Discoveries among Conjugated Macrocyclic Compounds.

THIRTEENTH PEDLER LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON THURSDAY, JANUARY 22ND, 1953, AND AT THE UNIVERSITY, ABERDEEN, ON THURSDAY, MARCH 12TH, 1953.

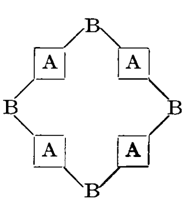
By R. P. LINSTEAD.

I MUST begin by defining my scope. The lecture will be concerned with macrocyclic compounds containing rings of 16 or more atoms with either perfectly conjugated or cross-conjugated systems of double and single bonds. There is no obvious geometrical reason why large conjugated rings of carbon atoms should not exist—why the *cyclo*octatetraene pattern should not, as it were, be extended—provided one is allowed latitude in the use of re-entrant angles and, if necessary, departure from planarity. However, such structures have not yet been substantiated, and the simplest conjugated macrocycles known to us are those in which four cyclic units A are joined by linking atoms B to make up the large ring (I). A and B must be of such a type as to permit conjugation.

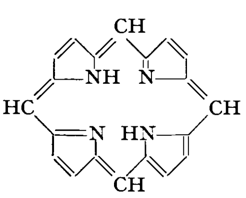
The group is of the highest importance. It includes chlorophyll, hæmin, and the other natural porphyrin pigments, whilst the widely distributed and vitally important iron-containing enzymes contain prosthetic groups based on the same structural pattern. In the space of a brief lecture, it is possible to look at only a few aspects of macrocyclic compounds, and I propose to survey the general range of their structures, the methods of synthesis, and certain aspects of their properties. Moreover, I shall speak mainly of the aza-linked macrocycles, where B is $-N=$, on which most of my own work in the field has been done.

The state of knowledge in 1930 can be roughly summarised in this way: the only important class of substances to which a conjugated macrocyclic structure had been given was the porphyrin group. For these the Küster formula, based on porphin (II) had been revived by Hans Fischer.[1] There was no rigid proof of this structure which rested largely on massive circumstantial evidence derived from the synthesis of various substituted porphyrins.

In 1927—1928 complex metallic compounds, subsequently recognised as derivatives of phthalocyanine, first came to light, the copper compound being made (although not identified) by de Diesbach and van der Weid [2] and the iron compound discovered in the Grangemouth factory of Imperial Chemical Industries Limited.[3] I started work on this group of compounds in 1929 at the Imperial College of Science and Technology. The parent compound, phthalocyanine, was soon synthesised [4] and the structural formula (III) was proposed in 1933.[5] Subsequently a considerable effort was devoted to proof of the constitution, examination of the chemical and physical properties, determination of the range of the structural type and of the ability to form complexes with metals.[6] There will be no need to go into details of this early work, which has already been summarised.[7] For our present purpose I will merely draw two general conclusions from the work done up to 1936. First, phthalocyanines and many similar compounds were very easily prepared and were remarkably stable (indeed, as is well known, many of them are nowadays made on an industrial scale). It may be concluded therefore that conjugated macrocycles of this kind are inherently favourable structures, and the difficulty in preparing some of them, such as the porphyrins, is in a sense accidental and derives from the instability of intermediates. Secondly, the structure of phthalocyanine and of its metallic derivatives was proved with complete certainty. The chemical evidence [5] on which the



(I)



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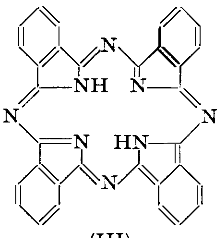


(III)

structure * (III) was first advanced was in itself conclusive, and received overwhelming support from the investigation carried out by J. M. Robertson by the *X*-ray method.[8] This moreover provided precise information on structural detail which was not otherwise available. Robertson's results may be illustrated by the electron density map for phthalocyanine shown in Fig. 1. The coincidence between the chemical and physical pictures of the molecule was summarised in an arresting phrase : [9] " This pattern may be said to provide the first purely physical demonstration of the truth of organic chemistry."

The rigid proof of a macrocyclic structure for the phthalocyanines invalidated the argument which had been used against the Küster formula for the porphyrins, namely, that it was of an unprecedented kind.

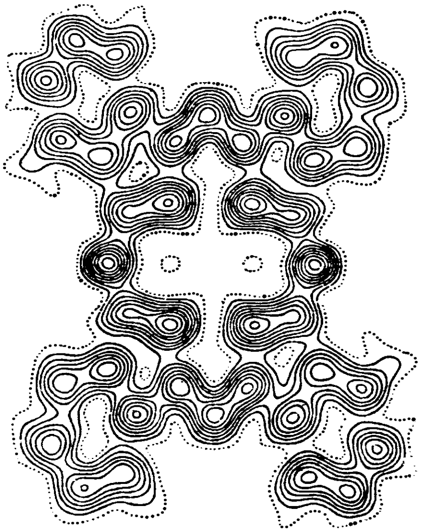
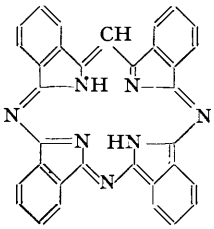


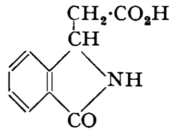
FIG. 1. *Metal-free Phthalocyanine* (J. M. Robertson).

Electron density map. Projection along b *axis. Each contour represents a density increment of one electron per* Å^2.

