion of bond angles or lengths (see IV). Consequently, all of these molecules will be strained. If now we examine the possibilities for

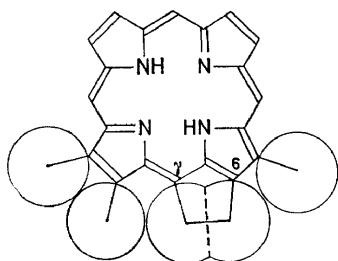


(IV)

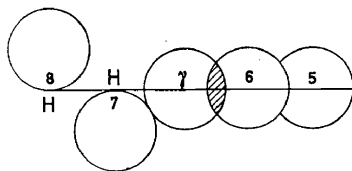


(V)

the relief of steric compressions in these systems, we find that the phenomena set down above are readily explicable. The ready decarboxylation of the highly substituted acids is a consequence of the extrusion of the elements of carbon dioxide from a site at which there is not enough room for them (see V), and the cyclization to 5-membered ring compounds may be viewed, in an unsophisticated but valid manner, as a process in which the atoms involved are literally pushed into union (see VI). Finally, it is clear that the removal of the hydrogen atoms from C-7 and C-8 of a chlorin substituted at those positions, accompanied, as it must be, by the transformation of those carbon atoms from the tetrahedral to the trigonal condition, will exacerbate steric compressions, particularly when the γ -position is also substituted. Conversely, we recognize that *there is a strong natural factor in such heavily substituted porphyrins which favours the transformation of trigonal*



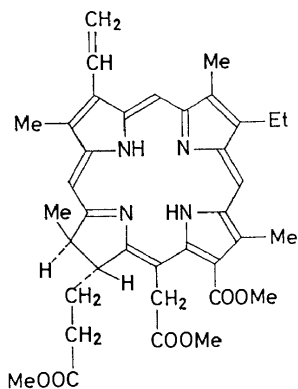
(VI)



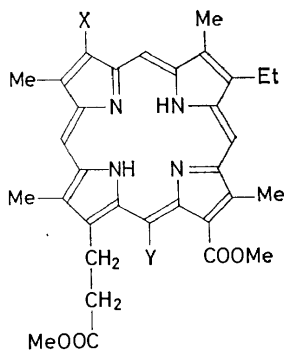
(VII)

peripheral atoms into tetrahedral ones (see VII). These simple but powerful considerations not only assuaged much of our doubt about the structure of chlorophyll, and permitted us to plan a synthetic attack with reasonable confidence that our objective had been correctly defined, but also provided the basis for our first major decision of policy. Thus, that portion of the chlorophyll molecule containing the extra hydrogen atoms must have seemed to any who might have contemplated the problem of synthesizing chlorophyll one of the most formidable obstacles to be surmounted. We decided that the inherent factors favouring the attainment of the saturated condition by C-7 and C-8 in heavily substituted porphyrins permitted us to pay little heed to that problem in the first stages of our investigation. We had in mind such possibilities as that hydrogen atoms, suitably coaxed, might well wander to the desired positions from another site in a suitably constructed porphyrin molecule. How far this general presumption was justified will become clear in the sequel. In any event, we turned our attention first to the development of a new porphyrin synthesis.

In order to define further our primary objective, we should point out at this time that, as is often the case in the study of complicated natural products, our problem had in some measure been simplified by earlier studies. The central magnesium atom of the chlorophyll molecule is easily removed by acids, and readily put back through the agency of basic magnesium halides. The phytol grouping of the molecule can be removed by hydrolysis, and



(VIII)

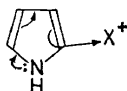


(IX)

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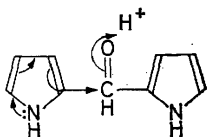
can be replaced smoothly, either by chemical or enzymatic means. Finally, the carbocyclic 5-membered ring can be cleaved or re-closed at will. That is to say, the product of all three changes—chlorin e_6 (trimethyl ester) (VIII), key substance in chlorophyll chemistry—can be converted into chlorophyll a itself by a short series of simple and well-known changes, and consequently it was chlorin e_6 which was our actual synthetic objective. The substitution pattern of the chlorin e_6 molecule is, to a considerable extent, simple, and led us to presume that we must devise a synthesis of a porphyrin of the structure (IX).

Now, the porphyrin syntheses of an earlier day, magnificent for their time, were most ill-suited to our purpose. Carried out under bold but brutal conditions, they led in almost all cases to very complicated mixtures of porphyrins, in small, frequently microscopic, yields. The structures of the substances produced could seldom be assigned with confidence on the

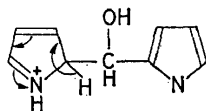


(X)

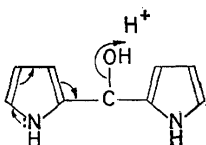
basis of a single synthesis, and the conditions were such that electronegative and other reactive substituents, and γ -substituents of any kind, survived only in part, if at all. By contrast, we required a method which would lead in high yield to a single product of known structure, containing substituent groups of variegated character—for we were well aware that we might have some distance to go after this primary objective had been achieved. The principle on which our projected method was based may be introduced through recollection of the great sensitivity of simple pyrroles to attack, at the α -position, by electron-deficient centres (see X, arrows). One of the best-known of such reactions is that in which a pyrrole with a free α -position



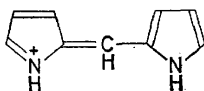
(XI)



(XII)

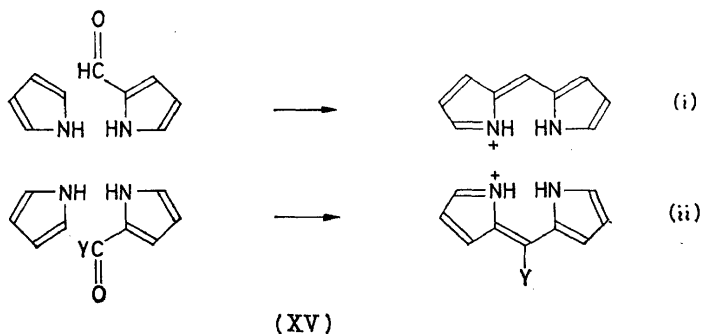


(XIII)

