SUBSTITUTED TETRAZAPORPHINS

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by

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ABSTRACT

Tetramethyltetrazaporphin has been prepared from mesacononitrile. A number of iron tetramethyltetrazaporphin compounds have been prepared, from citracononitrile, and evidence of a facile interconversion between iron-(II) and -(III) species is reported.

Tetra-(neo-pentyl)-tetrazaporphin has been prepared, starting from the hydrocarbon 4,4-dimethylpent-1-ene, and found to be a mixture of positional isomers. Partial separation of these isomers has been effected by chromatographic methods, and n.m.r. spectral data are reported. The nickel complex has been prepared and investigated by n.m.r. spectral methods.

A number of iron tetra-(neo-pentyl)-tetrazaporphin compounds, both iron-(II) and -(III), have been isolated, the n.m.r spectra and magnetic moments of some of these compounds have been determined. These compounds are similar to tetramethyltetrazaporphin iron compounds in their oxidation-reduction reactions and in their electronic absorption spectral characteristics.

ACKNOWLEDGEMENTS

The work recorded in this thesis extended over three years, the first two of which were spent at Imperial College and the last at Battersea College.

Throughout this period I have benefited from the advice and sagacious supervision of Professor J. A. Elvidge to whom I am deeply indebted.

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I wish to thank Imperial Chemical Industries for providing me with a maintenance grant and helpful advice, and also for gifts of chemicals.

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CHAPTER 1

INTRODUCTION

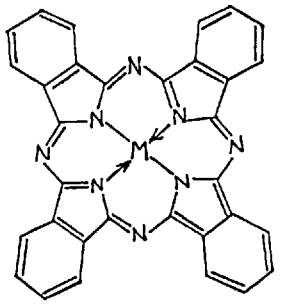
The first substantiated formation of a tetrazaporphin dates from 1927 when de Diesbach and von der Weid[1] heated o-dibromobenzene with cuprous cyanide and pyridine in a sealed tube. However, it seemed likely that a similar substance was obtained previously[2] on fusing o-cyanobenzamide.

In 1928 Scottish Dyes Ltd. (Grangemouth) isolated a blue pigment in the preparation of phthalimide by reaction of molten phthalic anhydride with gaseous ammonia. Linstead and coworkers[3] later showed this material to be iron phthalocyanine I (M ≡ Fe; i.e. iron(II) tetrabenzotetrazaporphin), the iron being provided by the vessel used in the preparation. Linstead's group then went on to show the product of de Diesbach and von der Weid to be copper phthalocyanine I (M ≡ Cu). Linstead[3] synthesized a number of similar metal derivatives mainly from phthalonitrile, but also from o-cyanobenzamide, including the parent compound phthalocyanine I (M ≡ 2H).

Phthalocyanine was of interest because it contained a basic structural unit (the so-called tetrazaporphin skeleton II) similar to that previously proposed for porphyrins, III, by Küster[4] and differing from it in having nitrogen bridges instead of methine bridges between the four pyrrole rings. X-Ray crystallographic measurements of phthalocyanine and some of its metal derivatives[5] soon confirmed the structure and provided powerful support for Küster's structure of porphyrins.

Phthalocyanines proved reasonably easy to prepare by the self-condensation of phthalic acid derivatives in molten urea, or of phthalonitrile with a metal or metal salt. The products were very stable to light and heat. This, together with their intense colour, brightness and low solubility, made the phthalocyanines exceptionally useful as pigments for a wide range of materials. This utility was quickly recognised in patents dating from 1928.[6]

The first compounds containing just the basic tetrazaporphin skeleton II were prepared in 1937 separately by two groups. Linstead's group[7] prepared octaphenyltetrazaporphin and some of its metal derivatives, as an extension of his work on phthalocyanines, by reaction of the stable dinitrile, diphenylmaleonitrile, with metal



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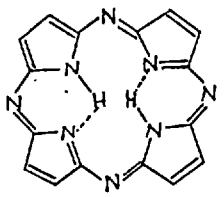

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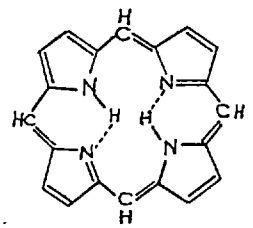

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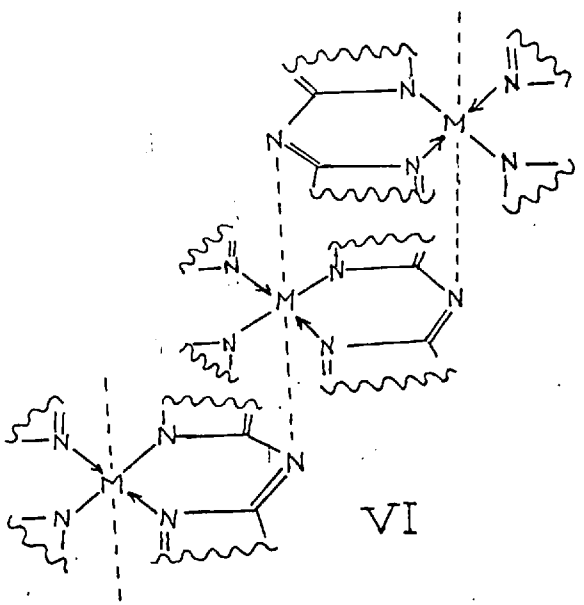
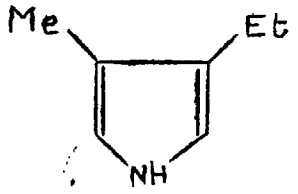


VI

salts at elevated temperature. As part of their studies of porphyrins Fischer and his coworkers investigated azaporphins and prepared tetramethyltetra-ethyltetraza-porphin in low yield from opsopyrrole IV by reaction with bromine and ammonia.(8)

This compound, which Fischer called tetraiminoaetio-porphyrin, was also prepared from di-isocyanato opsopyrrole V (X ≡ NCO) by reaction with base, in equally low yield.(9)



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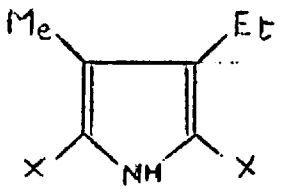

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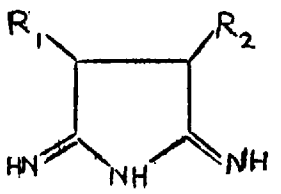


VII

The aromatic character of the phthalocyanine pigments made it possible to convert them by sulphonation(10) and chloromethylation(11) into "reactive" dyes. These in turn could readily be converted into soluble dyes. The tetrazaporphins are generally more difficult to prepare, are less resistant to acids and can only be sulphonated(12) and chloromethylated(13) in certain cases, and they have not as yet achieved any commercial importance. Like phthalocyanines they have also been used as polymerization(14)

and oxidation[15] catalysts as well as colouring agents[16] and photosensitizers.[17]

The main interest in tetrazaporphins has arisen out of their similarity in structure to the naturally occurring porphyrins. An obvious difference between porphyrins and tetrazaporphins is that the former are generally red while the latter are generally blue. However the comparison of the absorption spectra of the systems provides another point of similarity between the systems and shows the main differences , in both the metal-free and metallated pigments, to lie in the relative intensities of the visible and ultra violet absorption bands, e.g.

(a)	616;	568.5(s);	563;	520;	489.5;	395 mμ
$\log_{10}\varepsilon$	(2.95)	(3.64)	(3.72)	(3.52)	(4.20)	(5.42)
(b)	617;		545;			333 mμ
$\log_{10}\varepsilon$	(4.75)		(4.60)			(4.70)

(c)	562.5;	525.5;	399 mμ
$\log_{10}\varepsilon$	(4.49)	(4.15)	(5.56)
(d)	593	542	343 mμ
$\log_{10}\varepsilon$	(4.83)	(4.19)	(5.02)

(s) ≡: shoulder.

(a) Porphyrin in benzene[19] (b) Tetrazaporphin in chlorobenzene[20] (c) Copper octaethylporphyrin in benzene[21] (d) Copper octamethyltetrazaporphin in o-dichlorobenzene.[22]

The colour is also affected by the degree to which the ultraviolet band, known as the Soret band, extends into the visible region. This band is characteristic of the porphyrin (or tetrazaporphin) ring system and also occurs in reduced pigments as long as the inner 18π electron ring system (as in II, III, XII and XIII) is intact. This band occurs generally at longer wavelength in porphyrins than in tetrazaporphins.

Tetrazaporphins are easier to prepare than porphyrins but are significantly less soluble. In the crystalline state both kinds of molecule appear to stack in parallel planes, with considerable molecular overlap between adjacent planes, resulting in strong interplanar π bonding. Determination of the crystal structure of a number of phthalocyanines[5] by the X-ray method showed the most common feature to be that in part structure VI where a central metal atom (or pair of hydrogen atoms) is situated between the peripheral nitrogen atoms of adjacent molecules both above and below the molecular plane. The resulting N.....M.....N (M ≡ Metal or 2H) bonding which would be absent in a porphyrin structure, with no peripheral

nitrogens, possibly explains the lower solubility of tetrazaporphins as compared to porphyrins. In other respects azaporphins and prophyrins[18] have similar crystal structures.

Two principal ways of synthesizing tetrazaporphin have been developed:

(a) The reaction of maleonitrile derivatives with magnesium alkoxides in refluxing alcohols[23] to give magnesium pigments which can be demetallated easily with acids to the free pigment. In some cases fumaronitrile derivatives can be used.[24]

(b) The self-condensation of succinimidines VII, produced by the reaction of substituted succinonitriles with ammonia at elevated temperatures.[25] This mode of formation of tetrazaporphins was first reported by Endermann and Fischer,[9] when they prepared methylethylsuccinimidine VII ($R_1 \equiv$ Me; $R_2 \equiv$ Et) from the diazide V ($X \equiv N_3$) the yield, however, was very small.

In some cases the "urea melt" preparation method has been utilized.[26]

It was hoped to study tetrazaporphins by nuclear magnetic resonance (n.mr.) spectroscopy. In recent years numerous papers have appeared containing n.m.r. spectral date of porphyrins.[27,28,29,30]

The majority of these measurements were made on strongly acidic solutions (i.e. trifluoroacetic acid)[27,28] in which the porphyrins exist as the protonated dications. Other data for solutions of porphyrins in non polar solvents[28,29] is evidently of little use[30] as no account was taken of the concentration dependence of the signals observed.

Pople[31] used the n.m.r. line position of benzene, in relation to that of ethylene, to calculate the ring current in the former, aromatic system. Elvidge and Jackman[32] extended this concept to other (heterocyclic) aromatic systems. It was hoped to compare the spectra and ring currents of tetrazaporphins with those of porphyrins and other aromatic systems. In the case of porphyrins it is known that complexing a metal with the macrocycle,[29] or attaching peripheral alkyl substituents,[27] appears to decrease the ring current. Similarly it was hoped to make some estimate of the effect of metals on the ring current of tetrazaporphins.

It has been found possible to measure the magnetic susceptibility of a compound in a fairly dilute solution (approximately 0.05M) by n.m.r. techniques.[33] The position of the line from a standard reference substance in the solution is compared with that of the same standard

externally. The difference between the line positions is simply related to the magnetic susceptibility of the solute. By such means, the change in susceptibility accompanying the change in oxidation state of a complexed metal could be followed continuously during a redox reaction in the n.m.r. tube. Manganese phthalocyanine in pyridine solution is known to take up oxygen reversibly in contact with air[34] and so this could be studied. A similar reaction in a soluble system would lend itself readily to study, by the above method, as would the reaction of iron porphyrins with atmospheric oxygen. It was hoped to study similar reactions in the tetrazaporphin series, if a soluble system could be synthesized. The method has the advantage of allowing small quantities of metal complex (approximately 10 mg.) to be used, and it was primarily hoped to use this method for small scale susceptibility determinations.

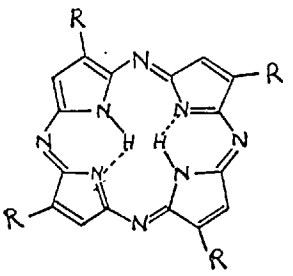
Tetramethyltetrazaporphin has been prepared[35] and found to be more soluble than either octamethyltetrazaporphin or tetrazaporphin. Hence it was considered that tetrasubstituted systems would be the best for study. Such systems would have peripheral hydrogen atoms and the proposed ring current calculations could be made from their chemical shifts.

Two methods of solublizing the system were investigated involving synthesis of tetrasubstituted tetrazaporphins with side chains containing:

(a) Bulky alkyl groups which would solublize the system in non-polar solvents.

(b) Quaternary ammonium groups which, it was hoped, would confer solubility in methanol on the system.