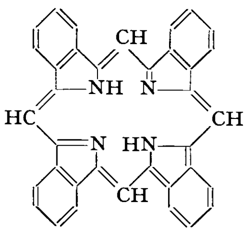
On the dual basis, therefore, that conjugated macrocyclic structures were stable and were certain, it was possible to advance with confidence. Much further work at the Imperial College has been done in two directions : first, an examination of the range of the porphin and azaporphin type of pigment exemplified by (II) and (III) ; secondly, an exploration of the possibility of making conjugated macrocycles of quite different kinds. Good progress has now been made in both fields, and I shall deal with them in turn.



(IV)



(V)



(VI)

An immediate objective was of course to bridge the gap between phthalocyanine and porphin itself. As the chart shows, this could be done in two ways—by keeping the *iso*indole units of phthalocyanine and linking them by methene groups instead of by nitrogen atoms or by keeping the nitrogen links and replacing the *iso*indole corners by pyrrole nuclei. In the next period (1936—39) most success came from the *iso*indole compounds. We were able to prepare compounds with one methene and three nitrogen,[10] with one nitrogen and three methene, and

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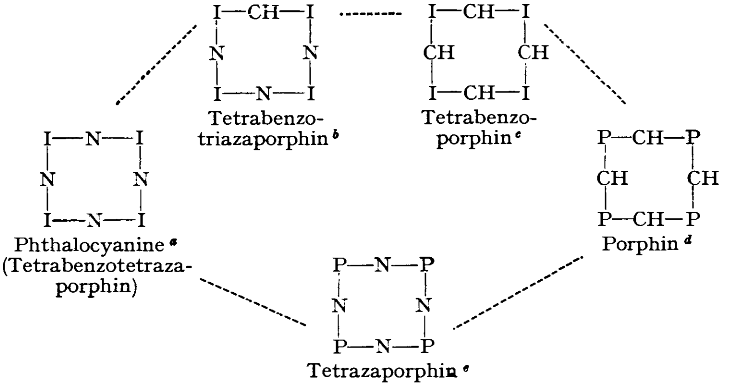
* Certain points of fine structure remain to be settled : for example, the mode of attachment of the two central hydrogen atoms, and the possibilities of tautomerism. This is a general residual problem in the group of tetrapyrrolic pigments.

with four methene links.[11] I will illustrate the rather unconventional methods used. If phthalonitrile is treated with methylmagnesium iodide or methyl-lithium it gives a product which when heated at 200° with a hydrogen donor gives magnesium tetrabenzotriazaporphin (IV) in about 40% yield.[10] The best intermediate for tetrabenzoporphin is 3-oxo*iso*indolin-1-ylacetic acid (V); when this is heated at 450° with zinc acetate it gives zinc tetrabenzoporphin (VI) in 15% yield.[11] The structures of these substances were established by chemical, supported by spectroscopic, evidence; moreover J. M. Robertson [12] showed that the triaza-compound (IV) was strictly isomorphous with phthalocyanine. Similar investigations were carried out independently by Helberger and his associates in Berlin.[13]

Basic structures connecting phthalocyanine and porphin.



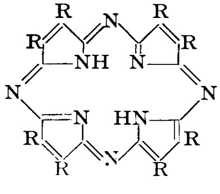
I = *iso*Indole unit. P = Pyrrole unit.

[a] Byrne, Linstead, and Lowe, 1934. [b] Barrett, Linstead, and Tuey, 1939. [c] Barrett, Linstead, Rundall, and Tuey, 1940. [d] Fischer and Gleim, 1936. [e] Linstead and Whalley, 1952.

On the other hand, progress towards tetrazaporphin and simple derivatives was very limited during the pre-war period, and in particular various attempts to prepare the necessary dinitrile of maleic acid failed to yield us a satisfactory product. The related diphenyl derivative, dicyanostilbene (VII), was however obtained and shown to yield macrocyclic pigments of the desired type, namely octaphenyltetrazaporphin (VIII; R = Ph) and its metallic derivatives.[14] Incidentally, it now appears that the key intermediate (VII) may have the *trans*- and not the *cis*-configuration, as has previously been supposed.[15] During the same period, and using quite different methods, Hans Fischer and his collaborators described the preparation of " imidoporphyrins " [16] and in particular tetraimido*ætio*porphyrin.[17] The absorption spectrum of this compound was almost identical with that of compounds recently prepared in my laboratories, which undoubtedly have the structure (VIII) where groups R are alkyl or part of a polymethylene ring.

$\mathrm{NC{\cdot}CPh = CPh{\cdot}CN}$

(VII)

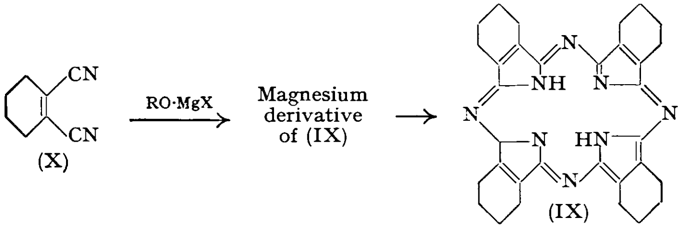


(VIII)

When I was able to resume investigations of azaporphins three years ago attention was again directed to the preparation of tetrazaporphin (VIII; R = H) itself and of its tetra*cyclo*hexeno-derivative (IX). By this time authentic maleic nitrile had been reported in the literature, although its preparation was still difficult, and an important advance had been made by chemists of the Dyestuffs Division of Imperial Chemical Industries Limited (1949—50).[18] They showed that when maleic nitrile or 3 : 4 : 5 : 6-tetrahydrophthalonitrile was heated with a metallic reagent, urea, and ammonium molybdate, a highly coloured pigment was obtained. From the method of preparation and general properties these were formulated as metallic tetrazaporphins.