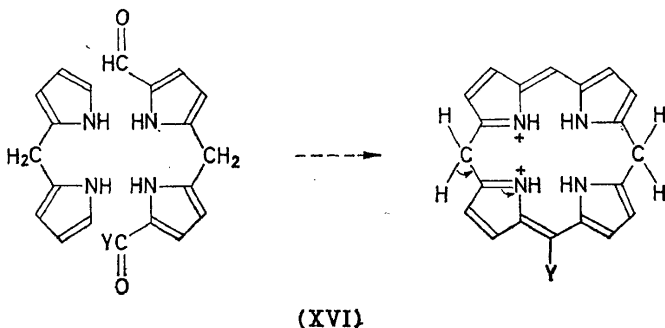


(XIV)

combines with a pyrrole α -aldehyde in the presence of acid to give a dipyrromethene (XI \rightarrow XII \rightarrow XIII \rightarrow XIV). This combination takes place with extraordinary readiness—frequently it proceeds rapidly even at temperatures far below the freezing point—and although it is usually necessary to define the best conditions in any individual case by extensive experimentation, the reaction can ordinarily be coaxed into giving a fairly high yield of the condensation product. The reaction can be brought about not only with pyrrole aldehydes (XV, i), but also, with only somewhat greater difficulty, with pyrrol ketones (XV, ii). We supposed that, if the components in

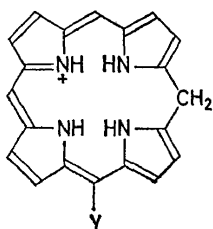


these separate schemes could be united in pairs, a condensation between molecules so constructed might permit the ready elaboration of the ring system present in the porphyrins (see XVI). We realized that the double dipyrromethene system shown as the possible proximate product of such a

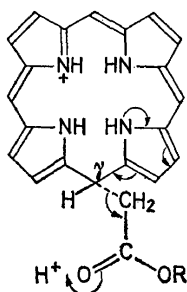


reaction was unlikely to remain as such, and considered that that doubly charged species might well readily lose a proton (XVI, *arrows*) to give a material containing the system (XVII), which should be capable of considerable charge resonance stabilization, with its single positive charge distributed over all four nitrogen atoms. Further, if such a cation were capable of tautomerization to (XVIII), we can foresee the possibility of the ready loss of an acetic acid chain from the γ -position (XVIII, *arrows*), with conversion of the nucleus to a fully aromatic porphyrin salt system (XIX). On these grounds we deemed it unwise to choose as our objective a porphyrin substituted in the γ -position by the acetic acid chain which chlorin e_6 contains in the corresponding position, and chose instead a β -propionic acid chain for that site; such a chain would not be susceptible to extrusion,

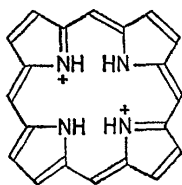
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(XVII)

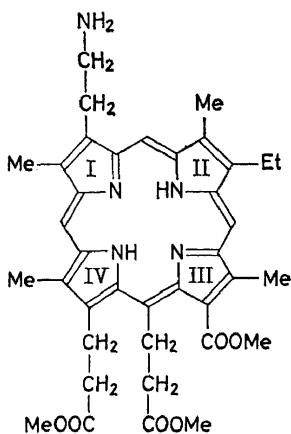


(XVIII)

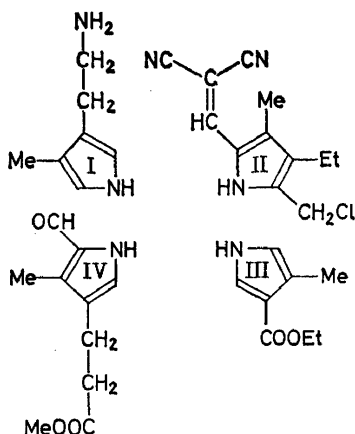


(XIX)

it offered manifold possibilities for transformation to the acetic chain ultimately desired, and it seemed a plausible candidate for utility in chlorin-forming sequences. Further, we considered it unlikely that a highly reactive and sensitive vinyl group could be carried through any considerable sequence of reactions without complication, and chose as a precursor for such a group a β -aminoethyl function, the elimination of whose nitrogen at an appropriate stage might accomplish our objective. The porphyrin we desired to synthesize had now been fully specified as (XX), and it defined our basic building blocks, in the sense of the four relatively simple monocyclic pyrroles shown in (XXI). The preparation of these substances,

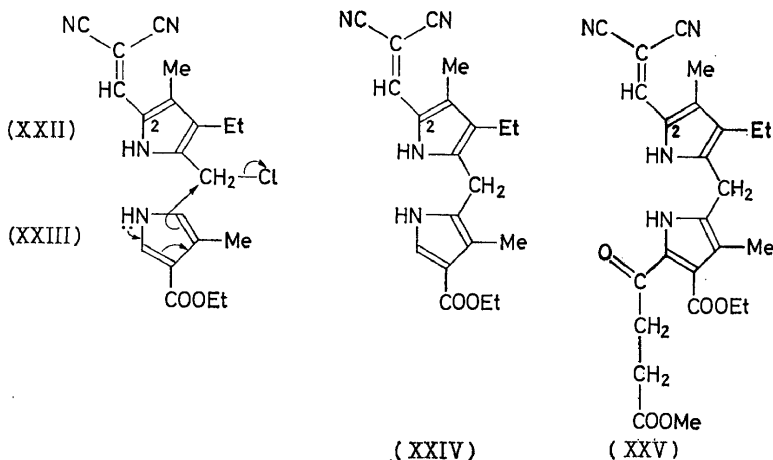


(XX)



