Following the isolation and elucidation of the structure of a natural compound there remain two additional goals: total synthesis and last, but not least, a deeper understanding of the molecule at hand by means of a closer study.

Chlorophyll, the green pigment of the plant kingdom, being in the first instance responsible for transforming light energy into chemical reactivity with the ultimate production of starch, and haeme, the red blood pigment which secures the transport of oxygen for maintaining respiration, have aroused the interest of scientists for more than 100 years. The names of Borodin, Willstätter, H. Fischer, Stoll, Conant, Linstead, and others are associated with isolation, structural problems, and a vast amount of primary chemical knowledge in this field. Woodward and his team achieved the enormous task of the total synthesis of chlorophyll a in 1960. And lately the final question of stereochemistry at the carbons 7 and 8 has been settled by Fleming.

For about 10 years scientists have tried with renewed intensity to learn more about this fascinating compound, naturally with the help of modern chemical and physical methods. To understand better the properties of chlorophyll and its derivatives a closer knowledge of its conjugated electron system seems important.

As can be seen from its structure chlorophyll is (I) the magnesium complex of a tetrapyrrolic macrocycle is held together by 4 methine bridges, the 8-peripheral carbons being substituted in different ways, and the conjugated electron-system being responsible for the green colour and its rather complex chemical and physical behaviour. The tetrahedral carbon atoms 7 and 8
are a most important feature of all chlorins, the name given to all members of the chlorophyll family. These so called "extra hydrogens" at 7 and 8 are responsible for the far reaching chemical difference of the chlorins to the fully aromatic porphyrin group which will be discussed more fully later. Protochlorophyll, dehydrogenated between carbon atoms 7 and 8 and therefore being a porphyrin, is an important precursor on the biochemical pathway to chlorophyll a. Addition and substitution reactions at the periphery were hitherto regarded as a good line for study. In connection with this more general aspect, two special partial synthetic problems emerged: First, how to convert chlorophyll a (I, R = Me) into chlorophyll b (I, R = CHO), which is a constant companion of chlorophyll a in green leaves, and differs only in having an aldehyde group in place of a methyl at position 3. Second, how to produce the interesting bacteriochlorophyll (II), the photosynthetic pigment of the purple bacteria, which is additionally hydrogenated at positions 3 and 4 in ring B, just opposite to the saturated carbon atoms 7 and 8 of ring D. Furthermore, there is in bacteriochlorophyll in position 2 instead of the normal vinyl group an acetyl group, but in all other respects this molecule is identical with chlorophyll a. Bacteriochlorophyll therefore is, according to the work of Hans Fischer, the magnesium complex of 2-desvinyl-2-acetyl-3,4-dihydrochlorophyll a, esterifed with phytol and

![Diagram](II)

methanol. It is easy to dehydrogenate bacteriochlorins to chlorins, but the reverse process viz. the transformation of chlorins to bacteriochlorins through hydrogenation has not yet been achieved. This raises the problem of saturation of the 3,4-double bond of the intricate electron system of chlorophyll a. In chemical language this means that we want to learn how certain peripheral double bonds can be brought into reaction selectively. We have hydrogenation primarily in mind but addition of oxygen or hydroxy groups are also regarded as attractive targets.

Finally, it should be possible to attack certain alkyl groups and methine carbons both in chlorins and porphyrins with the introduction of oxygen to form carbonyl groups. Central to all these questions stands the problems of the influence of the complexed metal on the chemical behaviour of the peripheral double bond system. Mg, Fe, Co, V, and Cu are used by nature; we have added to these Zn, Ni, Al and Sn. In fact a new line of our research
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has been started by Buchler, who is trying, starting from the central metals electronic situation, to work through to the periphery by chemical, physical and theoretical means.

In chlorin e₈-TME (TME = trimethylester) (III), prepared from chlorophyll a by known and easy reactions, the vinyl is replaced by an acetyl group as in bacteriochlorophyll. In attempting to hydrogenate the 3,4-double bond Jäger has concentrated on one special method: electrochemical reduction. It was quickly found that chlorins can be reduced polarographically and that they show at —0.5 volt under slightly acidic conditions only one polarographic step.