In our investigations of these two dinitriles we have concentrated upon their conversion into tetrazaporphin derivatives containing a labile metal. In this way a route was opened to the metal-free compound which could subsequently be converted into any desired metallic derivative. Dr. M. Whalley in my laboratories has successfully solved the delicate problems of the routine preparation of maleic nitrile and from it of magnesium tetrazaporphin. This is best made by the action of magnesium *n*-propoxide on the nitrile. The yield is about 20% and the product is readily purified by chromatography. The metal is eliminated by cold glacial acetic acid wthout destruction of the macrocycle.[19]

The corresponding compounds in which the β-carbon atoms of the pyrrole ring are substituted are more easily obtained, both the intermediates and the macrocycles being more stable. Dr. Ficken has found that 3 : 4 : 5 : 6-tetrahydrophthalonitrile (X) on treatment with a reagent formed by the decomposition of methylmagnesium iodide with amyl alcohol gave a 66% yield of magnesium tetra*cyclo*hexenotetrazaporphin, from which the metal-free compound (IX) could readily be obtained.[20] The structure of compound (IX), a hexadecahydride of phthalocyanine, has been established with certainty,[20] the main pieces of evidence being that (i) the method of preparation corresponds to the formation of phthalocyanine from phthalonitrile, (ii) two atoms of hydrogen are present which are replaceable by metal, (iii) the molecule undergoes oxidative fission to 3 : 4 : 5 : 6-tetrahydrophthalimide and ammonia, and (iv) it is readily dehydrogenated to phthalocyanine, for example, by the action of heat at about 300°.



(X) (IX)

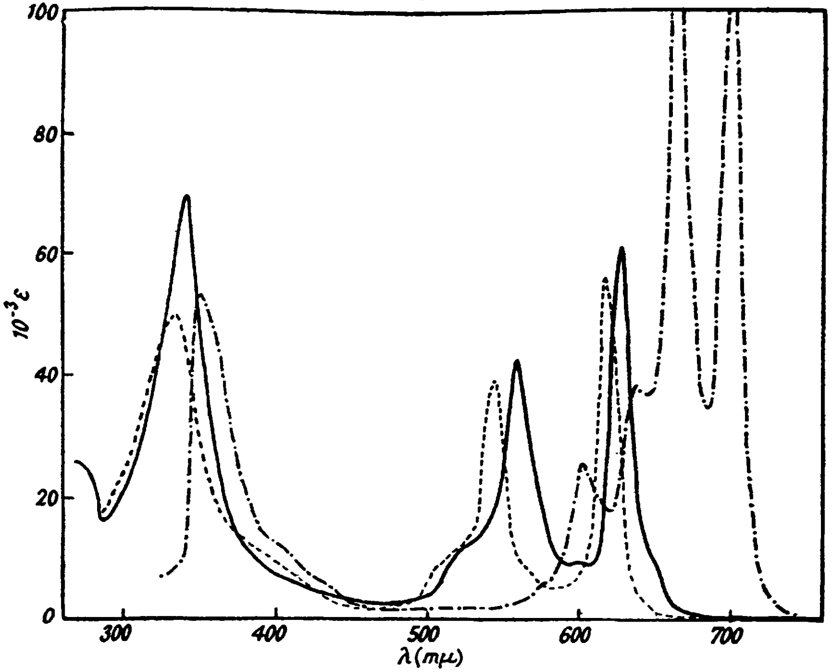
In the case of tetrazaporphin, the evidence of dehydrogenation was not, of course, available and, whilst the oxidative fission gave ammonia, the maleinimide was too unstable for isolation under the conditions of reaction. Hence only (i) and (ii) of the above lines of evidence were available. Fortunately, convincing spectroscopic evidence confirmed the structure (VIII; R = H). This is described later. The structures of the new tetrazaporphins can be regarded as firmly established.

In summary, therefore, the range of tetrapyrrolic conjugated macrocycles has now been greatly extended. Research in progress at the moment has led to further improvements in preparative methods and to the discovery of tetrazaporphins with unsymmetrical arrangements of the corner units.

I should next mention some of the remarkable and characteristic properties of the tetrazaporphins. First, the absorption of light in the visible and the ultra-violet region. This may conveniently be reviewed in comparison with that of the porphyrins. In the visible region all the simple * metal-free porphins and azaporphins have a multibanded absorption spectrum in the blue-green to vermilion region, between about 500 and 620 mμ. If benzene or similar rings are fused to the pyrrole nuclei the region of absorption is extended into the red, up to about 700 mμ. This is illustrated in Fig. 2. The intensity of the absorption is very greatly increased when the methene links of porphin are progressively substituted by nitrogen atoms (Fig. 3). This is shown particularly by the first band of the simple porphins and azaporphins which lies in the region of 620 mμ. The measurements made by Stern and Pruckner on the compounds prepared by Hans Fischer and his collaborators provide good evidence on this point in the series *ætio*porphyrin–tetraza*ætio*porphin.[21] Now, among the simple tetrazaporphins, the structure of the tetra*cyclo*hexeno-derivative (IX) has been conclusively proved by the chemical evidence summarised above. It is therefore of particular importance that the light absorption of this compound is found [20] to be virtually identical with Stern and Pruckner's measurements on tetraza*ætio*porphin (Fig. 4). This substantiates the structure of the tetraza- (tetraimido-)-materials made by the Münich school and links their work with ours. It is equally important that tetrazaporphin itself has a light absorption in the visible and near ultra-violet region very closely resembling that of the tetra*cyclo*hexeno-derivative (Fig. 2).[19, 20] There is a corresponding close resemblance between the spectra of corresponding metallic derivatives [19, 20] (Fig. 5). This puts the structure of tetrazaporphin on a firm basis.