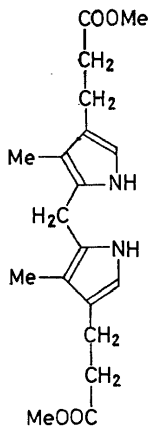
(XXI)

though arduous, need not concern us here; two were made by known methods², with some practical modifications, and the others were prepared from known compounds³ through short new sequences. Once they were in hand, we proceeded to combine them in pairs. In the first instance, the dicyanovinyl compound (XXII) was condensed with the ring III component (XXIII) in hot aqueous ethanolic hydrochloric acid (see XXII and XXIII, *arrows*) to give the dipyrrylmethane (XXIV). It may be noted that 3-methyl-4-carbomethoxy-pyrrole (XXIII) has two free α -positions, and

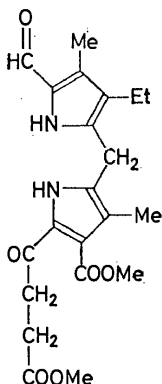


that condensation consequently might, *a priori*, lead to two differently substituted dipyrrylmethanes. However, we could assume with confidence that the condensation had taken the desired course, for steric and electronic reasons alike. Thus, the electron-withdrawing carbomethoxy group deactivates the adjacent α -position for attack by an electron-deficient centre. By contrast, the electron-releasing methyl group activates the proximate position, and is at the same time the smaller group. Though relatively less susceptible to attack, for the reasons just outlined, the single free α -position in the dipyrrylmethane (XXIV) can fortunately be coaxied into reaction, and our next step was to condense that methane with β -carbomethoxypropionyl chloride through the agency of anhydrous zinc chloride. It will have been observed that the dicyanovinyl grouping in the resulting (XXV) has served the function of a concealed, relatively unreactive, acid-stable surrogate for the aldehyde group actually desired at C-2; the protecting group was now removed by the action of hot 33 per cent aqueous sodium hydroxide. After re-esterification of the carboxyl groups, both of which were freed under the very vigorous basic conditions of the cleavage reaction, the desired dicarbonyl compound (XXVII) was obtained. This substance seemed in itself a suitable right-hand component for our projected porphyrin synthesis, and the scheme was forthwith put to the test, with the readily available symmetrical dipyrrylmethane (XXVI) as the second, left-hand component. We were pleased to find even in initial experiments that when (XXVI) and (XXVII) were condensed in the presence of acidic reagents under mild conditions, reaction mixtures were obtained, from

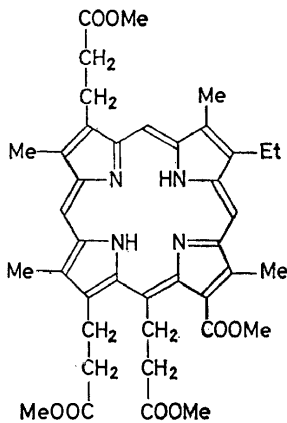
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(XXVI)

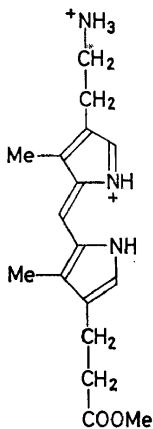
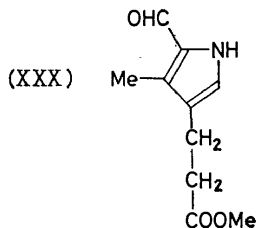
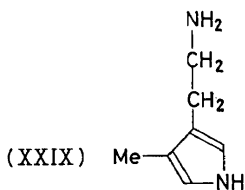


(XXVII)

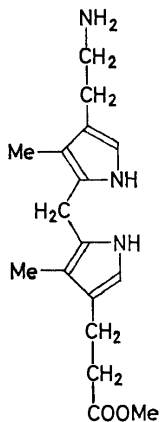


(XXVIII)

which, after oxidation with iodine, small amounts of porphyrin were formed, and more so to succeed, after assiduous variation of experimental conditions, in preparing the porphyrin (XXVIII) in the pure condition in a yield approaching 25 per cent. By any previous standard, this result approached the fabulous, but we knew that for our purpose it was still far from satisfactory. Let us consider the use, in such a reaction, of the actual left-hand component (XXXII) we had in mind. This substance was readily prepared by reduction of the dipyrromethene (XXXI), itself obtained by condensation of the aldehyde (XXX) with the aminoethyl pyrrole



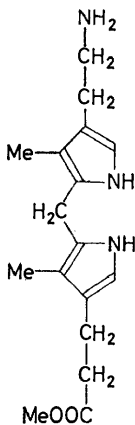
(XXXI)



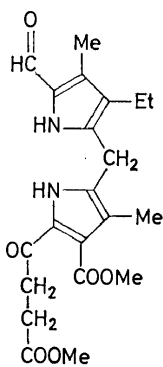
(XXXII)

(XXIX). We may note again that two products might have been formed in this condensation, but in fact only the desired dipyrromethene (XXXI) was produced, no doubt largely in consequence of the relatively small bulk

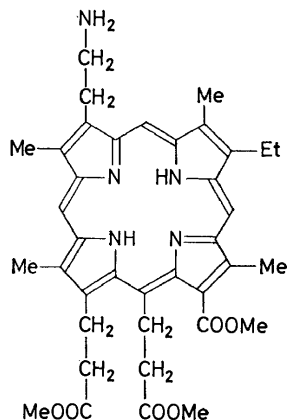
of the methyl group, but perhaps partly as a result of some electron withdrawal by the positively charged ethylammonium function. Now the new dipyrromethane (XXXIII) may be expected to, and in fact does, condense with the keto-aldehyde (XXXIV) to give, after the appropriate secondary treatment, the porphyrin (XXXV). But there is no reason to suppose that the components in this condensation will line up obligingly in that