Four isomeric tetrasubstituted tetrazaporphins are possible, represented by VIII, IX, X and XI. In VIII the molecule is symmetrical about the central perpendicular axis and the alkyl groups and aromatic protons are in equivalent environments. In IX the molecule has two mirror planes ab and cd, perpendicular to the molecular plane, and the alkyl groups and aromatic protons are equivalent. In X, the isomer of lowest symmetry, all of the alkyl groups and aromatic protons are non equivalent. In XI there is one plane of symmetry ab, and it can be seen that there are two groups of two equivalent alkyl groups; the same applies to the aromatic protons. As it seemed likely that these isomers would be distinguishable by n.m.r. spectroscopy it was hoped to be able to determine the isomeric composition of any soluble tetrasubstituted tetrazaporphin produced. If a mixture was



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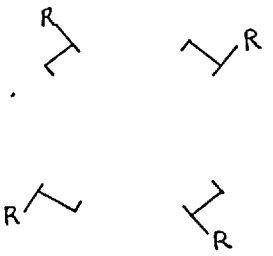
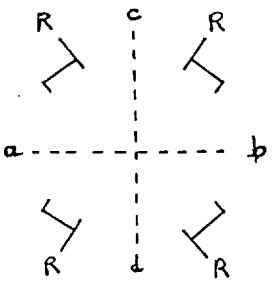
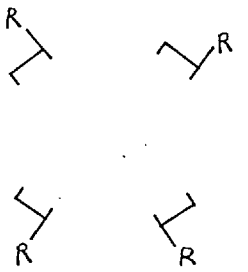


VIII ISOMER (i)



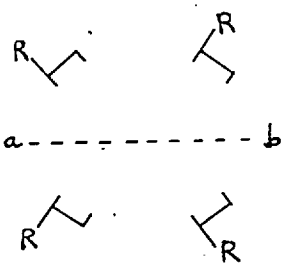
ISOMER (ii)

IX



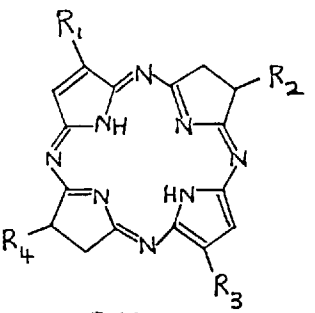
ISOMER (iii)

X

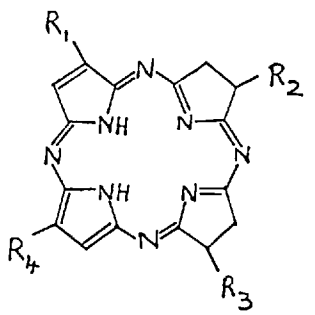


ISOMER (iv)

XI



XII



XIII

produced it was hoped that the isomers could be separated. Otherwise it was hoped that a single isomer might be produced specifically.

On hydrogenation, tetrazaporphins unlike porphyrins, give exclusively tetrahydrotetrazaporphins.[36] Hydrogenation is known to introduce hydrogens into the β positions of two of the pyrrole rings,[29,30] hence isomer (i), VIII, could give two possible products, XII resulting from hydrogenation of opposite pyrrole rings, or XIII resulting from hydrogenation of adjacent pyrrole rings. It can be seen that the two aromatic protons in XII are equivalent, whereas the aromatic protons in XIII are not. Indeed, in contrast to XIII, R_1 and R_3, R_2 and R_4, and the opposite hydropyrrolic protons are also equivalent in XII. Hence XII and XIII could be clearly distinguished by n.m.r. spectroscopy. Both tetrahydro forms are known in porphyrins and differ widely in absorption spectra.[38] Spectral studies conducted by Linstead and coworkers,[37] have indicated the presence of only one of the two forms, on reduction of a number of tetrazaporphins.

If a compound with the isomer (i) structure could be synthesized it was hoped to study the course of its reduction by n.m.r. spectroscopy.

CHAPTER 2

TETRAMETHYLTETRAZAPORPHIN

1. Introduction

Tetrazaporphin and some of its metal derivatives have been synthesized previously.[26,35] It has been observed[35] that, compared with tetrazaporphins and octamethyltetrazaporphins, tetramethyltetrazaporphins are considerably more soluble. This may result from the compound being a mixture of positional isomers. The idea derives from findings made with mixtures of phthalocyanine and tribenzotetrazaporphin[39]; mixtures were more soluble than either pigment alone.

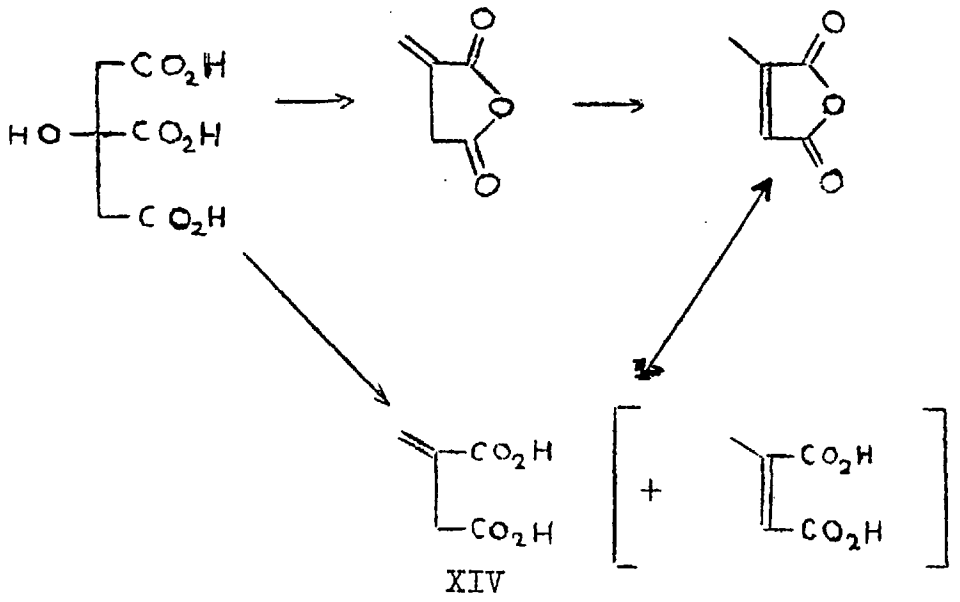
It was hoped that a metallated or metal free tetramethyltetrazaporphin might be sufficiently soluble in a powerful solvent to enable an n.m.r. spectrum to be obtained. It was also hoped that the improved solubility would aid investigation of potentially interesting metal derivatives such as the iron compound. Potassium dicyanoiron (II) phthalocyanine[40] has been prepared and found to be sufficiently soluble in methanol to produce a good n.m.r. spectrum, and it was hoped to prepare the analogue of this compound in the tetrazaporphin series.

Latterly long chain dialkoxysilicon phthalocyanine compounds have proved to be remarkably soluble,[41] so some similar investigations were also envisaged.

2. Pigment Precursors

(a) Citraconontrile

This compound was first synthesized by Brown et al.[35] via the rapid pyrolysis of citric acid to itaconic anhydride.[42] However, an itaconic acid (XIV)-citraconic acid mixture (85%-15%) could be obtained in high yield by slowly pyrolysizing citric acid in saturated aqueous solution at 300° under reduced pressure.[43]



XIV

When this acid mixture, or better, pure itaconic acid, was distilled in the presence of catalytic amounts of anhydrous sodium sulphate, dehydration and isomerization

occurred to give citraconic anhydride in high yield.[44] Potassium dihydrogen orthophosphate was found to be a less efficient catalyst for this reaction.

Acid catalysed esterification of citraconic anhydride produced the corresponding dimethyl ester which on prolonged reaction with '880' ammonia yielded citraconamide. This method gave moderate yields (a maximum of 62%), after 3 weeks reaction, which could not be improved upon by using ethanolic, or aqueous-ethanolic ammonia. A lower yield of amide (24%) was obtained, in a much shorter time (24 hr.), by dissolving ammonium chloride in the aqueous reaction mixture.

Phosphorus pentachloride reacted with citraconic anhydride at 150° to give, on distillation, an acid chloride containing considerable quantities of citraconic anhydride. On reaction with ammonia, no citraconamide could be isolated. Reaction of the acid chloride mixture with methanol produced mainly dimethyl mesaconate. Reaction of citraconic acid with phosphorus pentachloride under milder conditions gave mainly citraconic anhydride. The acid chloride product from itaconic acid[45] gave a mixture of dimethyl itaconate, -mesaconate and -citraconate. It was difficult to identify the acid chloride

products by spectroscopic methods. The composition of the ester mixtures, from the reaction with methanol, suggested that acid catalysed isomerization had occurred.

Citraconamide yielded the pigment precursor, citraconononitrile, by dehydration with phosgene/pyridine. An unsuccessful attempt was made to convert citraconic anhydride, by vapour phase reaction with ammonia at 400°[46], to citraconònitrile.

(b) Mesaconononitrile

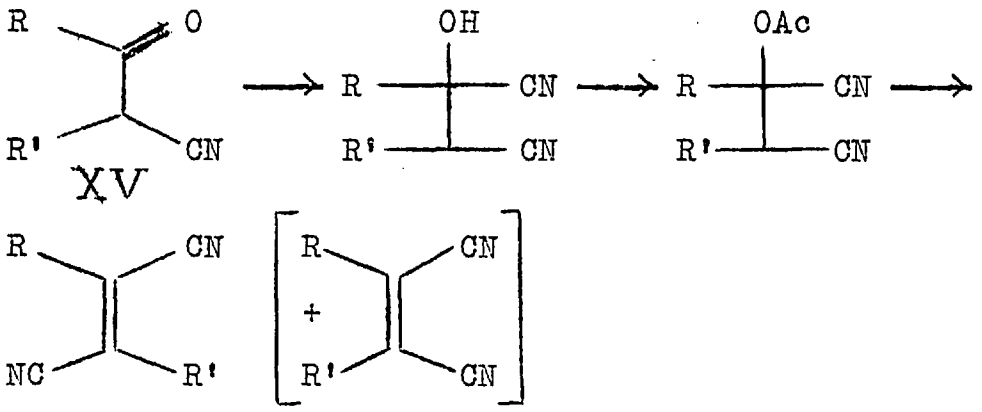
It was hoped to investigate mesaconononitrile as a precursor to tetramethyltetrazaporphin and hence to indicate the feasibility of using the generally more accessible, monosubstituted trans dinitriles as pigment precursors. Dimethyl fumaronitrile is known to be a precursor to octamethyltetrazaporphin.[24]

Mesaconononitrile was obtained[47] and found to contain sizable amounts of an impurity, either methyl β-cyanocrotonate or β-carbmethoxycrotononitrile [n.m.r. spectrum in carbon tetrachloride: vinyl proton (q) 3.62 τ, J = 1.6 c/s; ester methyl (s) 6.25 τ; methyl (d) 7.65 τ].

Only small amounts of pure mesaconononitrile could be obtained by small preparative scale G.L.C. (100 mg.).

Pure mesaconononitrile was hence prepared from the corresponding acid by converting its methyl ester to the amide. It was necessary at this stage to recrystallize the amide to remove traces of the half ester-half amide, presumably the precursor of the impurity in the above sample of mesaconononitrile. The nitrile was obtained by phosphorus pentoxide dehydration.

The applicability of the Beech-Piggott synthesis[48] to mesaconononitrile was investigated. This method for disubstituted dinitriles proceeds as indicated:



Beech and Piggott did not prepare a monosubstituted dinitrile and so had no occasion to prepare an intermediate β-ketonitrile unsubstituted in the α position (i.e. XV, R' ≡ H). Cyanoacetone (XV, R ≡ Me; R' ≡ H), prepared by the general method of Ziegler[49] for condensing

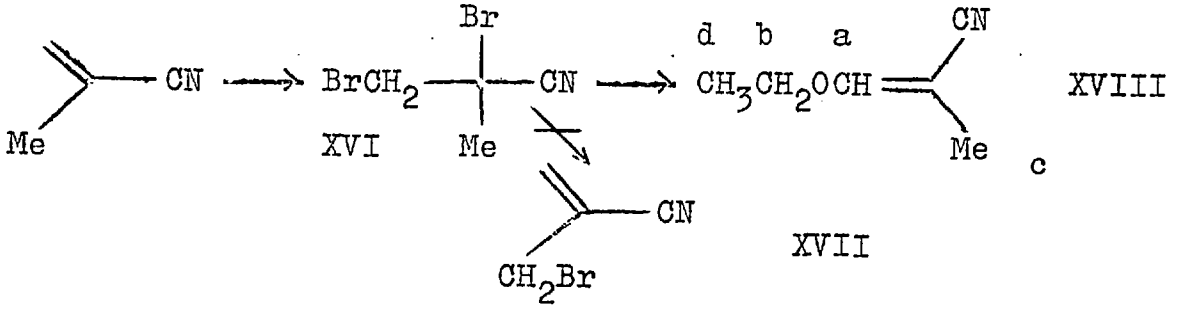
esters with nitriles, was found to polymerize on removal of solvent during the course of isolation. The product obtained by dimerization of acetonitrile, in the presence of phenyl lithium-diethylamine,[50] could be separated as an ethereal solution but the product in solution polymerized readily on standing, before a cyanohydrin could be formed.

(c) Itaconononitrile

Itaconononitrile has been synthesized by reaction of potassium cyanide with α-(bromomethyl)-acrylonitrile,[51] in turn prepared by chlorination of methacrylonitrile, in the vapour with chlorine,[52] followed by halogen exchange.[53]

It was hoped to synthesize α-(bromomethyl)-acrylonitrile by reaction of methacrylonitrile[47] with N-bromosuccinimide but in refluxing carbon tetrachloride only polymerization occurred.

Itaconamide was then synthesized from itaconic acid, via the dimethyl ester, but on phosgene/pyridine dehydration only an oily polymeric nitrile could be obtained.



Breckpot[54] was able to convert βγ-dibromobutyronitrile into γ-bromocrotononitrile by reaction with one equivalent of sodium ethoxide. In the hope that by analogy αβ-dibromo-α-methylpropionitrile XVI might give rise to α-(bromomethyl)-acrylonitrile XVII. The compound XVI was made from methacrylonitrile and reacted with an equivalent of sodium ethoxide under Breckpot's conditions. The product on distillation appeared to give a mixture of cis and trans (1:2) β-ethoxy-α-methacrylonitrile XVIII (30% yield) together with some non nitrilic product [n.m.r. spectrum XVIII:-

cis: a, 3.31 τ (q), J_{ac} = 1.5 c/s; b, 5.92 τ(q), J_{bd} = 7 c/s; c, 7.97 τ (t); d, 8.63 τ (t).

trans: a, 3.12 τ (q), J_{ac} = 1.2 c/s; b, 5.94 τ (q), J_{bd} = 7 c/s; c, 8.25 τ (t); d, 8.67 τ (t)].