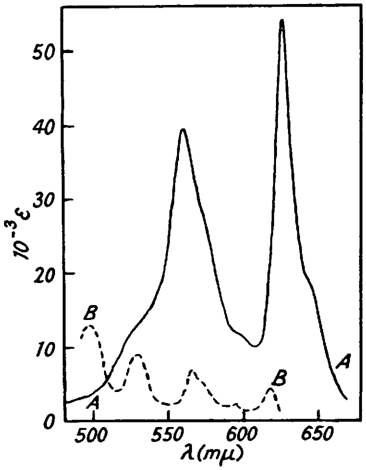
* *I.e.*, those without fused rings.

FIG. 2.



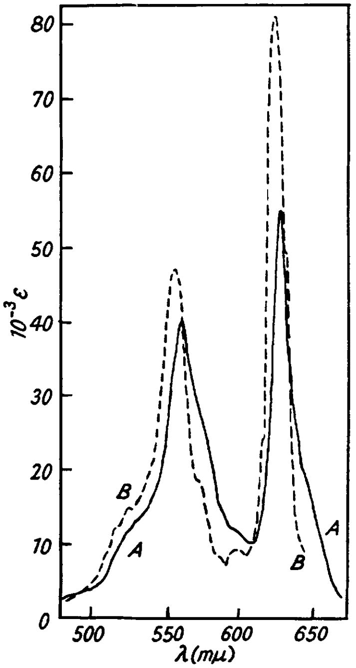
———————— *Tetra*cyclo*hexenotetrazaporphin* (*in chlorobenzene*).
- - - - - - - *Tetrazaporphin* (*in chlorobenzene*).
— · — · — *Phthalocyanine* (*in chloronaphthalene*).

FIG. 3.



A, *Tetra*cyclo*hexenotetrazaporphin* (*in pyridine*).
B, ætio*Porphin*-II (*in dioxan*).

FIG. 4.



A, *Tetra*cyclo*hexenotetrazaporphin* (*in pyridine*).
B, *Tetraza*ætio*porphin* (*in pyridine*).

Table 1 summarises important data, taken from Stern's work [21, 22] and our own,[19, 20] on the positions of the maxima in the visible region. It will be seen that there are some grounds for saying that the bands appear in approximately the same positions throughout, only the intensity varying with substitution of nitrogen for methene. This is evident enough for band I but the position is less clear-cut in the bands of shorter wave-length, in the green region.

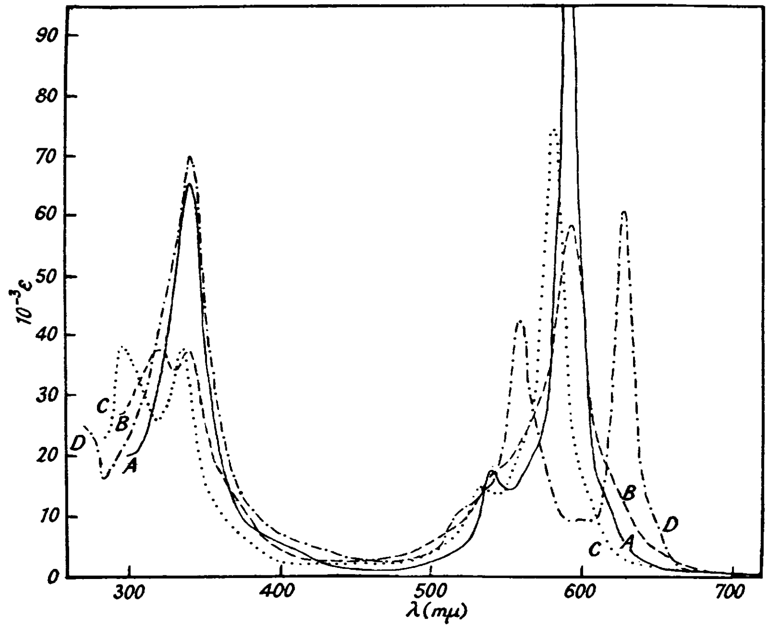
TABLE 1. *Light absorption in the visible region of metal-free porphin and azaporphins.*

		Maxima of absorption bands (mμ)					
Compound	Band	IV	III	II	Iȧ	I	Ref.
Porphin		490	518	(561)	(602)	(613)	1
*ætio*Porphyrin		497	529	(566)	(596)	(619)	1
Monoaza*ætio*porphyrin		501	534	560	(588)	610	1
βδ-Diaza*ætio*porphyrin		—	543	(569)	—	*620*	1
Tetraza*ætio*porphyrin		—	(526)	*556*(573)	(599)	*624*	1
Tetrazaporphin		—	(510)	*545*(565)	—	*617*	2
Octamethyltetrazaporphin		—	(525)	*556*	(597)	*627*	2
Tetra*cyclo*hexenotetrazaporphin		—	(525)	*560*	(600)	*628*	2

Strong bands italicised; weak bands in parentheses.