(XXXIII)

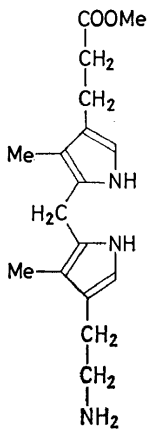


(XXXIV)

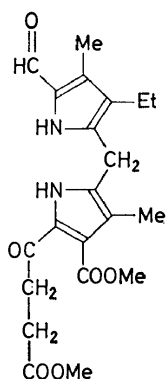


(XXXV)

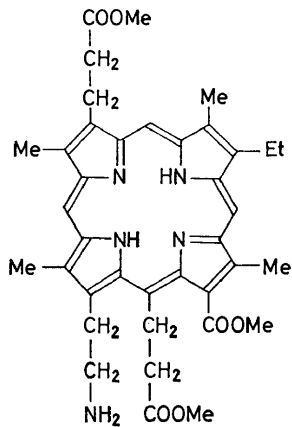
juxtaposition alone which leads to the desired product—nor do they. At the same time condensation takes place in the alternative sense (XXXVI + XXXVII), to produce a comparable amount of the isomeric porphyrin



(XXXVI)



(XXXVII)

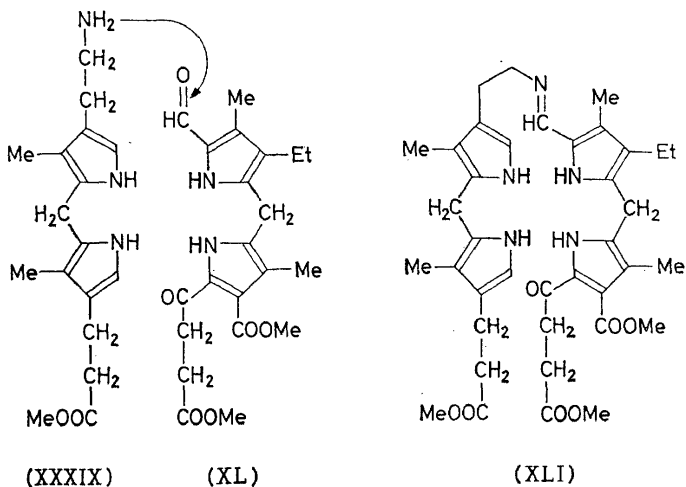


(XXXVIII)

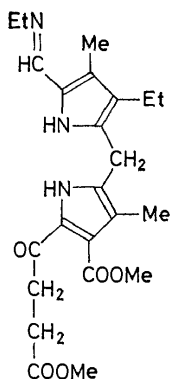
(XXXVIII). Although the combined yield of the two porphyrins was not far below that which could be achieved in the simpler case, the amount of product useful for our purposes was severely curtailed. And how were we to ascertain which of the porphyrins obtained was that of the desired structure? Such inelegance, not to say impracticality, could not be

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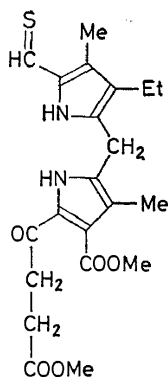
tolerated. Our plan for expunging it was simple in principle. We reasoned that a preliminary condensation between the aldehyde group of the right-hand component (XL) and the amino group of the left-hand component (XXXIX) might lead to a Schiff base of the structure (XLI), whose moieties



are held in a fixed relationship which would permit of no subsequent condensation other than that leading to a single product of the desired structure. The simplicity of this principle was by no means mirrored in a comparable ease of its reduction to practice. Indeed, its successful application required a long period of exacting and toilsome experimentation. First, it was found that pyrrole α -aldehydes, no doubt in consequence of interaction between the carbonyl group and the unshared electron pair on nitrogen, are relatively unreactive and do not condense with amines to give Schiff bases except under conditions of acid catalysis. We found that the aldehyde (XL) and other like substances could be brought into reaction with amines under acidic conditions as mild as those involving the use of a single molar proportion of triethylammonium acetate as catalyst in an inert solvent. But, dipyrromethanes such as (XXXIX), bearing only alkyl substituents, are diabolically sensitive compounds. They are torn to shreds and otherwise disastrously transmogrified in the presence of acidic reagents—even under the mildest conditions which we were able to define as necessary for Schiff-base formation. These circumstances conspired to yield a very clear-cut result in all of our early (and not so early) attempts to bring about our directed two-stage porphyrin synthesis—namely, not the slightest trace of porphyrin was obtained! Clearly, it was not possible to effect the desired preliminary reaction without rendering the left-hand moiety useless for the necessary subsequent changes. We did, however, in the course of these experiments, discover that the aldehyde (XL) was very smoothly converted, by ethylamine in the presence of acetic acid, into the simple Schiff base (XLII). Our next assault involved attempts to bring about the preliminary union of (XLII) with the left-hand component (XXXIX) by an amine-exchange reaction. These experiments showed some promise, and might

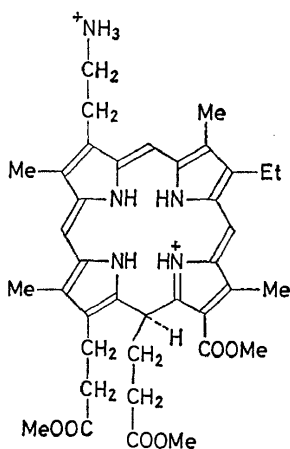


(XLII)



(XLIII)