Apparently substitution of primary bromide by ethoxide occurs more rapidly than HBr elimination.

(d) Methylsuccinimidine

Brown et al.[35] prepared methylsuccinimidine from methylsuccinonitrile and found it to be a precursor to tetramethyltetrazaporphin. Although the yield of pigment was not reported it was hoped that this route would provide sizable quantitaties of metal free pigment. Using

methylsuccinimidine as a precursor it would be possible to prepare directly metallated pigment in anhydrous, alcohol free conditions. Such conditions, for instance, would be necessary for the preparation of dichlorosilicon pigment, a key intermediate in the preparation of dialkoxysilicon pigments.

In agreement with Kurtz's observation,[55] refluxing hydrogen cyanide could not be added to methacrylonitrile under base catalysis. Also, in agreement with its observed insensitivity towards addition reagents generally,[56] methacrylonitrile would not react with p-toluene sulphonic acid in chloroform, or in a sodium acetate-acetic acid buffer of pH6, despite the fact that sodium bisulphate has been added under these conditions to methacrylonitrile.[57]

Methylsuccinimidine was eventually obtained from methylsuccinic acid which could be prepared from itaconic acid. Itaconic acid was reduced at atmospheric pressure rapidly and quantitatively with hydrogen over a catalyst comprising 2% palladium on strontium carbonate. Methylsuccinimide, prepared by dry distillation of ammonium methylsuccinate, yielded the corresponding amide with '880' ammonia and this in turn was dehydrated to methylsuccinonitrile with phosgene/pyridine. An n.m.r. spectrum confirmed the constitution of the product.

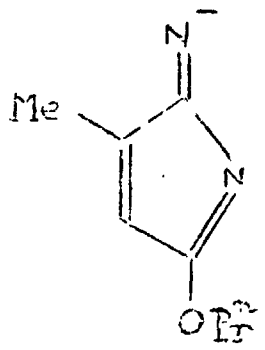
b a c
[MeCH(CN)CH_2CN. In 20% w/v solution in deuterochloroform the c proton signal was spin decoupled revealing the a and b proton signals to be approximately an AB_2 spin system:
a , 6.94 τ ; b , 7.26 τ ; c , 8.51 τ ; J_{ab} = 6.6 c/s; J_{ac} = 6.7 c/s].

On attempted conversion of the product into methylsuccinimidine the yields reported by Brown et al.[35] could not be achieved. They employed methanolic ammonia at 143-8° but by performing the reaction at 135-40°. good yields of the imidine were obtained.

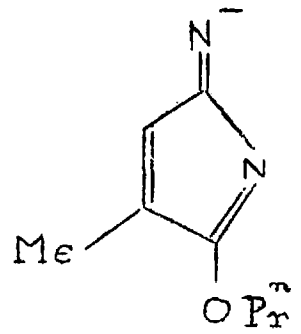
3. Magnesium Tetramethyltetrazaporphin

Reaction of citraconononitrile with magnesium n-propoxide yielded magnesium tetramethyltetrazaporphin. This pigment gave intensely coloured solutions in a wide range of solvents but appeared insufficiently soluble in common solvents for an n.m.r. spectrum to be obtained. Using dimethyl sulphoxide at 90° it was possible to observe a weak signal at 1.90 τ. [The weak internal standard (T.M.S.) line position was determined by running the trace a number of times over the expected region.] The signal observed was presumably due to the aromatic protons. The solvent absorption prevented observation of the methyl signals.

As previously mentioned (Chapter 1) 4 isomeric tetrasubstituted tetrazaporphins are possible. Only one aromatic signal was observed which might, conceivably, indicate the presence of only one symmetrical isomer [either isomer (i) or (ii)]. It may be possible that the isomers in the tetramethyl series are not distinguishable by n.m.r. spectroscopy at the low concentration used. The symmetrical isomer (i) would be produced from citraconononitrile providing the reaction with n-propoxide gave exclusively XIX or XX.



XIX



XX

Magnesium tetramethyltetrazaporphin could be prepared from mesaconononitrile in similar yields as from citraconononitrile, using the same method. The time between commencement of reaction and first appearance of the colour of the product was markedly longer. The

pigment was also prepared from crude mesaconononitrile[47] by reaction with magnesium n-butoxide, in refluxing n-butanol, in comparable yield.

Similar reaction of methylsuccinonitrile with n-propoxide also gave pigment, but only in very poor yield. No attempt was made to conduct the reaction in the presence of a suitable dehydrogenation agent, however.

4. Tetramethyltetrazaporphin

The demetallated pigment was prepared in good yield from the magnesium pigment and acetic acid, and also by self condensation of methylsuccinimidine in refluxing dry butanol-nitrobenzene (1:1), however, yields of pigment by this method were disappointing (approximately 5%) and markedly poorer than preparation via the magnesium pigment.

Unsuccessful attempts were made to prepare tetramethyltetrazaporphin by reaction of citraconic anhydride with molten urea in the presence of boric acid, ammonium molybedate and molybdenium powder.[58]

Tetramethyltetrazaporphin was found to be generally less soluble in polar organic solvents than the magnesium pigment and certainly not soluble enough in any common solvent for the n.m.r. spectrum to be obtained.

The metal free pigment was strongly adsorbed onto

alumina and silica thin plate chromatograms and would not move with benzene or chloroform. With methanol-chloroform (40:60) the pigment moved as a single spot on silica (70% of the solvent front). No separation into isomers was observed even using the technique of "multiple elution".

5. Nickel Tetramethyltetrazaporphin

Attempts to prepare this pigment from anhydrous nickel chloride and citraconic anhydride by "Urea Melt" method[24] was unsuccessful. However, nickel tetramethyltetrazaporphin could be obtained by reaction of citraconononitrile with magnesium n-propoxide in refluxing n-propanol in the presence of anhydrous nickel chloride. No trace of magnesium pigment (λ_{max} = 596 mμ) could be detected. The yield obtained was comparable with that for nickel pigment (λ_{max} = 585 mμ) from tetramethyltetrazaporphin, obtained via the magnesium pigment from citraconononitrile. The conversion of metal-free pigment into nickel pigment, first observed by Brown et al.,[35] was confirmed on a small scale (the yield being estimated from the visible absorption spectrum).

6. Iron Tetramethyltetrazaporphin

Iron tetramethyltetrazaporphins could be obtained in a similar manner to the nickel pigment, using anhydrous

ferrous chloride, directly from citraconononitrile, or from tetramethyltetrazaporphin. However, it has been considered advantageous to leave the consideration of these and other iron tetrazaporphins to Chapter 6.

EXPERIMENTAL SECTION

Pyrolysis of Citric Acid:

An aqueous solution of citric acid monohydrate (100 g . in 40 ml. of water) was added dropwise into a flask maintained at 280-300° and with the internal pressure at 30-40 mm. Most of the product was condensed in a Liebig condenser, the remainder being collected in a cold trap. The product was warmed to hydrolyse any anhydride and the excess water was removed under reduced pressure. Yields of up to 87% of itaconic acid, contaminated with citraconic acid, were obtained.(43)

A 34% yield of itaconic anhydride was obtained by rapid pyrolysis of citric acid at atmospheric pressure.(42)

Citraconic Anhydride:

Itaconic acid (300.8 g. . - B.D.H.), together with anhydrous sodium sulphate (4.5 g. .), was heated to 165-170° . until the theoretical amount of water (41.5 ml.)

had distilled out from the stirred reaction mixture. The residue was then distilled under reduced pressure giving 80% yield (208 g .; B.P. 116-120° /35 mm.) of citraconic anhydride.

Using the above itaconic-citraconic acid mixture a 72% yield of product could be obtained.

Dimethyl Citraconate:

Citraconic anhydride (118 g .), methanol (600 ml.) and concentrated sulphuric acid (33 g .) were heated together under reflux for 24 hours. Most of the methanol was taken off under reduced pressure and the residue was poured into water (120 ml.). The product was extracted with ether, dried over sodium sulphate and distilled giving 75% yield of product (85.8 g .; $n_D^{21} = 1.4470$). When a smaller proportion of sulphuric acid was used the product was contaminated with starting material.

Citraconamide:

Dimethyl citraconate (87.3 g .) and '880' ammonia (135 ml.) were mixed and cooled to 0° , liquid ammonia (5 ml.) was added and the whole was allowed to stand at 0° in the dark. After 3 days the first crop of product was filtered off. The filtrate was cooled to 0° and again saturated by adding liquid ammonia (5 ml.). This

procedure was repeated every 2 days over the course of 3 weeks, at the end of which a 62% yield (36.4 g .) of citraconamide was obtained. Yields sometimes fell as low as 45%.

A 24% yield of product could be obtained, by reaction of dimethyl citraconate with '880' ammonia in the presence of ammonium chloride (as for the preparation of fumaramide, [59]), within 24 hours. The product was recrystallized, from ethanol, sublimed 199-200° .

Citrac**o**nonitrile:

Citraconamide (27.8 g .) was suspended in dry pyridine (350 ml.) and a rapid stream of phosgene (dried by passage through concentrated sulphuric acid) was passed into the stirred mixture at 60° . When exothermic reaction commenced the mixture was cooled to within the range 65-75° . After 1 hour the mixture was cooled and ice was added carefully. It was then acidified with concentrated hydrochloric acid and continuously ether extracted for 3 days. Distillation of the dried extract gave an 84% yield (16.8 g .) of citracononitrile (B.P. 56-8° /0.3 mm.).

Reaction of Citraconic Anhydride with Phosphorus Pentachloride:

Citraconic anhydride failed to react with phosphorus pentachloride after 3 days at 100° . On raising the temperature above 150° phosphorus oxychloride distilled out. Distillation apparently produced some mesaconyl chloride (B.P.60-2° /10 mm.; 12% yield), the majority of the material distilled at a higher temperature (78-84° / 10 mm.). This appeared to be a mixture of acid chloride and citraconic anhydride. Reaction of the product with methanol gave a mixture of dimethyl, -mesaconate and -citraconate. Reaction with ammonia gave a sticky product which could not be crystallized.

Reaction of Itaconic Acid with Phosphorus Pentachloride:

Using the method in "Organic Syntheses"(45) itaconic acid appeared to give itaconyl chloride (74%). Attempts to react this with gaseous ammonia in ether, even at -50° ., gave a brown semi solid which was assumed to be polymeric. A similar product was obtained by heating the chloride with urea.

Reaction of the acid chloride with methanol and subsequent distillation gave only 33% of dimethyl itaconate. The remaining 49% yield consisted mainly of dimethyl citraconate and mesaconate.

Dimethyl Mesaconate:

This was prepared from mesaconic acid (in the same way as dimethyl citraconate) in 77% yield ($n_D^{21.5}$ = 1.4556; B.P.55° /0.15 mm.).

Mesaconamide:

Dimethyl mesaconate (5.2 g .) was stirred overnight with '880' ammonia (7.5 ml.) and ammonium chloride (0.75 g .). The mixture was then cooled in ice, for 1 hour, and filtered. The filtrate was resaturated at 0° by the addition of liquid ammonia (2 ml.) and after 24 hours a second crop was obtained. Total yield 64% (2.7 g.; M.P.173-6° .). Pure amide was obtained by recrystallization from ethanol (M.P.174-6°).

Mesacononitrile:

Powdered mesaconamide (1.7 g .) was shaken with phosphorus pentoxide (4.1 g .) and the mixture was heated to 200° at 30 mm. pressure. Mesacononitrile distilled out over 1 hour (36% yield, 0.44 g. after redistillation).

Attempted Preparation of Cyanoacetone (XV R ≡ Me; R' ≡ H):

(a) Acetonitrile was condensed with ethyl acetate in the presence of sodamide (molar ratio 1:1.5:1.5) in refluxing ether.[49] However, on acidification of the

product and removal of solvent, polymerization set in. In separate reactions both commercial (May and Baker Ltd.) and freshly prepared sodamide was used.

(b) Acetonitrile was added to an ethereal mixture of phenyl lithium and diethylamine (molar ratio 1:0.5:0.5) at -10° .[50] After 5 minutes the product was decomposed with water, rendered neutral, and the ether solution was separated and dried.

On attempting to prepare the cyanohydrin[48] of cyanoacetone, by adding the ether solution dropwise (over 20 hours) to ice cold hydrogen cyanide a polymeric solid separated from the ether solution.

Reaction of αβ-Dibromo-α-Methylpropionitrile (XVI) with Sodium Ethoxide:

The compound XVI was prepared by dropwise addition of bromine (4.95 g .) in t-butanol (7.5 ml.) over 1 hour to acrylonitrile (5 g .) in n-hexane (35 ml.) - t-butanol (7 ml.) solution. Sodium hydride (3.72 gm. of 53.3% suspension in mineral oil) was reacted with ethanol (25 ml.) and the resultant solution was added to the solution of XVI at 0°C over 1 hour. The mixture was filtered and the filtrate was distilled. The main fraction (1.8 g ., B.P.74-8° , n_D^{24} = 1.4548) appeared to be a 1:2 mixture

of cis and trans β-ethoxy-α-methylacrylonitrile XVIII (30% yield). Earlier fractions contained no nitrilic compounds.

Methylsuccinic Acid:

Itaconic acid (90.3 g .) in ethanol (500 ml.) containing 2% palladium on strontium carbonate (1 g .) catalysed the rapid and complete reduction with hydrogen at one atmospheric pressure (M.P.112-4°).