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The reduction products prepared from chlorins by controlled potential electrolysis are dihydrochlorins, and further chemical as well as physical data proved that in our case, and in more cases of the same type, only one dihydro compound is formed.

The electronic spectra of the reduction products are entirely different from those of the initial chlorins. The Soret band has disappeared and there is merely a broad band between 480 and 560 nm. This points to a fundamental change in the electron system of the nucleus and excludes the possibility of hydrogenation of a peripheral double bond. The results suggest the presence of a chlorin—phlorin structure (IV). Phlorins according to Woodward have one hydrogen at a methine bridge and the second at a nitrogen.

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Theoretically there can be formed α-, β-, γ-, or δ-chlorin–phlorin or a mixture of them. However the n.m.r. spectroscopic evidence of Krüger and Brockmann⁵, based on quite reliable correlations between a sufficient number of spectra with variation of substituents at the carbon atoms 2, 3, 4, 6, γ, and δ allowed us to assign the exact position for the introduced hydrogen as is shown in structure (IV).

In this somewhat complicated case additional proof of the method was sought by introducing electrochemical reduction in a deuterated solvent, with subsequent reoxidation. Chlorin–phlorins are rather susceptible to reoxidation, although this varies from compound to compound, and from group to group. In our case Mählhop⁶, ⁷ found that after one electrolysis in deuteromethanol to form a methylene group, and subsequent reoxidation only the signal of the β-methine proton was decreased and this by exactly 50 per cent (V). The figure 50 per cent indicates that only one methine group had been involved. The position γ is excluded by primary substitution, and the positions α and δ were excluded definitely by further n.m.r. data. The topographical formula (VI) illustrates that with the hydrogenation at the β-methine carbon the original steric strain between the groups at positions 6 and 8 is relieved by the rotation of ring C which is now possible out of the formerly rigid plane. It is noteworthy that the 7,8-chlorin–β-phlorin (IV) can now be prepared in practically quantitative yield, a result not often obtained in chlorophyll chemistry.

If chlorin–phlorins—in addition to this special case—are irradiated with visible light in the presence of oxygen, new compounds of the bacteriochlorin series are formed. It is interesting that monochromatic light with a wavelength above 730 nm gives the best yields. The electronic spectrum
which clearly shows with its most characteristic peak at 750 nm the constitutional analogy to the natural bacteriochlorins is given in Figure 1. The analytical figures of high resolution mass spectroscopy for the two compounds isolated, which proved to be isomers, demonstrated a formal uptake of CH$_4$O$_2$; their structure is represented by (VII). The characteristic electron spectrum indicated that the double bond between 3 and 4 of ring B is substituted. Together with i.r. data it became evident that two stereo-

![Figure 1. Electronic spectra of bacteriochlorins](image)

*Figure 1. Electronic spectra of bacteriochlorins*
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isomeric methoxy-hydroxy derivatives (VII, B₁ and B₂) had become generated from the starting material.

For clarification of the first question whether gaseous oxygen has entered ring B, heavy oxygen \(^{18}\text{O}_2\) was used for the photochemical oxidation. Mass spectroscopy again gave a clear answer: the molecular ion showed two mass units more (VIII), the fragment M—32 originated by loss of normal methanol, thus definitely proving that the heavy oxygen was located in the hydroxy group. In view of the uptake of one carbon atom an oxygen intermediate might have reacted with the solvent methanol. To clarify this possibility mono-C-deutero-methanol was used as solvent. Now the molecular ion of the product showed one mass unit more, and this was followed by an M—33 fragment, thus proving beyond doubt the elimination of CH₂D—OH (IX). Again the next fragmentation is characterized by a signal 29 mass units lower, this being the ethyl group from C₄ which can be split off only from a 3-methoxy-4-hydroxy-compound, according to Budzikiewicz.

Finally, if the photooxidation is performed in dioxane–water 3,4-diols are obtained.

To sum up specified electrochemical reduction of a natural 7,8-chlorin leads to a \(\beta\)-phlorin, in some other cases to a mixture of \(\beta\)-and \(\alpha\)-phlorins both behaving in the same way. The following photochemical oxidation converts these chlorin-phlorins into 3,4-dihydroxy derivatives of the bacteriochlorophyll series. The hydroxy groups are assumed to be \textit{trans} to one another, thus accounting for the two isomers. The overall yield is up to 15 per cent.