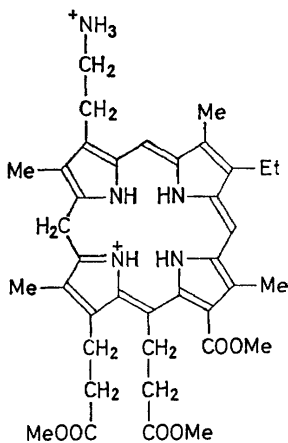
with considerable further expenditure of effort have been driven to a point at which they would provide a basis for a moderately satisfactory result, but they were rendered obsolete by the discovery that the *N*-ethylimino compound (XLII) could be converted smoothly, by hydrogen sulphide in benzene/methanol, to the thioaldehyde (XLIII). The latter was found to undergo extremely rapid condensation with primary amines in inert solvents, without necessity for catalysis. It was now no more than a matter of prolonged diligent experimentation to develop an entirely satisfactory method for the preparation of the extraordinarily sensitive Schiff base (XLI). The dipyrromethene (XXXI) is reduced in aqueous solution with a large excess of sodium borohydride, and the resulting dipyrrylmethane (XXXII) is extracted immediately into methylene chloride and treated at once with an equivalent amount of the thioaldehyde (XLIII). The methylene chloride solution is evaporated immediately, and the resulting Schiff base



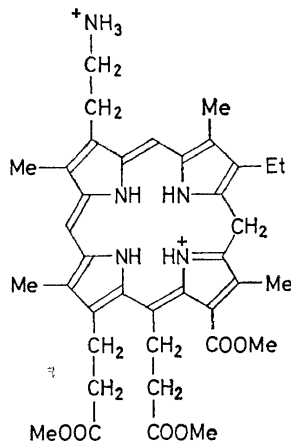
(XLIV)

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(XLI) is introduced without delay into saturated methanolic hydrogen chloride at room temperature. The acid treatment of the Schiff base brings about a rapid and smooth conversion to the cation (XLIV), which we were able to isolate in the crystalline state as the dibromide. It is clear that the formation of the cation must proceed through several stages. Spectroscopic examination of the course of the reaction has provided evidence that a different, but similarly constituted, cation is first produced, and there is every reason to suppose that an initially formed bis(dipyrromethene) (see XVI) is immediately deprotonated to give either or both of the cations (XLV) and (XLVI). Tautomerization then leads to the more

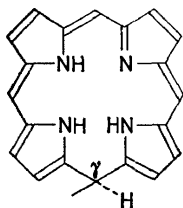


(XLV)



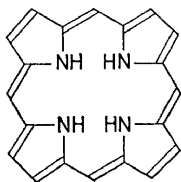
(XLVI)

stable isolable cation (XLIV); it is worthy of note that we see here, for the first time in our synthetic experiments, the operation of the steric compression factors which we discussed at some length earlier. The cation (XLIV) is a representative, in the salt form, of an entirely new class of substances. First found in the experiments just described, it will be encountered again in the sequel, and indeed we may mention further that we have prepared members of the class in several different ways. We feel certain that these substances will play a sufficiently important rôle in the future to justify their being given a class name, and we here designate compounds of the structure (XLVII) as *phlorins*. Phlorins give bright pure blue solutions in organic solvents, while similar solutions of the corresponding

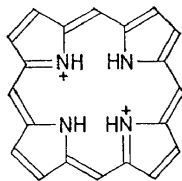


(XLVII)

salts are green. Except in one respect, the phlorin salts are remarkably stable substances. They can be kept in solution in concentrated sulphuric acid for long periods of time without change, and survive treatment in acidic or neutral solvents at elevated temperatures for extended periods. The one sense in which they show instability lies in the great ease with which they are converted to porphyrins by oxidizing agents, such as oxygen, chloranil, or the halogens. It is interesting to speculate that the phlorin salts might be deprotonated, from carbon, to give an isophlorin of the structure (XLVIII); that fascinating array contains a continuous cyclic conjugated system, but it is one containing 20 π -electrons ($\neq 4n + 2$), and it might be considered reasonable for it to lose two electrons with ease, to

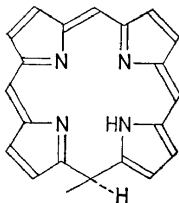


(XLVIII)

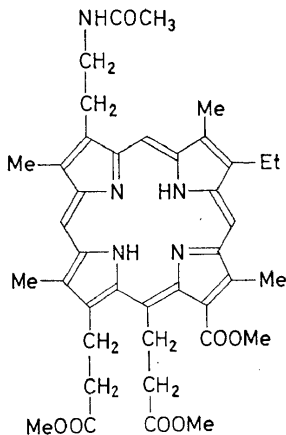


(XLIX)

give directly the porphyrin double salt (XLIX). Of course, it is also possible—and perhaps in acidic media more likely—that the oxidation involves direct attack of the oxidant upon the γ -hydrogen atom, or dehydrogenation of the true phlorin (XLVII) to an isoporphyrin (L). The latter species has not hitherto been encountered, or postulated, but we



(L)



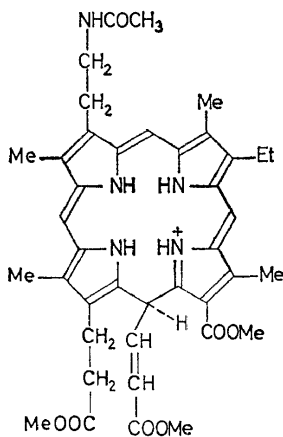
(LI)

hazard the opinion that it will be found to play a role in some base-catalysed reactions of the porphyrins.