Methylsuccinimide:

Methylsuccinic acid (90 g .) was evaporated to dryness with '880' ammonia (300 ml.) and the product was dry distilled. The crude imide was collected (75 g ., B.P.270-80°) corresponding to a 94% yield.

Methylsuccinamide:

The crude imide (75 g .) was stirred with '880' ammonia (75 ml.) for 2 days when methylsuccinamide could be filtered off. The filtrate was cooled to 0° and liquid ammonia (5 ml.) was added; on standing the solution yielded further crops of product. A yield of 56% (48.4 g .) was obtained (M.P. 228°).

Methylsuccinonitrile:

This was prepared, in the same way as citraconontrile

from methylsuccinamide (48 g .), dehydrated by phosgene in dry pyridine (330 ml.) at 75-85° . A 91% yield (31.7 g ., B.P.72-4° /0.4 mm.) was obtained.

Methylsuccinimidine:

Methylsuccinonitrile (2 g. .) was heated with liquid ammonia (8 ml.) and redistilled methanol (12 ml.) for 12 hr. at 135-40° in a Carius tube. The resultant solution was evaporated under reduced pressure to a semi solid which was triturated numerous times with dry ethyl acetate and filtered off in 82.5% yield (1.95 g .) as a yellowish brown solid.

Reaction at 145° gave an oily product on concentration which generally gave a low yield (for instance, 36%) of a dark brown solid after extensive trituration.

Magnesium Tetramethyltetrazaporphin:

(a) From Citraconononitrile:

Citraconononitrile (1.08 g. .) was added over 15 minutes to a suspension of magnesium n-propoxide (prepared from reaction of magnesium [0.5 gm.] with refluxing n-propanol [20 ml.], initiated by a crystal of iodine). The mixture was refluxed for 45 minutes and then carefully evaporated to a sticky solid under reduced pressure. The solid thoroughly mixed with kieselguhr, was Soxhlet extracted

for 6 hours with (50-50) benzene-methanol (493 mg. of solid were extracted). The concentrated extract was chromatographed on alumina (Spence 'H') in (50-50) benzene-methanol giving an overall 14% yield (175 mg.) of magnesium pigment monomethanolate.

(b) From Mesacononitrile:

(i) Using the same method as above (refluxing for a total of 90 minutes) pure mesacononitrile gave approximately 15% yield (estimated spectroscopically from the known[35] extinction coefficients of the visible absorption bands).

(ii) To methyl magnesium iodide (prepared from 340 mg. of magnesium) in ether was added dry n-butanol (10 ml.). The mixture was warmed, first to remove ether, then to reflux n-butanol. Crude mesacononitrile (1 g .) was added over 15 minutes and the mixture was refluxed for 6 hours. After evaporation to dryness the residue was washed thoroughly with water containing about 5% ethanol. The dried residue was then hot extracted with n-propanol (100 ml.). The concentrated extract was chromatographed on alumina (Spence 'H'). Evaporation of the eluate gave a solid which was assumed to be the n-propianolate of magnesium tetramethyltetrazaporphin (11.3% yield, 121 mg.) by analogy with magnesium octamethyl-tetrazaporphin.[24]

Tetramethyltetrazaporphin:

(a) Tetramethyltetrazaporphin could be obtained in virtually quantitative yields by shaking the finely ground magnesium pigment with excess acetic acid for 30 minutes, diluting with water and filtering the product. The product was washed with aqueous ethanol and dried.

(b) Methylsuccinimidine (200 mg.) was heated in refluxing (50-50) nitrobenzene-n-butanol (10 ml.) for 7 hours. The mixture was evaporated to dryness and chromatographed on powdered tartaric acid in benzene, twice. The best yield obtained was approximately 5%.

Nickel Tetramethyltetrazaporphin:

Magnesium (0.8 g .) was reacted with refluxing dry n-propanol (20 ml.). Anhydrous nickel chloride (2.2 g .; $Mg:NiCl_2$ = 2:1) was added followed by citraconononitrile (1 g .), the latter over 20 minutes. The mixture was refluxed for 1 hour and evaporated to dryness. The residue was hot extracted with chlorobenzene (100 ml.), the concentrated extract was passed through an alumina (Spence 'H') column and the product was eluted with chlorobenzene-ethanol (9:1). Yield 6.5% (25.4 mg.).

CHAPTER 3

Tetra-alkyltetrazaporphins

Introduction

It was hoped to synthesize a soluble tetrazaporphin so that the n.m.r. spectrum could be measured. This would yield information about the ring current induced in this kind of system and provide a measure of the aromatic character of the macrocyclic ring. For the purpose, it seemed best to obtain a tetrazaporphin which had both free, and alkyl-substituted positions arranged alternately round the periphery of the large ring.[32,60] Thus tetrazaporphins of the type XXII were chosen.

The crystal structure of tetrazaporphin is expected, by analogy with phthalocyanines and porphyrins, to be of the form shown in figure -1 (—— represents the cross-section of a tetrazaporphin molecule). Attaching bulky alkyl group to each of the pyrrole rings of the tetrazaporphin molecules, in the lattice, would result in increased steric repulsion between adjacent molecules. The lattice could adjust in the following ways to alleviate this strain:

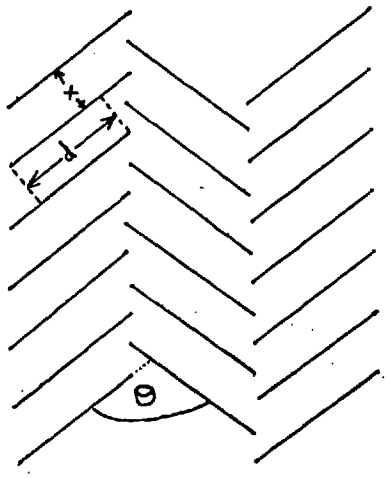


FIGURE 1

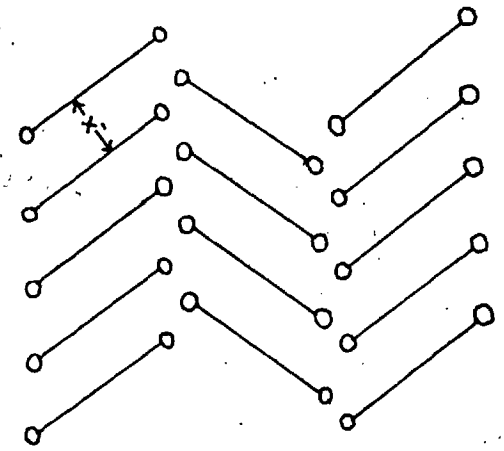


FIGURE 2 ; $x_1 > x$

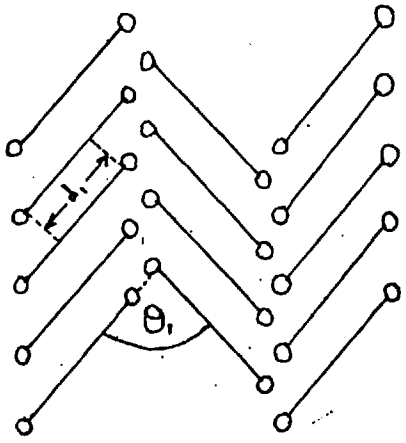


FIGURE 3 ; $\theta_1 < \theta$, $d_1 < d$

1. The molecular separation could increase, as illustrated in figure -2 (O——O represents the alkylated tetrazaporphin).
2. The angle, between the molecular planes in adjacent molecular stacks, could be decreased. It can be seen from figure -3 that this would separate alkyl substituents from alkyl groups of neighbouring molecules, hence reducing the steric repulsion between them. As a result the molecular overlap would be decreased.

In both cases 1 and 2 the lattice structure is so altered as to weaken the interplanar attractions, and make the tetra-alkyltetrazaporphin more soluble than tetrazaporphin.

Alkyl groups, with a point of branching close to the tetrazaporphin ring, would be expected to cause the biggest departure from the lattice of the parent macrocycle. In particular, a highly branched chain would be expected to increase the intermolecular distances, and hence the solubility, more than a straight chain with the same number of carbon atoms. As a consequence a point of side chain branching, near to the tetrazaporphin ring system, was considered a desirable part of the required tetrazaporphin structure.

Tetra-(neo-pentyl)-tetrazaporphin

It was decided to synthesize tetra-(neo-pentyl)-tetrazaporphin (XXII; R = $(CH_3)_3C$-) as it was hoped that its n.m.r. spectrum would be a simple one. This material might be prepared via neo-pentyl-succinonitrile, -maleonitrile or -fumaronitrile.

Most methods for synthesizing monosubtituted-succinonitriles, -maleonitriles or -fumaronitriles involve diacids or diesters as intermediates. These are generally produced by:

(a) Condensation between carbonyl compounds and ethyl succoinate[61] (Stobbe condensation) followed by double bond-migration or -reduction.

(b) Base catalysed rearrangement of ethyl aceto-(α-alkyl)-acetates.[62]

(c) Reaction of ethyl fumarate with Grignard reagents.[63]

(d) Addition of hydrogen cyanide to αβ-unsaturated esters,[64] followed by hydrolysis.

(e) Addition of hydrogen cyanide to ethyl cyanoacetate condensation products, with aldehydes, together with hydrolytic decarboxylation.[65,66]

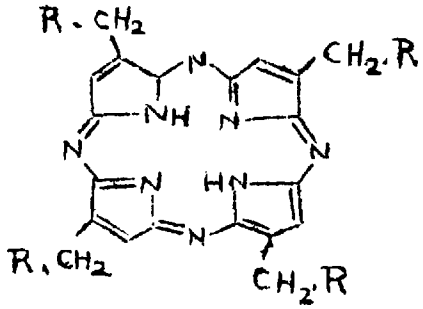
(f) Condensation between cyanohydrins and ethyl cyano-acetate followed by hydrolytic decarboxylation.[67]

It was hoped to prepare monoalkyl-succinonitriles, without proceeding through the diacid, by a less arduous method. Such compounds have been prepared by:

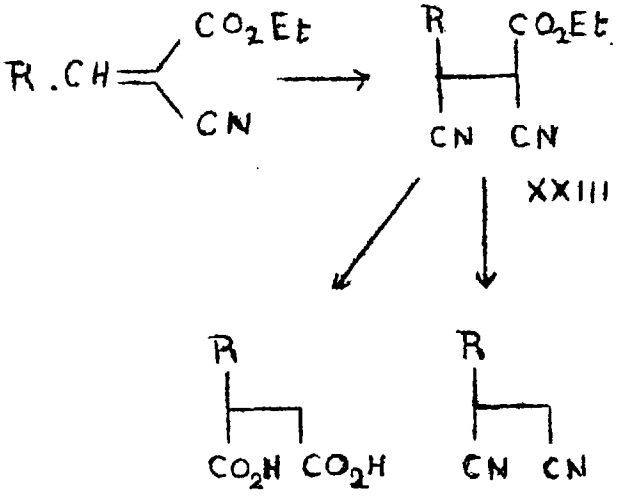
(i) The addition of hydrogen cyanide to αβ (or βγ) unsaturated nitriles.[64] This reaction only occurred in certain cases and then not always in good yields.

(ii) A modification of method (e) for monoalkylsuccinic acids, above.

Instead of completely hydrolyzing the intermediate αβ-dicyano ester XXIII to the diacid, in certain cases compounds of structure XXIII have been partially hydrolyzed, and decarboxylated, to the corresponding dinitrile.



XXII



XXIII

However neo-pentylsuccinonitrile (XXVI) was synthesized by yet another route, as follows:

$$Me_3C.OH \longrightarrow Me_3C.Cl \longrightarrow Me_3C.MgCl$$

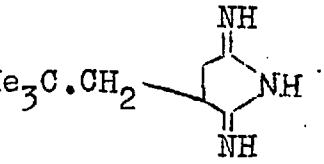
$$\xrightarrow{CH_2=CH.CH_2Cl} \underset{\substack{e \quad d \\ a}}{Me_3C.CH_2} \!\!\diagup\!\!\diagdown \!\!\begin{matrix} H\ b \\ H\ c \end{matrix} \xrightarrow{SO_2Cl_2}$$

$$Me_3C.CH_2.CHCl.CH_2Cl$$
$$f \quad d,e \quad a \quad b,c$$

XXIV

$$\xrightarrow{NaCN} \underset{f \quad d,e \ a \quad b,c}{Me_3C.CH_2CH(CN).CH_2CN} \xrightarrow{NH_3}$$

XXVI



XXVII

It was hoped that this method would constitute a general synthesis of monosubstituted-succinonitriles.

4,4-Dimethylpent-1-ene (XXIV)

Witmore and Homeyer[69] converted t-butyl chloride[70] into its Grignard reagent and reacted this with allyl bromide. The product, 4,4-dimethylpent-1-ene, was then fractionated. Repetition of this reaction and fractionation of the product (through a 60 cm. Steadman column)

gave a productwhich could be shown, by n.m.r. spectroscopy, to contain 43% of XXIV (representing a 26% yield). This was contaminated with 52% allyl bromide (α-methylene doublet, 6.15 τ; J = 7.3 c/s), and 5% t-butyl bromide (singlet 8.22 τ). Although allyl bromide could be removed from the product by reaction with cyclohexylamine, it was found better to prepare XXIV using allyl chloride. A pure product (33% yield) could then be obtained. [N.m.r. spectrum in carbon tetrachloride: a, 4.25 τ; b and c, 4.9 to 5.4 τ; d, 8.13 τ; e, 9.16 τ; J_{ab} = 18.5 c/s; J_{ac} = 8 c/s; J_{ad} = 7 c/s.]