[1] Stern's measurements on compounds of H. Fischer *et al.* (pyridine solutions). [2] Linstead, Whalley, and Ficken (chlorobenzene solutions).

FIG. 5.



*A, Copper tetra*cyclo*hexenotetrazaporphin (in dichlorbenzene).*
*B, Nickel tetra*cyclo*hexenotetrazaporphin (in dichlorbenzene).*
*C, Palladium tetra*cyclo*hexenotetrazaporphin (in dichlorbenzene).*
*D, Tetra*cyclo*hexenotetrazaporphin (in chlorobenzene).*

In addition to their visible selective absorption, all these macrocycles have an intense band in the near ultra-violet region, which (in the case of the porphyrins themselves) is generally called the Soret band. This is shown for various tetrazaporphins in Figs. 2 and 5. The Soret band differs from the visible bands in the effect of the introduction of nitrogen links. Whereas the first visible band (for example) changes enormously in intensity but hardly at all in position, the ultra-violet band changes considerably in position but hardly at all in intensity. The evidence is summarised in Table 2, from which it is seen that the maximum of the Soret band for porphyrins lies at about 400 mμ with log $\varepsilon_{max.}$ about 5·1. For tetrazaporphins the corresponding figures are about 340 mμ and 4·9. One consequence is that the ultra-violet band is much the strongest for porphyrins whereas in the tetrazaporphins the strongest visible bands are of comparable intensity.

Replacement of the two acidic hydrogen atoms of tetrazaporphins by an atom of bivalent tetraco-ordinate metal leads to a simplification of the light absorption in the visible region. The effect can be summarised by saying that the two strong bands (λ *ca.* 627 and 558 mμ in a substituted tetrazaporphin) are replaced by an intense band of intermediate wave-length (*ca.* 590 mμ) with a weak band or inflexion on the short-wave side (*ca.* 545 mμ). As will be seen, for example, in Fig. 5 the nature of the metal affects the intensity but only to a minor extent the position of the main visible band. The first ultra-violet band of the tetrazaporphins is also present, not much changed in position, in their metallic derivatives. There is some variation in intensity with the nature of the metal and in a few cases the bands are divided into two.[19, 20] This is illustrated in Fig. 5 and in Table 3.

TABLE 2. *Effect of linking groups in simple tetrapyrrolic pigments on the intensities and positions of the first bands in the ultra-violet and the visible region.*

	Ultra-violet		Visible (band I)		
Linking groups	λ	$\log \varepsilon_{\max.}$	λ	$\log \varepsilon_{\max.}$	Ref.
4 CH, no N	398—405 [a]	5·05—5·24 [a]	622	3·76	1
3 CH, 1 N	376	5·06	610	4·43	1
2 CH, 2 N	373—375 [a]	5·01—5·16 [a]	620	4·67	1
no CH, 4N	333—343 [a]	4·70—4·98 [a]	617—628 [a]	4·75—4·79 [a]	2

[a] This denotes the range of values encountered in representative compounds of the class.

[1] Stern's measurements on compounds of H. Fischer *et al.* (pyridine solutions). [2] Linstead, Whalley, and Ficken (chlorobenzene solutions).

TABLE 3. *Effect of central metal on the ultra-violet absorption of some tetrazaporphins.*[20]

Nature of metal		None (metal-free)	Mg	Co	Ni	Cu	Pd
Tetra*cyclo*hexenotetraza-porphin	$\lambda_{\max.}$	343	344	350	342	343	338
	$\log \varepsilon_{\max.}$	4·84	4·96	4·67	4·57	4·81	4·58
Phthalocyanine	$\lambda_{\max.}$	350	347	—	351	350	347
	$\log \varepsilon_{\max.}$	4·74	4·73	—	4·57	4·76	4·69

Many of the regularities noted above are reproduced among the more complex structures in which rings such as benzene are fused to the porphyrin or azaporphin system. A noteworthy effect is the bathochromic shift of about 80 mμ in the main visible bands caused by the fusion of four benzene rings to the pyrrole nuclei when we pass from tetrazaporphins to phthalocyanine. This is accompanied by a great intensification of absorption in both the metal-free and the metallic derivatives.[11, 23]

Haurowitz [24] regards the visible band system of the porphyrins as representing different vibrational bands corresponding to one electronic transition, and the Soret band as due to a separate electronic transition. This is in keeping with the small effect of structural modifications (including the introduction of metal) on the Soret band compared with their considerable effect on the system of bands in the visible region. The same phenomena occur among the tetrazaporphins and may be attributed to the same causes.

It is worthy of note that tetrazaporphin has a normal absorption spectrum [19] which resembles that of its alkyl derivatives (Fig. 2 and Table 1). The position is different for porphin, the parent substance of the porphyrins. This is a rare compound, for which the only reported preparations are those by Fischer and Gleim [25] and by Rothemund.[26] Fischer's material had a " phyllo "-type of spectrum [22] rather than the normal " ætio "-type illustrated in Fig. 3. This means that although the four main visible bands are more or less in the normal position, the intensity of band II is greater than that of band III. There seems no obvious reason why the alkylation should produce a different effect in the tetraza- and the tetramethene series and a reinvestigation of porphin is desirable. In Rothemund's preparations the position is more obscure owing to the presence of material at different hydrogenation levels, as Aronoff and Calvin have shown.[27]

Among all these tetrapyrrolic compounds the phthalocyanines possess particularly sharp and intense absorption bands in the visible region and, as they are also remarkably stable, they function as brilliant and stable pigments of technological value. By suitable substitution the chemists of Imperial Chemical Industries Limited have been able to convert them into water-soluble dyes capable of application to textiles.