To return now to the central topic of porphyrin synthesis, we found, in practice, that it was not desirable to isolate the intermediary cation (XLIV). Rather, the acid condensation reaction mixture was treated directly with excess iodine to effect oxidation; further, to facilitate isolation, the resulting

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porphyrin was acetylated directly with acetic anhydride in pyridine. After this sequence, the porphyrin (LI) could be isolated in the pure crystalline condition in an overall yield of 50 per cent from the components (XXXI) and (XLIII), introduced at the beginning of the series of five reactions. Moreover, no other porphyrin was produced as a contaminant. After our description of the development of the method, it will come as no surprise that the experimental protocol for the sequence is exacting in the extreme; but to place the method in perspective, we may point out that our experience has demonstrated time and again that a skilful, patient and knowledgeable investigator can prepare the porphyrin (LI), almost a gramme at a time, in a precisely reproducible manner, and that during the course of our investigations, we have prepared upwards of 50 g of that substance. It is of some interest that the reactions are not carried out under conditions of high dilution, and that what might have been regarded as a formidable problem—the closure of a sixteen-membered ring—in fact presents no occasion for difficulty. No doubt the considerable elements of rigidity in the backbone of the open-chain precursor render the ring-formation reaction essentially comparable with that of a five- or six-membered ring from simpler progenitors.

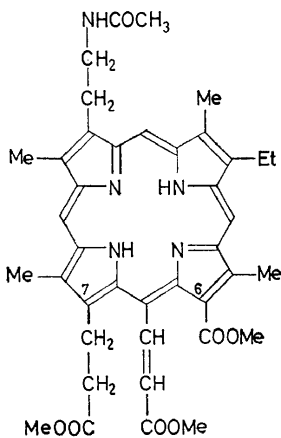


(LII)

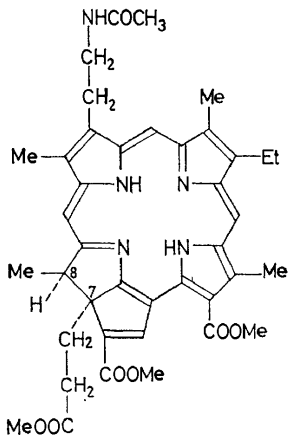
We turn now to the second major phase of our investigation. With the porphyrin synthesis well in hand, we had to come to grips with the problem of introducing the extra hydrogen atoms—those at positions 7 and 8 in chlorin *e*₆. It will be recalled that we considered in our planning the possibility that hydrogen atoms might be induced to wander to the desired positions from another site in a suitably constructed porphyrin. Were (LI) such a suitably constructed porphyrin, it was now time for the wandering to begin—and begin it did—though it stopped short of our desire! When the porphyrin (LI) was heated in acetic acid for a short time in the absence of air, a reaction mixture was obtained whose spectrum we recognized at once. It was that of a phlorin salt, and it soon became clear that the porphyrin had suffered ready acid-catalysed conversion to (LII). No doubt

we see here again the operation of the important steric factors to which we have repeatedly alluded; the formation of the phlorin salt is certainly assisted by the accompanying relief of strain, as the γ -carbon atom becomes tetrahedral, and the large attached chain is removed from the crowded molecular plane. Now it is easily possible to conceive of a plausible series of protonations and deprotonations which would provide a path for the conversion of phlorins into the isomeric chlorins. We have not as yet been able to realize this change. It is tempting to conclude that the great stability of the phlorin salts gives them a preferred position in any possible equilibrium with corresponding chlorins. But we regard that conclusion as premature. As far as we can say at present, it is quite as likely that at some point there is a high barrier between the two classes which we have not yet been able to surmount.

Like other phlorin salts, (LII) is readily oxidized by air, and, in consequence, when the porphyrin (LI) was warmed in acetic acid for a short while on the steam bath, without exclusion of air, it was converted quantitatively into the new porphyrin (LIII). When the latter, in its turn, was heated in acetic acid, for thirty hours at 110° under nitrogen, it was smoothly



(LIII)

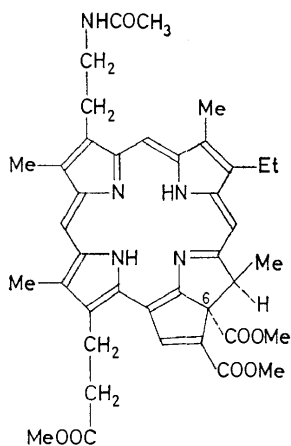


(LIV)

equilibrated with the purpurin (LIV) (purpurins are members of a sub-class of chlorins; the introduction of unsaturated substituents into the γ -position of the chlorin system frequently results in a change from the normal green to a purplish hue). *This remarkable reaction represents the first instance ever observed of reversible interconversion of a porphyrin and a chlorin.* Now we had come full circle! At the outset of our investigations we viewed the presence of a fused five-membered carbocyclic ring in the proposed formula for chlorophyll as a basis for suspicion of that formula, but were able to rationalize the difficulty on simple but cogent steric grounds. And here at this point in our work we encountered the smooth closure of a not dissimilar ring, in a process which must certainly be driven forward by just the same factors of steric compression which we discerned so much earlier. For it is not

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difficult to conceive of a path which permits the interconversion of our porphyrin and our purpurin, but it may be doubted that the purpurin would predominate as much as it does in the equilibrium between the two substances were its ring not forced shut by the crowding in the highly substituted porphyrin. In fact, the equilibrium constant is 5:3 in favour of the purpurin, and since the equilibrium is cleanly established, it is possible, through recycling, to effect the preparation of the purpurin (LIV) from its precursor in almost 70 per cent yield. A second point relevant to this equilibrium is of great moment. Why does the reaction proceed in the sense indicated, rather than to give the alternative product (LV), by a similar cyclization involving formation of a new bond to C-6? It is of