1,2-Dichloro-4,4-dimethylpentane (XXV)

The olefin XXIV could be converted, in good yield, into 1,2-dichloro-4,4-dimethylpentane by reaction with sulphuryl chloride[71] in refluxing carbon tetrachloride. [N.m.r. spectrum in carbon tetrachloride: a, b and c, 5.8 to 6.7 τ; d, 8.15 τ; e, 8.34 τ; f, 8.98 τ; J_{ad} = 7.7 c/s; J_{ae} = 2.4 c/s; J_{de} = 15.2 c/s.]

Neo-Pentylsuccinonitrile (XXVI)

Generally, alkali metal cyanides give no more than a 30% yield of alkyl nitrile on reaction with alkyl bromides in aqueous ethanol, and alkyl chlorides are even

less reactive. However, by using such solvents as dimethyl formamide and, more particularly, dimethyl sulphoxide, secondary alkyl nitriles can be prepared in good yields. Alkyl bromides give low yields of nitriles on reaction with sodium cyanide in dimethyl sulphoxide, as bromides are susceptible to oxidation by dimethyl sulphoxide under alkaline conditions.[72] A number of authors[73,74] have now found it possible to convert chlorides, both primary and secondary, into nitriles in yields ranging up to 70% for secondary - and up to 100% for primary - chlorides. Smiley and Arnold[73] were also able to convert diprimary chlorides into dinitriles in good yields (e.g. succinonitrile was prepared in 56% yield), and so it was hoped that monoprimary-monosecondary dichlorides would be useful precursors to monosubstituted succinonitriles.

Reaction of 1,2-dichloro-4,4-dimethylpentane XXV with sodium cyanide in dimethyl sulphoxide at 130-145° gave neo-pentylsuccinonitrile XXVI in 60% yield. [N.m.r. spectrum in carbon tetrachloride: a, b and c, 6.9 to 7.5 τ; d, 8.19 τ; e, 8.54 τ; f, 8.93 τ; J_{ad} = 9.4 c/s; J_{ae} = 3.6 c/s; J_{de} = 13.8 c/s.]

From the distillation fore run, 18% of the dichloride (XXV) was recovered, on refractionation. A lower boiling fraction (9%) was obtained, half of which appeared to be starting material, the remainder was made up by two other compounds. These compounds were olefinic, non nitrilic and present in roughly equal amounts (as shown by the gas liquid chromatogram and the infra red and n.m.r. spectra).

Neo-Pentylsuccinimidine

The pigment precursor, neo-pentylsuccinimidine (XXVII) was obtained, in 80% yield, by reaction of the dinitrile with methanol ammonia in a Carius tube at 150-155°.(75) A reaction at 145-150° gave only a 65% yield. The imidine decomposed at approximately 160° (giving no trace of pigment), afforded a crystalline picrate, and was hydrolysed by boiling water to the corresponding imide.

Reaction of neo-pentylsuccinonitrile with methanolic ammonia in an enamel lined autoclave gave a reduced yield of imidine contaminated with a significant amount of a metallated pigment. This was presumably because of access of the reaction mixture to metal.

Metal-free Pigment

When neo-pentylsuccinimidine was refluxed in n-butanol (or n-propanol) containing nitrobenzene, tetra-(neo-pentyl)-

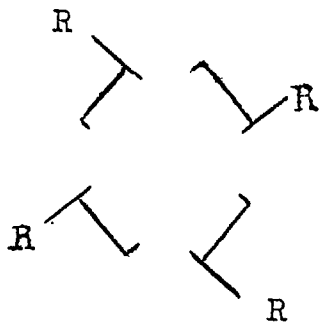
tetrazaporphin was produced. The solvents were removed by steam distillation and the crude pigment was filtered from the remaining hot water. A colourless solid often crystallized from the cooled filtrate. This solid proved to be neo-pentylsuccinamide. The crude pigment was dissolved in benzene, the solution was filtered, and the undissolved material found to contain considerable quantities of the succinamide. The benzene solution was dried and chromatographed on alumina (Spence 'H'), when the pigment was eluted as a fast moving band. On some occasions there was a slight indication of splitting of the pigment band. This observation was confirmed by thin-layer chromatography of the pigment in benzene, on both neutral alumina and silica (Merck 'G').

On alumina three pigment spots were clearly indicated with (averaged) R_F values of 0.70, 0.65 and 0.58. On silica the separation was better and the second spot even showed signs of being resolved into two spots. In the few chromatograms where four spots were discernible, the average R_F values for the components A,B,C,D were 0.69, 0.47, 0.33 and 0.25. It was necessary to dry the silica plate and elute twice more with benzene in order to effect a complete separation of the two closest moving components.

The pigment was sufficiently soluble in deuterochloroform to enable the n.m.r. spectrum to be obtained. However, the material first examined gave a broad lined spectrum, indicating the presence of paramagnetic impurities. Careful rechromatography removed this contamination. In some later preparations pigment free from paramagnetic impurity could be obtained directly. The random occurrence of contamination suggested that traces of metals were being picked up from some of the various batches of chromatographic alumina. When the imidine was heated in n-butanol-nitrobenzene, together with 10% palladized charcoal as an additional dehydrogenating agent, the pigment obtained was contaminated with a significant amount of its palladium derivative. This illustrated the great ease of formation of metal pigment.

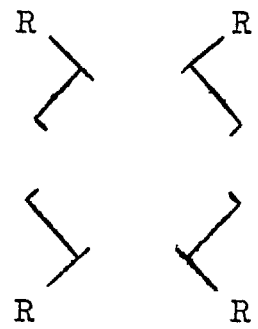
The n.m.r. spectrum of the purified pigment was consistent with the material being tetra-(neo-pentyl)-tetrazaporphin. The t-butyl and aromatic proton signals appeared as multiplets and this, together with the banding of the material on thin-layer chromatograms, confirmed that the product was a mixture of all of the four possible isomers [VIII, IX, X and XI; R ≡ $CH_2.CMe_3$]. Attempts to chromatograph the pigment on silica, even on a short

column, resulted in a certain amount of irreversible adsorption, leading to considerable loss of material. The intense colour of the adsorbed material made it difficult toobserve banding on the column. In another experiment, the pigment was chromatographed in dry benzene on a (100 x 4 cm.) column of (Brockmann) grade 2 alumina (Spence 'H'). Three bands were clearly seen but the second, main, band showed no sign of splitting into two components, as had been observed in the thin-layer system.



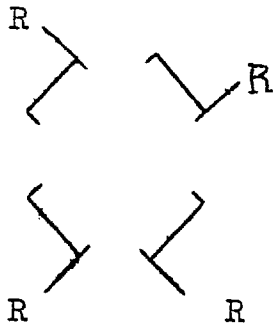
VIII

isomer (i)



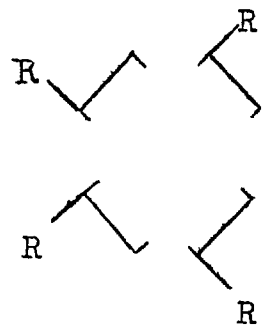
IX

isomer (ii)



X

isomer (iii)



XI

isomer (iv)

The three bands were eluted, the first (isomer A) and the second (isomer B + C) could be separated cleanly. The third band could not be separated from the tail of the second band and was found to be a mixture of isomers B, C and D, despite the rejection of an intermediate fraction between the collection of the second and third bands. When the pigment was chromatographed on B.D.H. alumina (100 x 4 cm. column) of grade 3 to 4 no separation of the isomers was observed.

N.m.r. Spectra

Isomer A

The first band on the alumina column chromatogram could be eluted and the component, isomer A, isolated as a purple solid, which under a microscope appeared as needle crystals. Its n.m.r spectrum in deuterochloroform showed four sharp singlets the positions of which were variously dependent on concentration, e.g.:

Ring protons (4 protons), 0.95 τ; methylene protons (8 protons), 5.97 τ; t-butyl protons (36 protons), 8.68 τ; N-H protons (2 protons), 12.62 τ.
The observed concentration dependence of the absorption signals was consistent with the molecules forming aggregates in solution.

In an applied magnetic field the induced ring current of the aromatic system establishes a magnetic field at its centre opposed to the applied magnetic field, as represented in figure 4. In this respect the system is equivalent to a magnetic dipole of the orientation shown in figure 4, situated at the centre of the macrocycle.

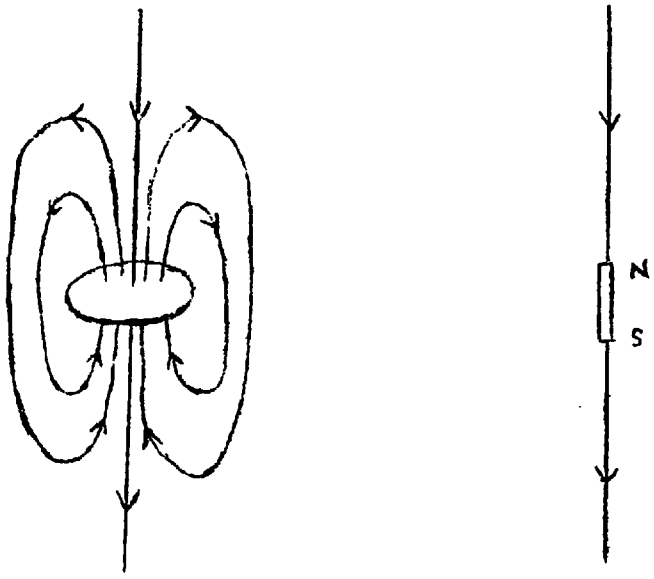
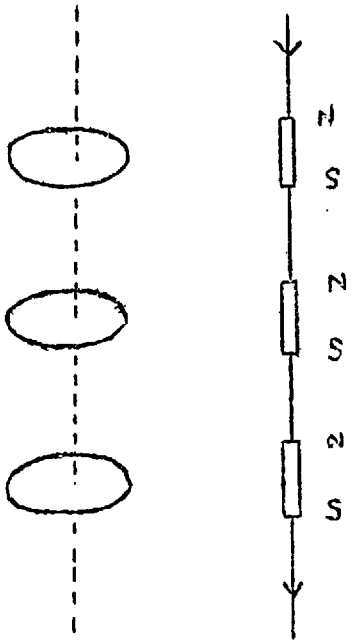


Figure 4

The position of the N-H protons near the region of highest induced magnetic flux caused them to be greatly shielded. Their resonance position is thus at about 12.5 τ, as compared to 2 τ for the N-H protons in pyrrole.

On concentration of the solution all the proton signals move to a higher field.

A proton placed above the plane of the molecule would be shielded by an amount depending on the distance of the proton from the plane, and the maximum shielding would be experienced by a proton directly above the centre of the macrocycle. The N-H protons showed the greatest rate of increase of line position with concentration. This suggested that, of the groups of protons, the average positions of the N-H protons were nearest to the centres of the neighbouring molecules in the aggregate, indicating an aggregate of the form represented in figure 5(a). This form of aggregation may be due to the application of the magnetic field. The induced molecular dipoles would attract each other and tend to align with the magnetic field, in the manner illustrated in figure 5(b). The system contrasts with the aggregation occurring on crystallization. As shown in figure 6, the molecules then tend to aggregate in offset planes, the governing factor being the bonding between the macrocycles of the sort represented in VI (Chapter 1). Were this latter system of aggregation to persist in solution, in the applied magnetic field, the peripheral proton signals would be expected to be more concentration dependent than the N-H protons, which was not the case.



(a) (b)

Figure 5

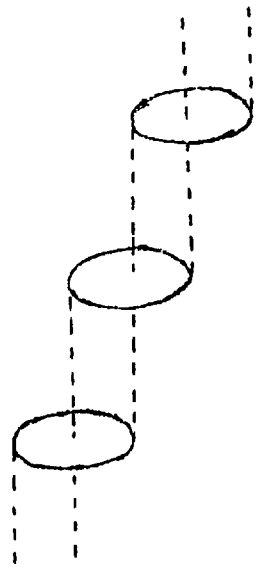


Figure 6

As noted in Chapter 1 the four possible isomers of a tetra-alkyltetrazaporphin are likely to be distinguishable by n.m.r. spectroscopy. The simplicity of the spectrum of isomer A would suggest it to be either isomer (i) or (ii) [VIII or IX] in which the t-butyl, methylene and aromatic protons would be equivalent.