The mechanism of this photo-oxidation may be formulated in the following manner. Oxygen attacks the \(\beta\)-phlorin-hydrogen, or in the same manner an \(\alpha\)-phlorin-hydrogen, forming a peripheral hydroperoxide. This loses water producing an epoxide, which is then cleaved by the solvent, either methanol or water.
With this result the original aim had been achieved in principle, though in an unexpected way. It was to be expected that these hydroxy derivatives would be rather reactive towards acidic reagents. In the pyro-methylpheophorbide series, Mengler treated the 3-methoxy-4-hydroxy compounds with HCl at 40° in methanol. Loss of water, followed by attack of methoxide ion and finally elimination of methanol generates a 4-α-methoxychlorin.

With the restoration of the 3,4-double bond an entirely new type of chlorophyll compound is created. The same reaction in dioxane–water leads to the 4-α-hydroxy product. Finally, at 90° the elements of water are split off for a second time and a 4-vinyl group appears (X). This is interesting because a 4-vinylchlorophyll is said by biochemists to be one of the last precursors of chlorophyll a in the biosynthetic pathway. Oxidation of the 4-α-hydroxyl leads to a 4-acetylchlorin, previously unknown, and so far accessible only in this way (XI).

But this is not the end of the possibilities. To affect the 3-methyl group, the 3,4-diol instead of the 3-methoxy product was chosen as starting material. 3,4-Dihydroxy-bacterio compound of chlorin e₈-TME was prepared in the
manner described, the closest compound to chlorophyll a which can easily be reconverted into chlorophyll a. If this new diol (XII), either from the pure trans isomers or a mixture of the two, is treated with HCl in dioxane–water at 40°, two new isomeric alcohols are generated besides other products. One of them proved to be the normal 4-α-hydroxy product, the other one was the anticipated 3-methyl-carbinol (XIII), the rhodinol, which could be oxidized to the known rhodin g7-TME (XIV), the derivative of chlorophyll b, completely identical with the natural compound. These transformations complete the total synthesis of chlorophyll b, based of course on the fundamental Harvard synthesis of chlorophyll a².
We now come to the porphyrin chemistry. The partial synthesis will be described of spirographisporphyrin (XV) as dimethylester. The iron-chelate of this compound constitutes the prosthetic group of the blood pigment of some worms. The spirographis compound contains in the 2-position an aldehyde instead of the vinyl group. The direct partial degradation of one of the two vinyl groups, is not a good process, because isomeric mixtures are obtained, which are difficult to separate.

Starting with protoporphyrin IX-DME, the iron-free chlorohaemin, Brockmann and Bliesener first converted this product by photooxidation into the known photoprotoporphyrin IX-DME. The structure (XVI) that was assigned to the latter proved to be correct during the course of our work. The vinyl group had therefore been modified to an allylic aldehyde, and C-atom 1 oxidized to a tertiary carbinol. The mechanism of the formation of the photoproduct can be formulated as follows: \((a \rightarrow b \rightarrow \text{XVI})\).

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Under the action of light a porphyrin-diradical (a) is probably first formed which then reacts with the oxygen by 1,4-addition to give an endoperoxide (b). The latter no doubt rearranges immediately to photoprotoporphyrin (XVI). In the course of the reaction only one of the vinyl groups reacts either at position 2 or 4, the second one does not, as is observed in other porphyrin cases where two equal possibilities exist. After separation of the two isomers—with reference to the two vinyl groups—the one shown was reduced with sodium-borohydride to (c), then the allylic diol was rearranged with acid and the resulting glycol (d) was simultaneously cleaved with
periodic acid to the aldehyde (XV), which proved to be identical with spirographisporphyrin-DME\textsuperscript{8}.