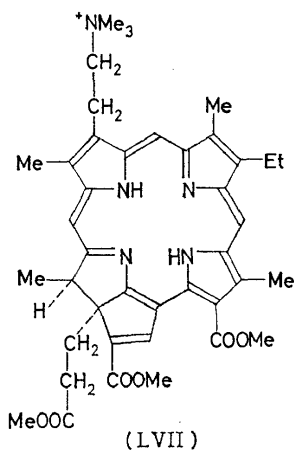
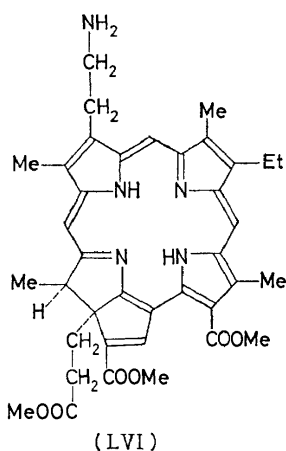


(LV)

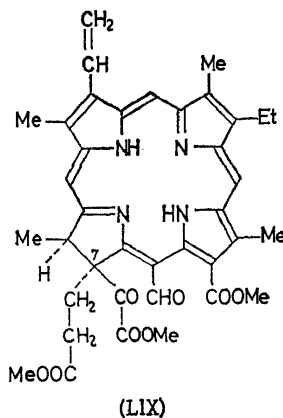
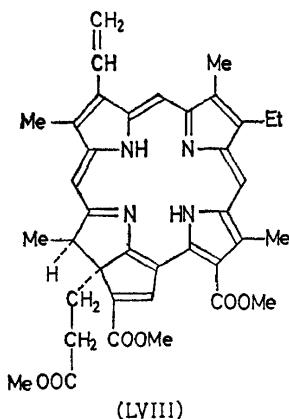
much interest that (LV) is, in fact, a very minor participant in the equilibrium system; it too has been isolated and characterized, and its properties leave no doubt about its relationship to (LIV). It will be noted that, in the formation of (LV), the carbomethoxy group at C-6 is removed from conjugation, while no such adverse factor is involved in the formation of the major product (LIV). Further, it may be suspected that the difficult steric situation in the porphyrin (LIII) is more effectively relieved by the changes leading to (LIV) than by those which give (LV). Finally, we should take note of the fact that the stereochemistry of our purpurin may be adopted with confidence as written, since in an equilibrium process the more stable of two possible stereoisomers will be formed; there can be no doubt that (LIV) represents a more stable arrangement than that in an isomeric substance whose methyl and propionic ester groups, at C-8 and C-7 respectively, are on the same side of the molecular plane.

In the purpurin (LIV), our task of placing hydrogen atoms at C-7 and C-8 was half done, in that one of the two needed had been placed at C-8. Further, we should emphasize that the method of its placement is a most satisfying one in that it is structurally significant—that is, the reaction involved is one which can place the atom in question only at the desired position and no other. It was now necessary to consider the removal, and

replacement by another hydrogen atom, of the platform from which the first was delivered. But first a simple but important change elsewhere in the molecule should be described. The acetyl-amino-group of the purpurin (LVII) was readily hydrolysed, by hot 1*N* methanolic hydrogen chloride, and when the resulting amino-compound (LVI) was treated with excess of methyl sulphate and methanolic sodium hydroxide, the vinyl purpurin (LVIII) was produced directly in high yield. Clearly, the intermediary trimethylammonium compound (LVII) not surprisingly, suffers very ready



Hofmann elimination. Now the new purpurin (LVIII) was found to be susceptible to a most extraordinary and useful change. When it was illuminated strongly with visible light, in the presence of air, it was rapidly and smoothly transformed into the keto-aldehyde (LIX). It should be

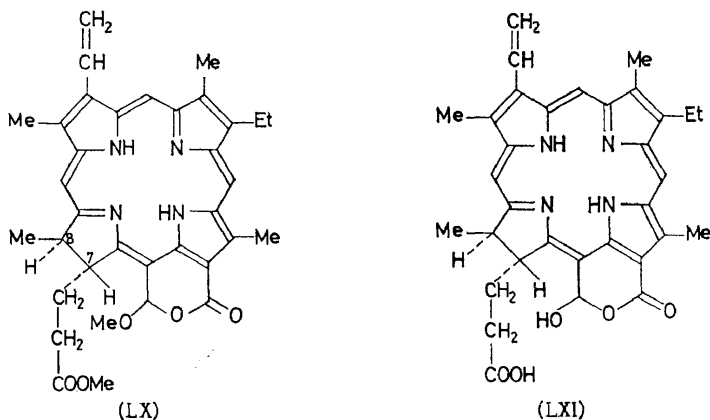


noted that the reaction is highly selective, in that neither the chlorin ring system nor the attached vinyl group is attacked in the slightest degree. It is quite possible that the strain within the five-membered ring of (LVIII) is a factor in bringing about this high selectivity, but we suspect that special

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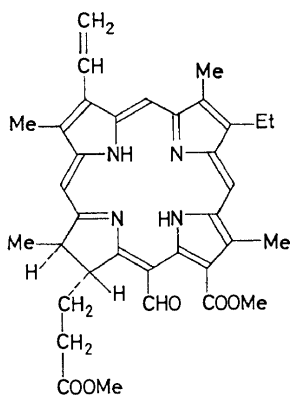
electronic factors beyond our present powers of delineation may be involved at least in equal measure. In any event, it may be regarded as singularly appropriate that a photochemical reaction should play a prominent role in the synthesis of chlorophyll.