For similar substances two main factors will govern their rate of elution from a chromatogram:

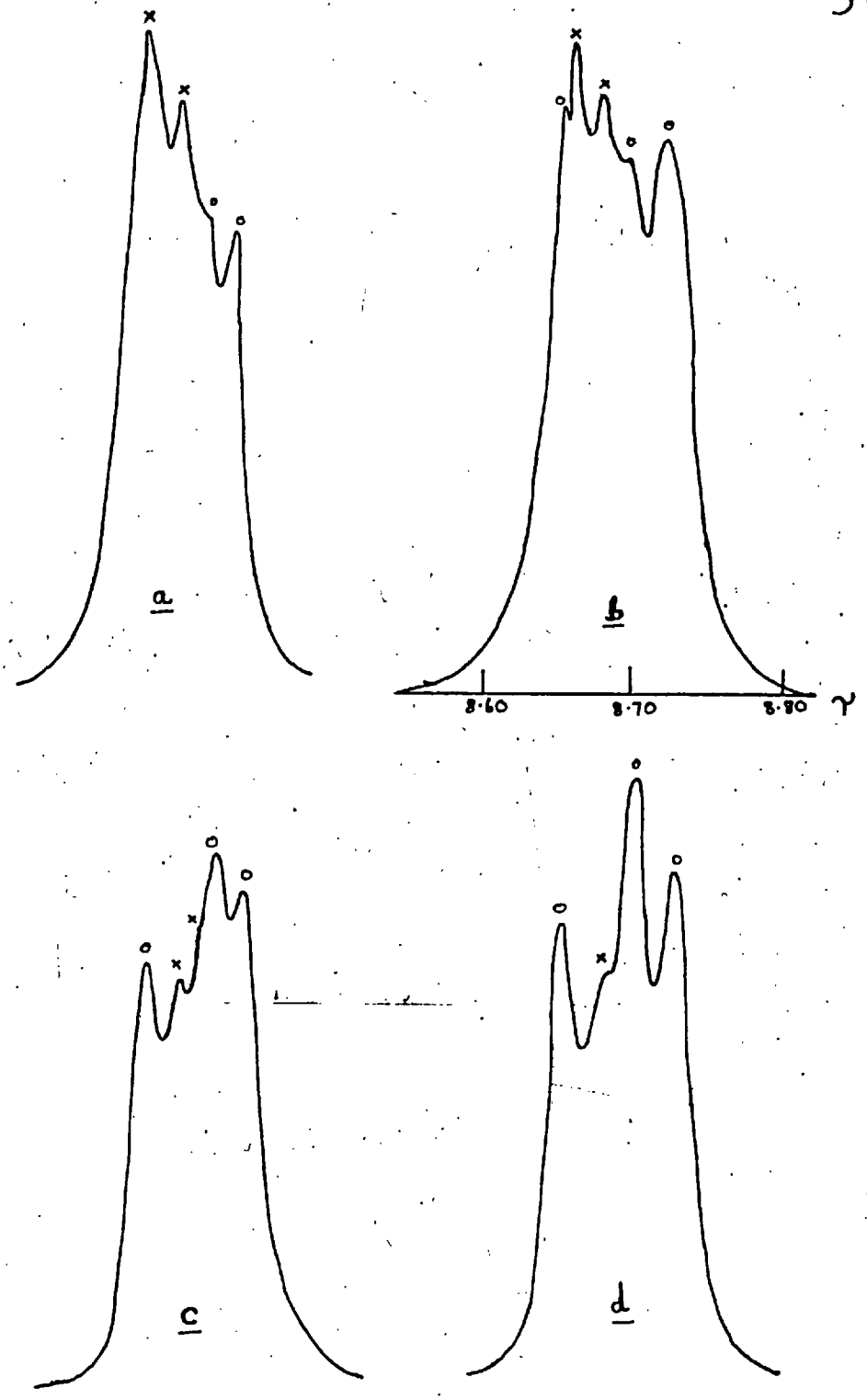
(a) The relative solubilities of the substances concerned. The most soluble would be eluted preferentially.

(b) The polarity of the substances. The most polar would be held most strongly by an adsorbent such as alumina.

Of the fractions isolated from the column the first fraction (isomer A) was noticeably the least soluble fraction, so factor (a) appears of least importance. Of the two possibilities for isomer A, isomer (ii) would be the most polar; in fact it would be the most polar of all the four isomers. Hence it would seem reasonable to assign structure VIII (isomer (i)) to isomer A. It is hoped to confirm this suggestion by X-ray crystallographic studies.

Isomers B and C

By taking fractions of the second band, as it was eluted from the alumina column, mixtures of isomers B and C could be obtained in varying proportions. This variation was shown by thin-layer chromatography of the fractions on silica. Alumina therefore did differentiate between isomers B and C although no sign of this was shown on an alumina thin-layer chromatogram. The n.m.r. spectra of these fractions showed numerous t-butyl and aromatic proton signals, and showed, in "high" concentration (above 5% w/w solution in deuterochloroform), two methylene signals. The t-butyl signals for a number of mixed fractions are reproduced in figure 7. The proportion of isomer C increased in passing from (a) to (d). In (a),



× ≡ Isomer B Signals ○ ≡ Isomer C Signals

Figure 7

isomer B dominated and in (d), C greatly dominated. [Spectra (a),(c) and (d) were of saturated solutions (at 37.5°) and spectrum (b) was of a 4.5% w/w solution.] The solubility of the fraction giving spectrum (b) was found to be about 5.25% w/w at 20° in chloroform. It can be seen that isomer B appeared to give two t-butyl signals while isomer C gave three.

Consideration of the possible isomeric structures showed that isomer (iv) [XI] would have two distinguishable types of side chain. Hence isomer B corresponded to structure XI [R ≡ $CH_2.CMe_3$]. It could also be seen that isomer (iii) [X] alone had more than two distinguishable side chains, therefore isomer C most probably has the structure X.

On dilution all of the signals moved to lower field and in the case of the t-butyl main proton signals the shift on diluting from 4.5% w/w to 0.17% w/w was less than 0.02 τ. Over the same concentration change the N-H proton signal shifted by 0.82 τ, the methylene proton signal by 0.10 τ and the aromatic proton signals by 0.21 τ. In figures 8, 9 and 10 the positions of the aromatic, methylene and N-H proton signals are shown, plotted against concentration. By extrapolation, the following line positions at infinite dilution have been obtained - aromatic

TETRA-(NEO-PENTYL)-TETRAZAPORPHIN

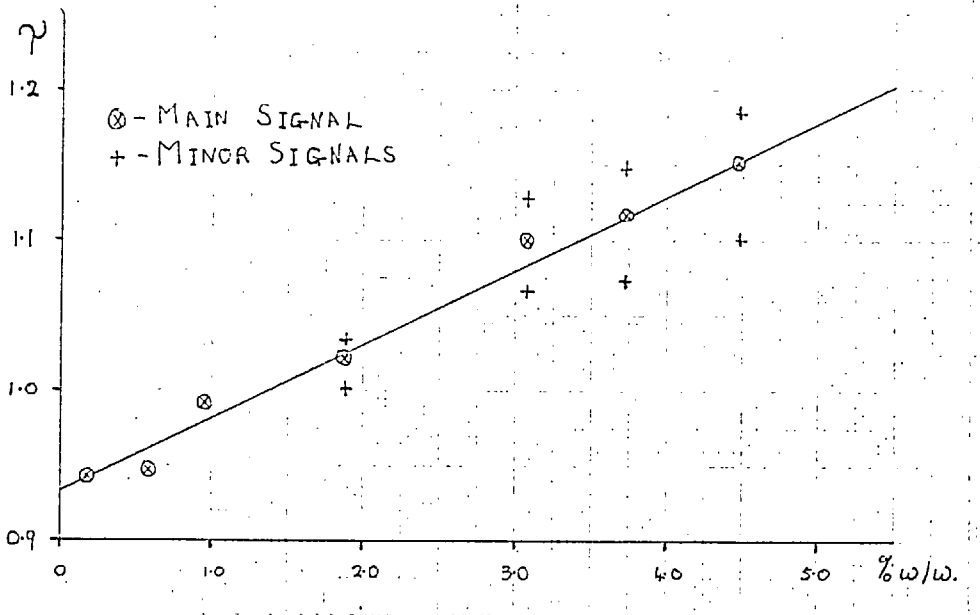


FIGURE 8 AROMATIC PROTONS

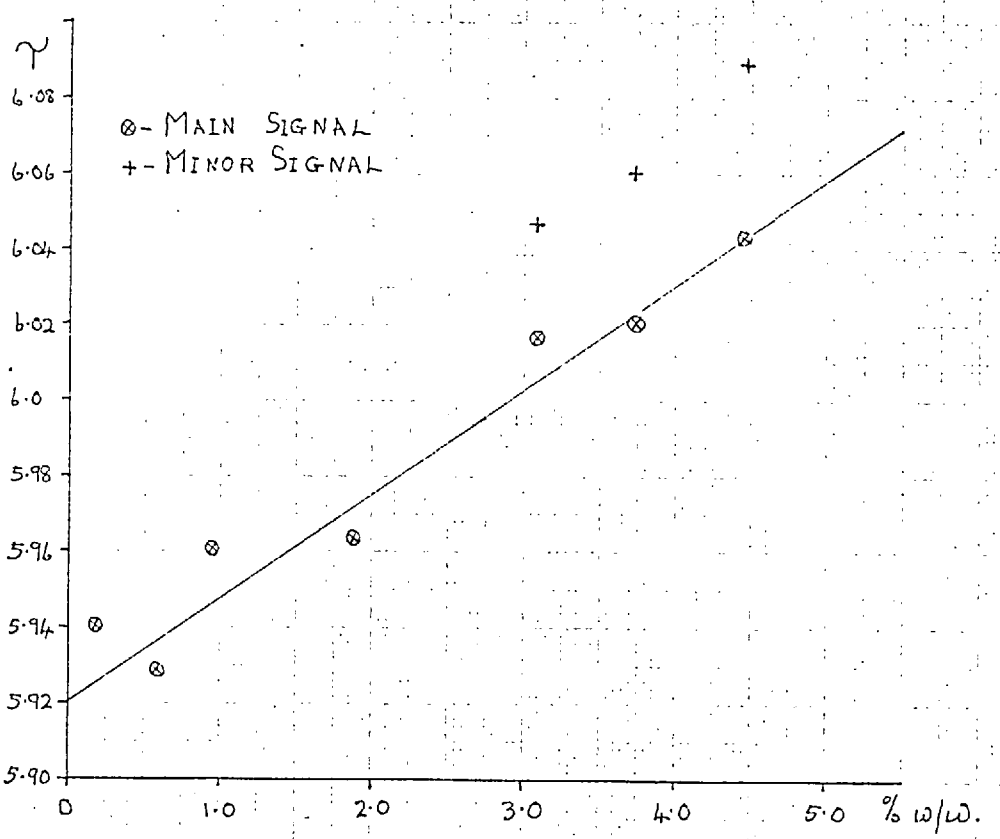


FIGURE 9 METHYLENE PROTONS

TETRA-(NEO-PENTYL)-TETRAZAPORPHIN

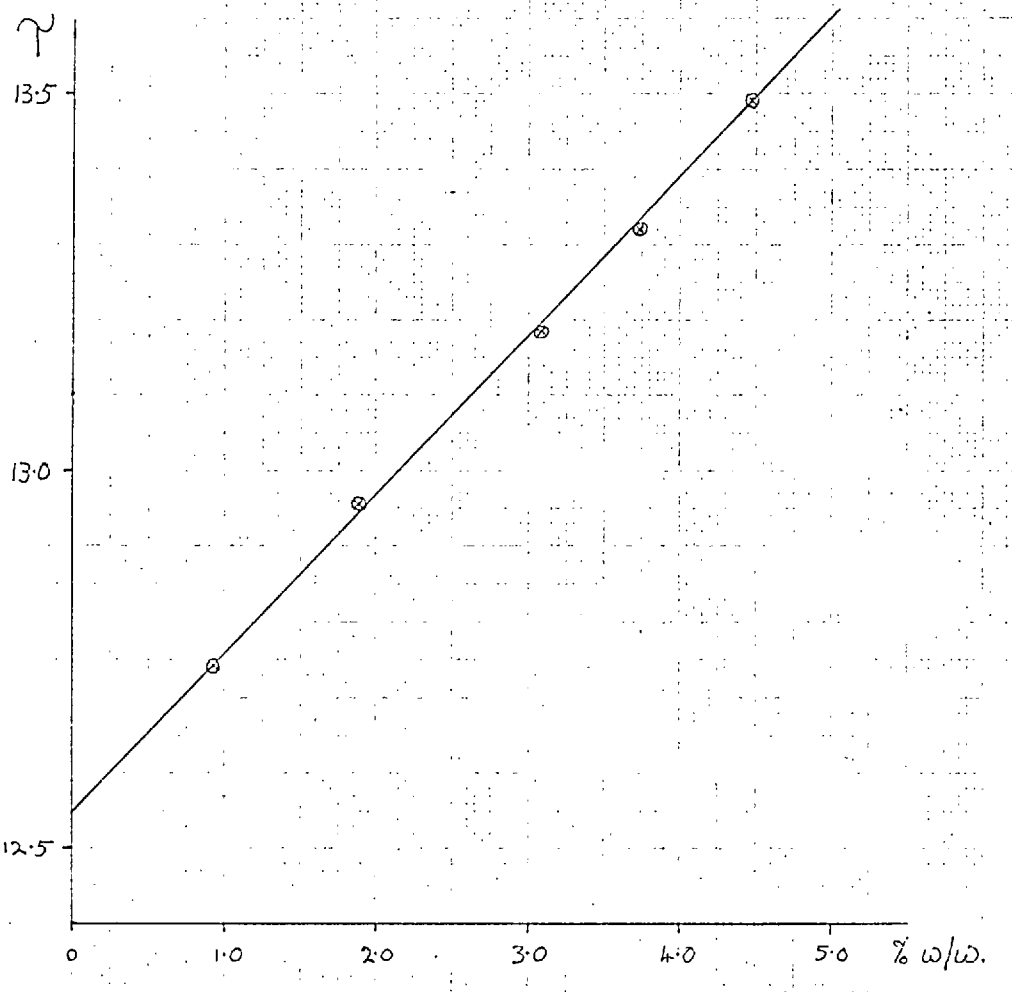


FIGURE 10

N-H PROTONS.

protons 0.93 τ; methylene protons 5.92 τ; N-H protons 12.55 τ. These should be the line positions of the respective protons in the hypothetical unassociated molecule. Calculations are in hand, using these line positions, to estimate the extent of the ring current in the macrocycle.