However the unsymmetrical substitution of protoporphyrin was, as it always has been, a tremendous obstacle to further progress, namely to a longer reaction sequence, which might change the fundamental structure of the porphyrin at hand completely. For this reason we turned to a simple as well as symmetrical porphyrin, which certainly seemed useful as starting material, but here the difficulty was that only small quantities could be prepared. Timely help soon came and we received through the courtesy of Professor Pommer, head of the Hauptlabor of the Badische Anilin, some 3 kg of OEP (octaethylporphin) XVII. Now we could start on the transformation of this simple porphin into a compound that might become one day a close analogue of what Eschenmoser\textsuperscript{9} has synthesised and called a corphin (XVIII).
What were and still are the chemical problems? Geminal alkyl groups had to be generated and going beyond Eschenmoser's corphin carbonyl groups were needed to build up propionic and acetic side chains. An old Fischer reaction turned out to be a good starting point. Fischer prepared from OEP with hydrogen peroxide and sulphuric acid a compound he thought to be an oxide. But we showed it to be what I call a gemini-ketone (XIX), probably formed by pinacol rearrangement of an intermediate diol. Having enough OEP, Nolte could devote more to this reaction and succeeded in rearranging a second ring, for instance C or D. Now isomerism turns up not only because of reaction in two different rings, B and C or B and D, but also with two possibilities within one ring. We isolated 4 isomeric gemini-diketones of the 5 which are theoretically possible and to which the structures, shown later, could be easily assigned by n.m.r. spectroscopy. Even a gemini-triketone turned up, a third ring having been affected.

Our first problem consisted in developing the mini-process of the oxidation-rearrangement reaction into a large scale operation and maintaining the original yield of 25 per cent. The three parameters: concentration, temperature and time do not allow much variation. Most probably the methine double bonds are at least as reactive as the peripheral ones, this unpleasant circumstance leading to opening of the ring system to give bile pigment analogues. We will see later how it may be possible to reduce or hinder the reactivity of the methine double bonds. The gemini-diketones, produced in the course of this direct combined operation, could be isolated only in yields of about 1-2 per cent each. But we will learn how quickly yields can be improved when the need arises.

The gemini-monoketone (XIX) was treated with OsO₄ instead of H₂O₂ and the resulting diol (XX), which was formed quantitatively, rearranged with sulphuric acid, Nolte isolated the two gemini-dike-tones in a combined yield of nearly 90 per cent; these products correspond to the modification of ring D in the two possible ways as shown below:
We learn two things from these facts concerning yield and constitution:

(i) The oxidation is the critical reaction. (ii) The double bond opposite to the gemini ring turns out in this case to be the most active, and furthermore steric hindrance with OsO₄ perhaps plays an important role in eliminating addition at the methine double bonds.

![Diagram of Diketones IV and V]

The remarkable difference between the yields of the two ketones (XXI and XXII) is probably an outcome of the dissimilar electronic situation with regard to the original different positions of the two hydroxy groups, that means in relation to their former distances from the primary keto group or from the primary geminal alkyl group respectively.

We now come to the gemini-triketone (XXIII) already mentioned, at first isolated within well below 1 per cent yield. It possesses geminal alkyl groups at carbons 3, 5 and 7. It is now produced in a new way (XXII → XXIII). The aforementioned gemini-diketone V (XXII) on treatment according to Fischer–Bonnett, yields the gemini-triketone in 10 per cent.

![Diagram of Reaction of Diketone V with H₂O₂]

The arrow is only formal, the same triketone emerges from affecting ring A of the symmetrical diketone V. But for the important triketone we have at present one more possibility. The third of the gemini-diketones, in which rings B and C have been modified, with the number II (XXIV) yields the triketone in 70 per cent yield with our two-step process, no other
triketone being isolable. Also in this case the arrow is formal, attack of ring A will yield the same triketone. The keto groups of the gemini-diketones can be reduced, whereby gemini-dichlorins are obtained, for instance (XXV). This one, of course, shows the typical bacteriochlorin spectrum with maximum at 740 nm. Acetylene as well as acetylene derivatives can be added, for instance ethoxy-acetylene, followed by allylic rearrangements to give e.g. (XXVI).

Fischer–Bonnett reaction may result from the following observation. $\alpha,\gamma$-Dinitro-OEP (XXVII), obtainable according to Bonnett in good yield, was changed into one of the two possible gemini-monoketones (XXVIII). The increased yield (35% as compared with 25%) showing that the reactivity of the methine double bonds can be influenced.