I turn next to the fluorescence of the tetrazaporphins. The experimentalist working with these materials soon becomes aware that some, but not all, of them show a vivid fluorescence when exposed to visible or ultra-violet light. This is best shown by the magnesium compounds.

It was observed for magnesium phthalocyanine and magnesium octaphenyltetrazaporphin before the war [14] and had long been known for the chlorophylls.[28] More recently we have observed that magnesium derivatives of tetrazaporphin and its alkyl derivatives fluoresce brilliantly when exposed to visible or ultra-violet light.[19, 20] The results may be exemplified by the tetra*cyclo*hexenotetrazaporphin series. The parent compound shows a weak visible fluorescence and a strong rose-red ultra-violet fluorescence, whilst its copper, nickel, and cobalt derivatives virtually do not fluoresce. The fluorescence of the magnesium compounds is shown by solutions in pyridine, alcohol, or dioxan; it is red in visible light, vermilion in ultra-violet light. Solutions of the magnesium compound in benzene or chlorobenzene show practically no fluorescence but the addition to these of a drop of alcohol or pyridine at once activates the fluorescence.[20, 29] These results at once recall those of Livingstone and his collaborators [30] on the activation of the fluorescence of chlorophyll and we in fact find that there is a general agreement between the two series in the nature of the activators and in the rough order of their effectiveness. In considering the relation of these properties to structure, two pieces of evidence are relevant. First, the metal-free tetrazaporphins show no similar activation; secondly, the magnesium derivatives of phthalocyanine and of the new tetrazaporphins have the property (unusual among metallic azaporphins) of crystallising in solvated forms containing molecules of water, alcohol, or base. We therefore agree with Evstigneev, Gavriola, and Krasnovskii [31] in attributing the activation of fluorescence to a process involving the co-ordination of the central magnesium atom with the activating solvent, a proposal which has recently been accepted by Livingstone and Weil.[32]

The similarity between chlorophyll and the magnesium azaporphins also extends to the quenching of their fluorescence. We find [29] that substances such as nitro-compounds and quinones powerfully suppress the fluorescence of magnesium tetra*cyclo*hexenotetrazaporphin and that the order of quenching by different agents is very similar to that observed by Livingstone and Ke.[33] Among quinones the quenching efficiency roughly follows the redox potential, quinones of high potential having the largest effect.

I must also refer briefly to the catalytic properties of metallic tetrazaporphins first investigated by A. H. Cook.[34] Amongst these the most striking is the decomposition of the peroxides contained in aged samples of terpenes and similar hydrocarbons by means of magnesium phthalocyanine and similar compounds. This occurs at temperatures of about 180° and is accompanied by a vivid red chemiluminescence. The effect is also shown by chlorophyll. We have now found that it is given by magnesium tetrazaporphin, so that it is presumably connected with the presence of a magnesium atom bound to four nitrogen atoms in the macrocyclic environment, although we do not yet know how many of these structural factors are obligatory.

Conjugated Macrocycles of Other Types.—It is evident that what may be called the tetrapyrrolic type of large ring structure is capable of fairly wide variation, and that compounds possessing it are often easily prepared, very stable, and striking in their properties. The question arises as to whether it is possible to branch out from this structure into new types of conjugated macrocycles. We can indeed construct on paper a considerable number of tolerably plausible formulæ. But in this lecture I will confine myself to a group of compounds in which such speculative blue-prints have been converted into experimental fact and in which the resulting structures can be regarded as fully established.

As indicated earlier, the known conjugated macrocycles (formula I) contain four corner units, A, held together by linking atoms, B, all the known A units being pyrrole or fused pyrrole rings. An inspection of formulæ (II) and (III) shows that one canonical structure has one true pyrrole ring, two pyrrolenine rings, and one ring of a maleinimide type. If now two of the pyrrole groups are replaced by benzenoid or pyridine rings, we arrive at compounds such as (XI) and (XII). Such structures do not violate our general conceptions of molecular geometry, and there seems to be no *a priori* reason why they should not be realisable. Nevertheless certain differences from the azaporphin type follow the introduction of the six-membered rings as building units, and in particular the symmetry and conjugation of the system are altered. In the tetrazaporphin molecule the central hydrogen atoms can be accommodated with equal (or nearly equal) convenience on any two of the pyrrole rings, and similarly in their metallic derivatives the metal can be attached by primary valencies to any two of the pyrrole nitrogen atoms.* If we examine the pyridine-containing macrocycle, the formula (XII), with the

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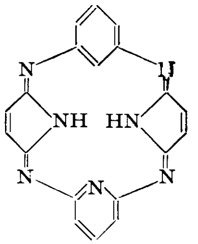
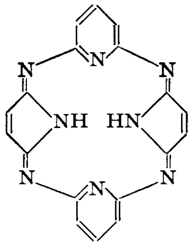
* The interesting question as to the degree of sharing of the metal or of the two central hydrogen atoms between the pyrrole nitrogen atoms, and the consequential degree of degeneracy of the system, must be passed over in this lecture.

central hydrogen atoms on pyrrole nitrogen, is inherently more probable than the isomeric form in which the hydrogen atoms are carried on the pyridine nitrogen, and we may expect that (XII) would make a much larger contribution to the structure. If the pyridine rings remain aromatic then the other double bonds will take up the positions shown in (XII). The macrocycle is thus cross-conjugated, and not fully conjugated as in tetrazaporphin (VIII; R = H). These arguments of course would apply *a fortiori* to the benzenoid macrocycle (XI). It will be noted, however, that the pyridine macrocycle (XII) resembles tetrazaporphin in having the four re-entrant nitrogen atoms with two hydrogen atoms in a position suitable for formation of metal complexes. In summary, therefore, we would expect compounds (XI) and (XII) (*a*) to be capable of existence, and (*b*) to resemble the tetrazaporphins in many respects, but (*c*) to differ from them in those properties derived from the full conjugation of the molecule, such as the light-absorption properties. The pyridine, but not the benzene, macrocycle would form metal complexes. There will also be differences in the mechanism of fission, which are mentioned later.