In the more concentrated solutions investigated, the ill defined aromatic proton absorption appeared as three signals. On dilution these proton signals collapsed to a sharp singlet. The methylene signals similarly reverted to a singlet on dilution. Abraham et al.[30] reported the n.m.r. spectra in deuterochloroform of the isomers of coproporphyrin tetramethyl ester and found that in 0.2M solution the isomers were distinguishable. On dilution these isomers became indistinguishable. This was ascribed to the formation of aggregates in solution which caused some buckling of the macrocycle. The relative positioning of the side chains would control the degree of aggregation hence causing the difference between the isomers.

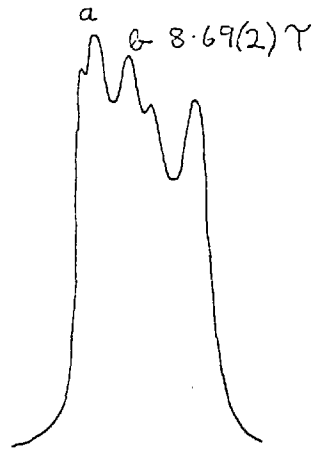
The shifts, on dilution, of the methylene and aromatic proton signals in the tetra-(neo-pentyl)-tetrazaporphin isomers would appear to support these conclusions. However, even in 0.17% w/w solution more than one t-butyl

proton signal was clearly visible. The changes, on dilution, of the t-butyl signal are reproduced in figure 11. The separation between the signals a and b, assigned to isomer (iii), appear to move further to low field than the signals from isomer (ii). The former signals progressively became more masked by the latter signals.

The behaviour described suggests that even at infinite dilution the t-butyl signals would be distinguishable.

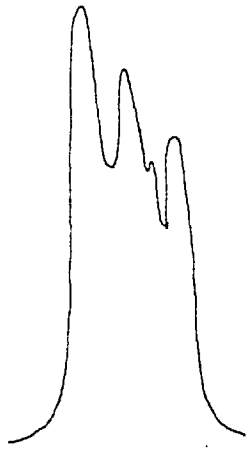
Isomer D

The fourth isomer could not be separated from isomers B and C. The mixed product obtained, unlike the mixture of isomers B and C, was crystalline. This crystalline product proved difficult to dissolve in deuterochloroform without boiling, hence the n.m.r. spectrum of this fraction was not of a saturated solution. The aromatic, methylene and N-H protons all appeared as singlets at 0.95, 5.95 and 12.58 τ, respectively. This suggested that the spectrum would be best compared with the 0.58% w/w solution ofisomers B and C. [Singlets at 0.95, 5.93 and 12.62 τ.] The t-butyl signals shown in figure 12, have an extra signal in the spectrum of the mixture of 3 isomers, (a), compared with that of the two-isomer mixture, (b). This singlet was at higher field [8.74 τ] than any other t-butyl proton signal observed, and was presumably due to



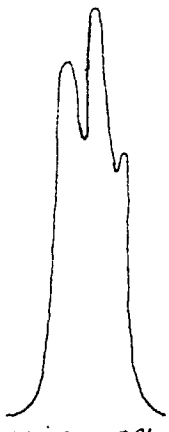
(a) 4·47 % w/w.

(b) 3·74% w/w.

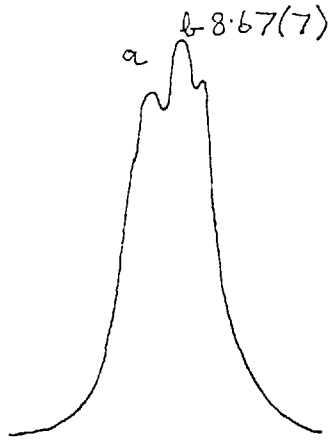


(c) 3·08% w/w.

(d) 1·89% w/w.



(e) 0·58% w/w.



(f) 0·173 % w/w

FIGURE 11

isomer D. It can be seen that the remaining isomer, (ii) [IX], can be expected to give a single t-butyl proton signal. Each side chain in this isomer is in close proximity to another side chain. If steric hindrance between these side chains causes them to spend a large proportion of their time above (or below) the molecular plane then the t-butyl groups would be expected to be less deshielded than other such groups which could attain averaged positions nearer the plane of the ring system.

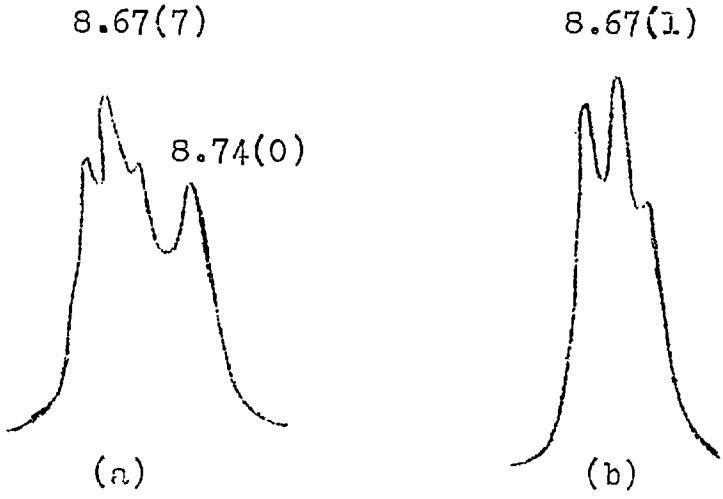


Figure 12

From the n.m.r. spectral data of deuterochloroform solutions it can now be concluded that the probable order of elution of the isomers from the alumina column was (i), (iii), (iv), (ii) [i.e. VIII, X, XI, IX corresponding to isomers A, B, C, D]. Of the isomers only (i) could be isolated pure.

N.m.r. Spectrum in Trifluoroacetic Acid

Abraham et al.[30] found that the spectra of porphyrins in trifluoroacetic acid did not vary with concentration. This was because in this media the molecules exist in the diprotonated form. The positively charged molecules repel each other and then have no tendency to aggregate. Tetra-(neo-pentyl)-tetrazaporphin, isomers B and C, in trifluoroacetic acid solution showed two signals for the t-butyl protons, the main signal at 8.53 τ and the minor signal at 8.57 τ. The methylene and aromatic protons appeared as broad singlets at 5.79 τ and 0.55 τ. The protons attached to nitrogen could not be located.

Chromatography of tetra-(neo-pentyl)-tetrazaporphin on alumina in benzene gave approximately 11% of isomer A, 70% of the mixture of isomers B and C, and 7% of the mixtures of isomers B, C and D (the remaining 12% was rejected in intermediate fractions). Assuming formation of the pigment mixture by random condensation of neo-pentylsuccinimidine units, the mixture would contain 12.5% isomer (i) [i.e. A]; 25% isomer (iii) [i.e. B]; 50% isomer (iv) [i.e. C] and 12.5% isomer (ii) [i.e. D]. It was noticeable that the first two fractions taken from

the above column (isomer A; isomers B + C) corresponded well with the expected isomeric constitution.

It was found that isomer A did not melt below 300° but that all mixtures of isomers melted in the range 240-250°.

Metallated Derivatives

It was found possible to prepare metallated pigments directly from neo-pentylsuccinimidine by condensing it with an anhydrous metal salt in a refluxing nitrobenzene-butanol mixture. This method was successful for preparing hydroxyl iron(III) tetra-(neo-pentyl)-tetrazaporphin from ferrous chloride (Chapter 6). The nickel and magnesium pigments could be prepared (~ 30% yield) by this method, free from the metal-free pigment, but containing reduced tetrazaporphins. The reduced pigment could not be removed by chromatography on alumina; chromatography of nickel tetra-(neo-pentyl)-tetrazaporphin on silica resulted in extensive irreversible adsorption. The reduced pigment produced with the nickel pigment appeared not to be oxidized by heating in air for 3 hours at 100°.

The magnesium pigment could be prepared, with considerable amounts of reduced pigment, by reaction of neo-pentylsuccininitrile with magnesium n-propoxide in

refluxing n-propanol. Most of the starting material could be recovered after 24 hours, suggesting that higher reaction temperatures (i.e. using higher alcohols) might be advantageous. The magnesium pigment was demetallated to the metal-free pigment, with acetic acid, and this could be separated by chromatography from reduced pigment. The product (10% yield with respect to the unrecovered dinitrile) was a mixture of isomers.

Silicon tetrachloride, in the presence of four equivalents of pyridine, appeared to form a complex which reacted with neo-pentylsuccinimidine in chlorobenzene to give a green pigment which rapidly went blue on exposure to air (λ_{max} = 585 mμ). The mass spectrum of the isolated pigment showed no parent ion and no trace of chlorine. The initial product was assumed to be dichlorosilicon tetra-(neo-pentyl)-tetrazaporphin which was rapidly hydrolysed on isolation to the dihydroxy species. The product persisted in the presence of acid, showing it was not a pyridinium salt of the metal-free pigment.(76) The isolated product would not react with refluxing n-butanol to give the silicon diether pigment.

Anhydrous stannic chloride, in the presence of four equivalents of pyridine would not react with tetra-(neo-pentyl)-tetrazaporphin in refluxing chlorobenzene.

It was hoped that under these conditions the stannic chloride would react with two moles of metal-free pigment to give di-[tetra-(neo-pentyl)-tetrazaporphin] tin analogous to diphthalocyanine tin.(77) This compound appeared to have a tin atom "sandwiched" between two phthalocyanine ring systems. A reaction did occur when a further equivalent of stannic chloride was added to the reaction mixture. The blue product then obtained (λ_{max} = 354; 596 mμ) was chromatographed on powdered tartaric acid in chlorobenzene. No satisfactory analysis could be obtained for the product, however.

Nickel Tetra-(neo-pentyl)tetrazaporphin

This was prepared by reaction of the metal-free pigment with anhydrous nickel chloride in refluxing n-butanol. A thin-layer chromatogram of the product on silica (Merck 'G') in benzene showed three separate spots (R_F values 0.70, 0.45, and 0.33), however, unlike the metal-free pigment no splitting of the central spot could be detected. Chromatography in benzene on a (B.D.H.) silica column resulted in extensive irreversible adsorption. Use of alumina as adsorbent was more encouraging but a separation of the isomers was not attempted.

NICKEL TETRA-(NEO-PENTYL)-TETRAZAPORPHIN

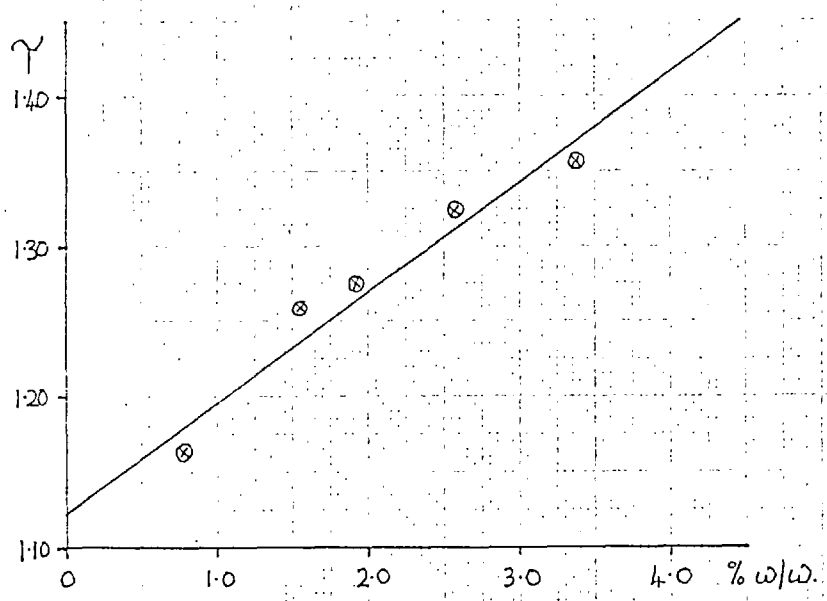


FIGURE 13 AROMATIC PROTONS

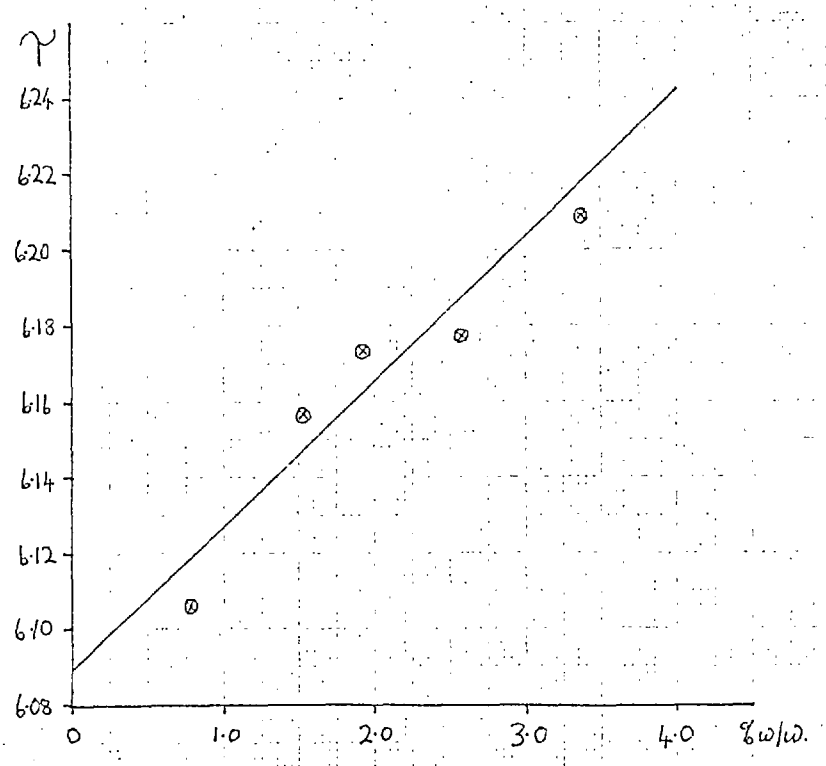


FIGURE 14 METHYLENE PROTONS

The diamagnetic nickel pigment was found to be sufficiently soluble in deuterochloroform for an n.m.r. spectrum to be obtained. The spectrum of a solution, more concentrated than about 3% w/w, showed broad bands only. On dilution distinct splitting of the t-butyl proton signal was observed. In intermediate concentrations, 1.5 to 2.5% w/w, two signals were observed separated by 0.02 to 0.03 p.p.m. Both the aromatic- and methylene-proton signals were unsymmetrical. It was not known whether the general broadening effect was due to traces of paramagnetic impurities or high viscosity of the solution.