Bearing in mind that the corrin nucleus contains two meso-methyl groups, we tried to introduce such carbons directly on a preformed por-
phyrin-macrocycle. Having in our case no meso-carbonyl groups at hand but only methine carbons, this aim did not seem easy at first. However Buchler developed the following surprising process. When he added—according to Closs and Closs—two electrons to the zinc complex of OEP (XXIX) with the help of sodium anthracenide he obtained a dianion with two negative charges in the most distant $\alpha,\gamma$-positions (XXX). Treatment of this dianion–Zn complex with excess methyl iodide yielded directly, including reoxidation by air of the intermediate XXXI and demetallation, the $\alpha,\gamma$-dimethyl-OEP with an overall (XXXII) yield of 20 per cent. This "reductive-meso-methylation" is new with porphyrins. In the case of the nickel complex (XXXIII) the stability of the intermediate dihydro-dimethyl compound XXXIV is such that it can be isolated. Furthermore if the solution of the dimethyl-dihydro-zinc complex is kept away from air and treated with a copper- or nickel salt, the readily exchangeable zinc is replaced by the more stable copper or nickel, herewith making it possible also in this case to isolate the intermediate dihydro compounds (XXXV). These interesting hitherto unknown $\alpha,\gamma$-dimethyl-$\alpha,\gamma$-dihydroporphin–metal chelates invite further study.

Meso-oxidation has already been achieved by Hans Fischer using lead dioxide. Fuhrhop has shown that this reagent transforms, for example, OEP into meso-tetraketo-OEP (XXXVI) in yields up to 70 per cent.
If this meso-tetraketo compound is treated with an excess of methyl-lithium and after hydrolysis, water is eliminated an $\alpha,\gamma$-dimethyl-$\beta,\delta$-diketoporphin is obtained, of which the dimethylene isomer is the predominant form (XXXVII $a + b$). We will develop this reaction sequence into a second route to meso-dimethyl-porphins, to be followed by the Fischer–Bonnett reaction to meso-methyl-gemini-ketones. The meso-oxidation and gemini-ketone production steps may also be interchanged.

Gossauer treated the gemini-monoketone (XIX) with lead tetraacetate, and isolated 3 of the possible 4 meso-acetates, namely the $\beta$ (XXXVIII) in 7 per cent, the $\gamma$ in 10 per cent, and the $\delta$ in 1 per cent yield. The $\alpha$-isomer could not be detected. N.m.r. spectroscopy definitely assigned the structures to the 3 isomeric meso-acetates. Again the use of a metal complex, zinc in this case, has proved helpful. When the zinc complex (XXXIX) was treated
in the same way, the \( \beta \)-acetoxy derivative (XL) was isolated in 30 per cent yield, no other meso-oxidation product being detectable.

Saponification led to a compound comparable with the so-called oxophlorins of Lemberg and Kenner. The structure of the \( \beta \)-oxophlorin-gemini-ketone (XLI) is obvious because of hydrogen bonding clearly seen in the i.r. spectrum. With the \( \gamma \)-oxophlorin (XLII) we have to leave open its definite structure, because we do not know at the moment where the hydrogen stands.

At this stage in the development of the main problems the question arose whether it would be wise to keep to the primary concept of building everything from OEP. The corphin from OEP yes, but for the visualized corrin-analogue a corrole would be a better starting point. The latest line therefore
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starts with the decamethyl-corrole (XLIII), its symmetrical figure not being distorted by ethyl groups, and the diethoxycarbonyl-octamethyl-corrole (XLIV) both as nickel complexes\(^\text{18}\). Hydroxylation of the decamethyl-corrole with OsO\(_4\) led in high yield to a mixture of one dihydroxy- and one tetrahydroxy-corrole only (ignoring stereoisomerism) both being easily separated. N.m.r. analysis facilitated by the two angular methyl groups proved that rings I and IV had not reacted with OsO\(_4\) (XLV and XLVI).
Finally, treatment of the dihydroxy-corrole with sulphuric acid led to a mixture of the two possible gemini-monoketo-corroles as nickel complexes (XLVII and XLVIII) as Ullrich found.

References
5 H. Brockmann, Jr. Angew. Chem. 80, 234 (1968).