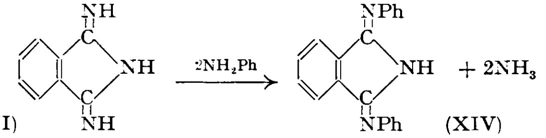


(XI)



(XII)

About two years ago investigations with Dr. J. A. Elvidge opened up a line of experimentation by which these structures might be approached. Work at the Imperial College [35] and in the laboratories of Imperial Chemical Industries Limited [36] and of the Bayer Company [37] had led to the preparation of di-imino*iso*indoline (XIII) both as the free base and in the form of its salts. This readily available and highly interesting compound has, we find, a number of ready modes of reaction. For our present purpose the important one is that it combines with primary amines with evolution of ammonia and the formation of *N*-substitution products. The reaction with aniline is typical:



(XIII) (XIV)

It was therefore obvious that reaction of di-imino*iso*indoline with a suitable diamine might give rise to a macrocycle through a series of condensations of this kind.

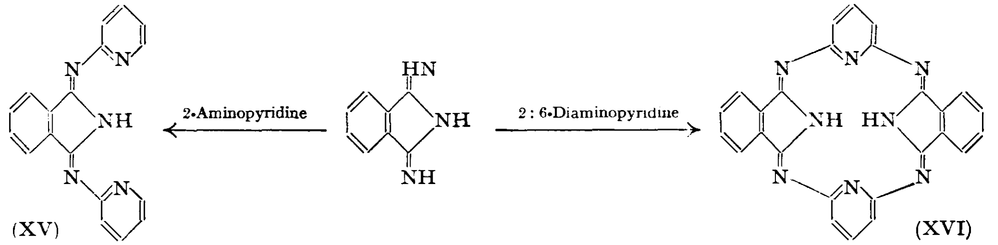
This possibility was first tested [35] using aminopyridines as the secondary component because this would permit the use of metal complexes to keep the molecule in a stereochemically favourable form. In fact, however, as will be seen, this was an unnecessary precaution. It was first found that 2-aminopyridine reacted readily with di-imino*iso*indoline in boiling butanol, to give ammonia and the dipyridylimino*iso*indoline (XV). The structure of this was proved by its easy hydrolysis to phthalimide and 2-aminopyridine. With 2 : 6-diaminopyridine in place of the monoamine a sparingly soluble orange-red crystalline product was obtained in some 40% yield. This substance has been conclusively proved to have the macrocyclic structure (XVI). The evidence is briefly as follows : [35] (*a*) Analysis of the red compound corresponds to $C_{13}H_8N_4$ and the molecular weight to double this. Hence the preparative reaction is :

$$\underset{\text{Di-imine}}{2C_8H_7N_3} + \underset{\text{Diamine}}{2C_5H_7N_3} = \underset{\text{Macrocycle}}{C_{26}H_{16}N_8} + 4NH_3$$

(*b*) On treatment with acid the compound yielded equivalent amounts of phthalimide and 2 : 6-diaminopyridine. No oxidation was involved, as in the fission of a phthalocyanine or tetrazaporphin. The reaction is :

$$C_{26}H_{16}N_8 + 4H_2O = 3C_8H_5O_2N + 2C_5H_7N_3$$

This hydrolysis shows the presence of the intact pyridine and *iso*indole rings which must be linked together by extranuclear nitrogen atoms. Moreover, these units must be alternate as otherwise diaminopyridine could not be re-formed. These facts can only be explained on the basis of formula (XVI). Any linear counterpart would have end groups which would be detectable by elementary analysis or on fission or both. (*c*) The macrocycle extracted metals from their salts with the formation of complex metallic derivatives of the type shown below



(XV)

(XVI)

The nickel compound (XVII), for example, was prepared[35] when the macrocycle in nitrobenzene was treated with nickel acetate in formamide. It melted at 386° and sublimed at about 300°/10^{-5} mm., both without decomposition. The colour was a brownish-green and the absorption spectrum considerably changed from that of the parent compound. The hydrolysis products were nickel ion and the same organic compounds as were produced from the metal-free compound.