The methoxalyl group at C-7 in the purpurin (LIX) is so placed that it may be expected to suffer ready cleavage from the nucleus to which it is attached by basic reagents. And indeed, when (LIX) was treated with dilute methanolic potash, the anticipated change did occur. At the same time, independently, the base attacked the aldehyde group in an entirely predictable manner, and the product of the reaction was the methoxylactone (LXI). The latter is the racemic form of a known substance,

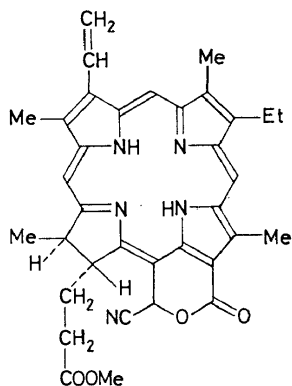


isopurpurin 5 methyl ester, which was prepared⁴ many years ago—though formulated in a different, incorrect, manner—in Fischer's laboratory, by degradation of chlorophyll. Consequently, at this point we were able, for the first time, to establish a connection with natural materials; the quantitative infra-red spectra in solution, and the visible spectra of the synthetic racemic ester and the corresponding optically active material of natural provenance were identical in every respect. It is of importance to note that the method of synthesis of isopurpurin 5 methyl ester confirms the *trans* disposition of the hydrogen atoms at C-7 and C-8. For, in addition to the normal preference for retention of configuration in electrophilic displacements at carbon, there is in the case at hand the added factor that inversion at C-7 would involve passage of the propionic ester chain at C-7 through a molecular plane much crowded by the substituents in the γ -position.

When the synthetic isopurpurin 5 methyl ester was hydrolysed with very dilute sodium hydroxide in dioxane/water, it was transformed into racemic chlorin 5 (LXI), which was then converted into a mixture of the corresponding diastereomeric quinine salts. The resolution of the mixture was not especially easy, since both salts crystallized, but, when the proper conditions had been defined, it proceeded with high efficiency. One of the salts so obtained was identical in every respect with a similar substance prepared from natural materials, as was the chlorin 5 regenerated from it⁵.



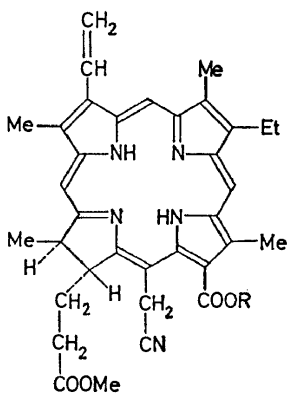
(LXII)



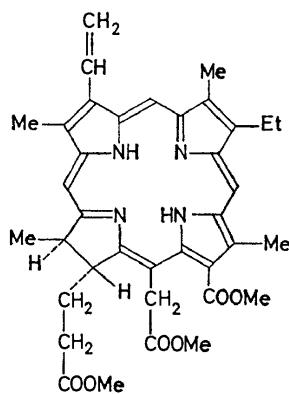
(LXIII)

Further, when the resolved chlorin 5 was treated with diazomethane, it was converted to totally synthetic optically active purpurin 5 dimethyl ester (LXII), which was identical in all details with a sample of natural origin⁶.

When purpurin 5 dimethyl ester (LXII) was treated briefly with hydrogen cyanide in dichloromethane in the presence of triethylamine, it was converted in very high yield into the cyanolactone (LXIII)⁷. The lactone, treated for a very short time with zinc and acetic acid, was reduced to the acid (LXIV, R = H), which, with diazomethane, gave the ester (LXIV, R = Me). Treatment of the latter with methanolic hydrogen chloride at room temperature resulted in methanolysis of the nitrile group, and chlorin *e*₆ trimethyl ester (LXV ≡ VIII), identical in every detail with an authentic sample, was obtained. Our objective had now been reached, and the total synthesis of chlorophyll *a* was complete, since, as we have mentioned earlier, the short path from chlorin *e*₆ back to the chlorophyll *a*, from which the key intermediate is readily obtainable, had been laid down in the early work of Willstätter and Hans Fischer¹. Thus, Dieckmann cyclization of the ester under the influence of sodium methoxide gives methyl phaeophorbide *a* (LXVI, R = Me), one of whose methyl ester groups can be

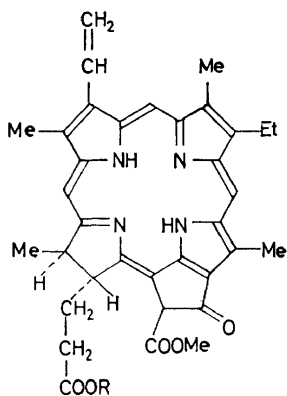


(LXIV)

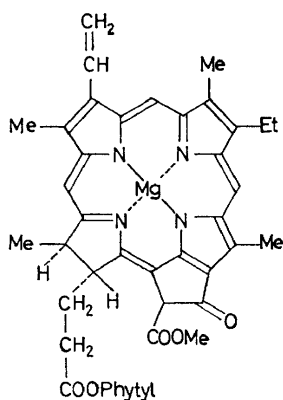


(LXV)

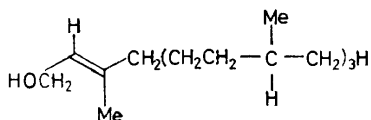
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(LXVI)



(LXVII)



(LXVIII)

replaced by a phytyl group, either by chemical or enzymatic means. Then, the magnesium atom may be introduced into the resulting phaeophytin *a* (LXVI, R = Phytyl), through the agency of basic magnesium halides, to give chlorophyll *a* itself (LXVII \equiv I). We should not neglect to acknowledge at this point the contribution of Burrell, Jackman, and Weedon, who only last year established the stereochemistry of, and synthesized, optically active phytol⁸ (LXVIII), which, though its rôle in the chemistry of chlorophyll is minor, is none the less an integral part of the complete molecule.

Now that the synthetic 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. 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. 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 dipyrromethane 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. Finally, all of us wish to express our warm appreciation to the National Institutes of Health, the National Science Foundation, and Research Corporation for generous support, to Chas. Pfizer and Co., Inc., for support and invaluable assistance in the preparation of primary intermediates in quantity, to Professor Dr Arthur Stoll and Sandoz A.G. for a handsome gift of methyl phaeophorbide *a*, and to Drs Stephan Sallay and Wolfgang H. F. Sasse for their co-operation in certain phases of our work.

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