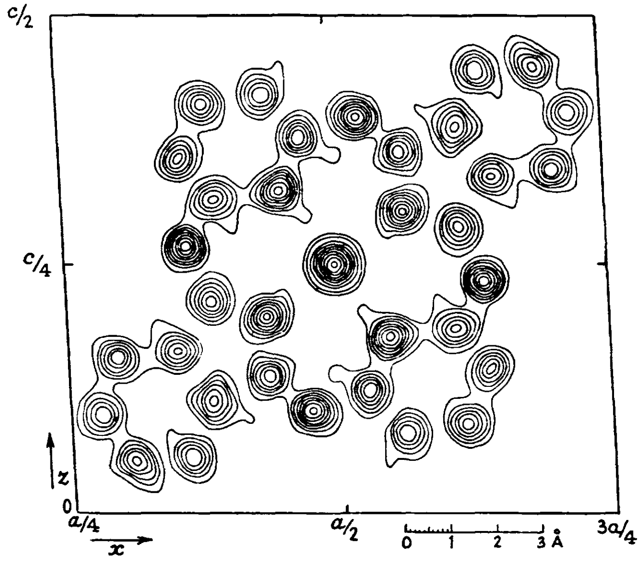
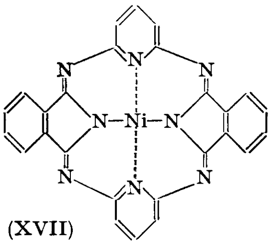


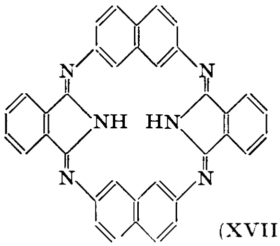
FIG. 6. *Nickel compound* (XVII). *Electron density projected along* b-*axis.*

Dr. J. C. Speakman[38] of the University of Glasgow has investigated the crystals of the nickel compound by the *X*-ray method and has very kindly allowed me to report his findings. The crystals presented a very favourable case for analysis because the unit cell has one very short axis (which implies that a good projection of the structure should be attainable) and the nickel atoms are in special positions. The heavy-atom method, used with such effect by Robertson for the metallic phthalocyanines, could therefore be applied, although the relative smallness of the crystals made it difficult to obtain accurate intensity data. The structure represented by formula (XVII) is confirmed by the *b*-axis projection of the electron density. This is shown in Fig. 6. The molecule (in the crystal, at any rate) is however not planar, as were those of the phthalocyanines. Instead the nickel atom lies on a two-fold axis of symmetry, the eight nitrogen atoms are approximately co-planar with it, and the *iso*indole rings are tilted out of this plane by about 25° in one direction whilst the pyridine rings are similarly tilted in the other direction. The approximate molecular configuration is illustrated in Fig. 7.

Research into this new type of macrocycle is being extended by Mr. P. F. Clark to other aromatic and heterocyclic series, and we find that a considerable range can be obtained.[39] For example, we have replaced the pyridine groups of (XVI) by benzene, naphthalene, and acridine units. The naphthalene macrocycle (XVIII) is particularly easily obtained, as it is formed in about 70% yield when 2 : 7-diaminonaphthalene is heated with di-imino*iso*indoline. It is noteworthy alike for its central cross-conjugated great ring of 20 atoms and for its stability.



(XVII)



(XVIII)

Its melting point is in the region of 500° and it can be sublimed without decomposition at about 400°/15 mm. It resists the action of aqueous alkali and of boiling concentrated hydrochloric acid. As would be expected it fails to form complex metallic derivatives.

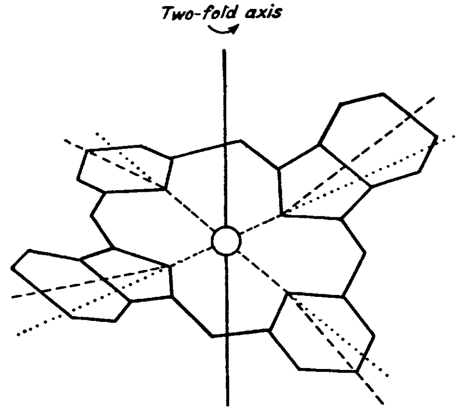


FIG. 7. *Nickel compound* (XVII). *Approximate molecular configuration in crystal.*

Because of the departure from complete conjugation, the new type of macrocycle shows a very different type of light absorption from the azaporphins. Thus the metal-free pyridine compound (XVI) has two strong bands but these are well in the ultra-violet region (λ 301, 354 mμ in morpholine), and there is only end absorption in the visible region. The colour is accordingly orange. The metallic derivatives have markedly different spectra. In particular the nickel derivative has a complex multibanded spectrum with one strong maximum in the visible region (λ 440 mμ, ε 35,800, in dimethylformamide). The introduction of metal has a far greater effect than in the azaporphin series; we attribute this to the fact that in the new type of macrocycle the metal increases the degree of resonance and the participation of forms other than the main structure (XVI), whereas this is not true for the azaporphins.[35]

The Pedler Lecturer is charged with the duty of pointing out those directions in which further research is desirable. I can interpret this in a narrow and in a wide way. From the narrow point of view these seem to be the most interesting and fruitful lines of further investigation of the macrocycles : First, much remains to be done on the exploration of the possible range of structure. Secondly, we need to rationalise the reactions, often obscure, by which azaporphins and porphyrins are formed; and as a pendant to this the mechanism of the remarkable easy biosynthesis of porphyrins is of exceptional interest. Thirdly, the catalytic properties and oxidation–reduction behaviour of macrocycles provide a most interesting field. Fourthly, many problems of fine structure remain to be settled.

There is also a wider issue which may be touched on. In organic chemistry today there is, quite rightly, very great activity in the fields of natural products, in the determination of the mechanisms of reactions, and in the refinement of the interpretation of known structures. But all this should not blind us to the fact that large tracts of organic chemistry still remain completely unexplored and that we are far from finality in our knowledge of the various manners in which carbon, hydrogen, oxygen, nitrogen, and the other hetero-atoms can combine and the consequences of these combinations. The discoveries among the macrocycles which I have touched on today provide only a few examples of the rich structural jewels which still await the explorer.

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