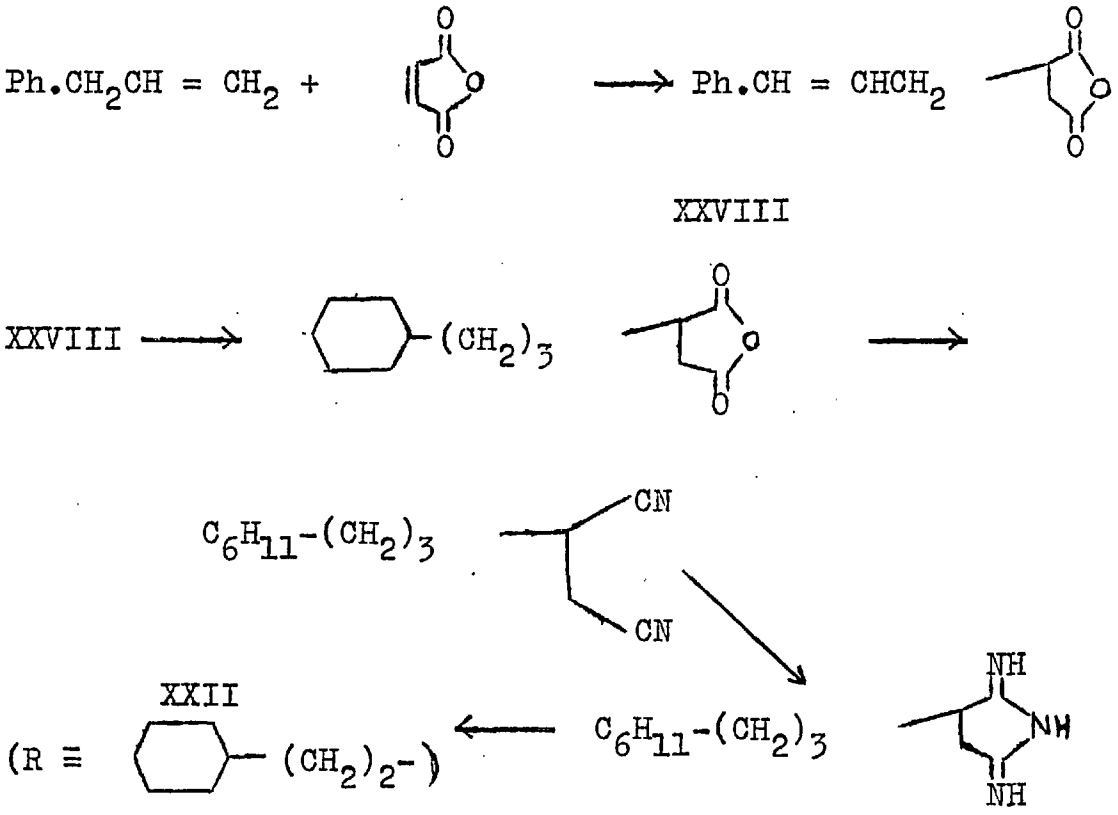
The positions of the signals were, like those of the metal-free pigment, dependent on concentration. Over the concentration range 3.4 to 0.8% w/w the aromatic, methylene, and t-butyl proton signals moved down field by 0.2, 0.1 and 0.03 p.p.m. In figures 13 and 14 the aromatic- and methylene-proton signal positions are plotted as functions of concentration. By extrapolation, the line positions at infinite dilution were obtained as 1.12 τ and 6.09 τ, respectively.

The diamagnetic shift on introducing a metal into the system could be attributed to a reduction in the ring current or to an increase in electron density over the

ring system, or both.

Tetra-(γ-phenylpropyl)-tetrazaporphin

Because of the limited success reported above, in separating isomers of a simple tetrasubstituted tetrazaporphin, it was thought desirable to synthesize a tetrazaporphin with much bulkier substituent groups. Such a product ought to be separated into its isomers much more readily by chromatography. Attempts were made therefore to synthesize tetra-(γ-cyclohexylpropyl)-tetrazaporphin by the following scheme:



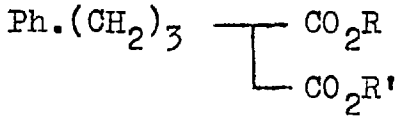
(γ-Phenylallyl)-succinic Anhydride (XXVIII)

Allylbenzene was synthesized from phenyl magnesium bromide and allyl bromide[78] and was condensed with maleic anhydride in refluxing o-dichlorobenzene[79] to give (γ-phenylallyl)-succinic anhydride XXVIII. Condensation under pressure in both benzene and chlorobenzene at temperatures ranging from 170 to 210° (for 12 hours) gave lower yields of product.

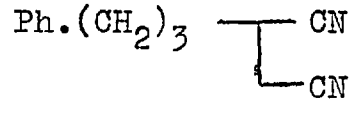
Attempted preparation of (γ-Cyclohexylpropyl)-succinic Anhydride (XXIX)

(a) Attempts to reduce (γ-phenylallyl)-succinic anhydride (XXVIII) with Adams catalyst (B.D.H. or freshly prepared catalyst[80]) in acetic acid, even at 60° under 5 atmospheres of hydrogen for 24 hours, resulted only in the reduction of the olefinic double bond to (γ-phenylpropyl)-succinic anhydride.

(b) Attempts to effect the reduction in ethanol with freshly prepared 'W4' Raney nickel,[80] at 140° and with 100 atmospheres pressure of hydrogen produced only a half ester of (γ-phenylpropyl)-succinic acid (XXX).



XXX



XXXI

R or r' ≡ Et or H

Considerable amounts of material were lost as an insoluble nickel compound.

(γ-Phenylpropyl)-succinimide

Due to the difficulty of reducing the phenyl group it was decided to synthesize tetra-(γ-phenylpropyl)-tetrazaporphin instead.

Both (γ-phenylpropyl)succinic anhydride and the half ester XXX were hydrolysed under alkaline conditions to the corresponding diacid. The solution was then evaporated to dryness with an excess of '880' ammonia and heated slowly to 275°. Under these conditions the required imide was formed.

(γ-Phenylpropyl)-succinamide

(γ-Phenylpropyl)-succinimide, even when finely ground, showed no sign of reacting with '880' ammonia during 2 days.

On a small scale (0.5 g.), the finely ground imide could be converted completely into amide on prolonged reaction with a methanol-liquid ammonia mixture. However, on a larger scale only mixtures were produced. On the large scale it was necessary to heat the reaction mixture in a sealed vessel to 100° before complete reaction occurred.

Lack of time prevented further work in this direction.

EXPERIMENTAL SECTION

4,4-Dimethylpent-1-ene (XXIV)

Magnesium turnings (100 g.; 4.33 moles) were covered with ether (200 ml.; sodium dried) and t-butyl chloride (400 g.; 4.33 moles, prepared from t-butanol[70] in 87% yield) was added in ether (1 litre) over 7 hours. The mixture was allowed to stand overnight, filtered and added over 15 hours to allyl chloride (337 g.; 4.33 moles) in ether (200 ml.) at -10° . The mixture was maintained below 5° during addition and was then kept overnight. The mixture was poured on to ice, the magnesium salts were dissolved by addition of ammonium sulphate and the ether layer was separated. The aqueous layer was extracted with ether (2 x 100 ml.) and the total ether solution was dried over sodium sulphate and fractionated through a 60 cm. packed column fitted with a variable take-off head.

The fraction b.p. 71.5-72.5°/771.5 mm. (104 g.; n_D^{21} 1.3907) was collected and the residue was slowly fractionated through a 15 cm. vacuum-jacketed packed column, using a variable take-off head. A further amount of product (35 g.; n_D^{21} 1.3908) was obtained, b.p.72-73.5°/765.5 mm. Total yield 33%.

1,2-Dichloro-4,4-dimethylpentane (XXV)

4,4-Dimethylpent-1-ene XXIV (104 g.; 1.06 moles) in carbon tetrachloride (100 ml.) was warmed gently to reflux. Redistilled sulphuryl chloride (141 g.; 1.06 moles) in carbon tetrachloride (90 ml.) was added dropwise over 1.5 hours and the mixture was refluxed for a further 1.5 hours. The product was washed with water (75 ml.), then shaken with saturated sodium bicarbonate solution (150 ml.). Solid sodium bicarbonate was added in small portions until no more carbon dioxide was evolved. Water was added to dissolve the excess of solid, and the organic layer was separated, washed with water (2 x 50 ml.) and dried over calcium chloride. The solution was fractionated through a 15 cm. vacuum-jacketed column (packed with Fenske helices). The product boiled at 78-79°/32 mm. (129.3 g.; 73.5% yield; n_D^{21} 1.4472). The product was refractionated b.p. 76-77°/29 mm.; n_D^{25} 1.4448.

Found, C, 49.72; H, 8.45; Cl, 41.86. $C_7H_{14}Cl_2$ requires C, 49.71; H, 8.34; Cl, 41.93%.

Neo-Pentylsuccinonitrile (XXVI)

1,2-Dichloro-4,4-dimethylpentane XXV (18 g.; 0.11 moles) was added during 1 hour to a stirred slurry of

sodium cyanide (11.5 g.; 0.24 moles) in dimethyl sulphoxide (60 ml.; dried by distillation from calcium hydride) at 130°. The mixture was stirred for 2.5 hours at 135-145°. On cooling, chloroform (100 ml.) and saturated brine (75 ml.) were added. The mixture was shaken thoroughly, filtered, and the chloroform layer was separated. The aqueous layer was washed with chloroform (25 ml.) and the total chloroform extract washed with saturated brine (2 x 25 ml.). The chloroform solution was dried over calcium chloride and concentrated on a steam bath. [The distillate was fractionated to give a residue, after removal of chloroform, which was 50% starting material. The remainder comprised ω to α olefines.] The concentrate was distilled under reduced pressure giving some starting material (18%) together with a 60% yield of product, b.p. 95-99°/0.55 mm. (9.7 g.). On refractionation the product boiled at 78° /0.2 mm.; n_D^{24} 1.4412.

Found, C, 71.76; H, 9.34; N, 18.54. $C_9H_{14}N_2$ requires C, 71.97; H, 9.39; N, 18.64%.

Neo-Pentylsuccinimidine (XXVII)

Neo-Pentylsuccinonitrile XXVI (5 g.) was heated in a Carius tube with liquid ammonia (8 ml.) and dry methanol

(12 ml.) to 150-155° for 12 hours. The resultant mixture was evaporated under reduced pressure to a dark semi-solid. The product was then triturated thoroughly with dry ethyl acetate (10 ml.) and filtered. The solid product after being washed with further quantities of ethyl acetate (2 x 4 ml.), was dried under vacuum and so obtained as a pale yellow solid (4.5 g.; 80.8% yield). Even though the imidine could be recrystallized from chloroform-ethyl acetate ($\lambda_{max.}$ = 236 mμ, $\log_{10}\varepsilon$ = 4.26 in dry ethanol) no very satisfactory elementary analysis could be obtained.

Found, C, 64.06; H, 9.64; N, 26.08, 24.45. $C_9H_{17}N_3$ requires C, 64.61; H, 10.24; N, 25.12%.

Neo-Pentylsuccinimidine Picrate

Recrystallized neo-pentylsuccinimidine (76 mg.) in dry ethanol (2 ml.) was added to dry picric acid (105 mg.) in ethanol solution (2 ml.). The mixture was allowed to stand overnight and the product collected. It was recrystallized from chloroform several times to give a yellow crystalline solid (90 mg.) melting sharply at 222-223° with decomposition.

Found, C, 45.24; H, 5.37; N, 21.16. $C_{15}H_{20}N_6O_7$ requires C, 45.46; H, 5.09; N, 21.21%.

Neo-Pentylsuccinimide

When neo-pentylsuccinimidine (200 mg.) was refluxed in water (2 ml.) for 1 hour, neo-pentylsuccinimide crystallized from the solution on cooling, in virtually quantitative yield. The product sublimed above 160° without melting. Found, C, 63.48; H, 8.60; N, 8.47. $C_9H_{15}NO_2$ requires C, 63.89; H, 8.94; N, 8.28%.

Tetra-(neo-pentyl)-tetrazaporphin

Neo-Pentylsuccinimidine (3.7 g.) was refluxed in 1:1-nitrobenzene/n-propanol (120 ml.) for 12 hours and then the mixture was steam distilled. The residue was dissolved in benzene, and the solution was filtered and dried over calcium chloride. The concentrated solution was chromatographed on grade 2 alumina (Spence 'H') in benzene (30 x 4 cm. column). The solution of pigment obtained was concentrated and again chromatographed (100 x 4 cm. column), when three bands were clearly observed. The first fraction was evaporated to dryness, and slightly wet methanol was added. The mixture was warmed and filtered, the insoluble pigment was filtered off and washed with a little methanol. The crystalline product (80.7 mg.) was dried at 80°/0.1 mm. overnight, however small traces of benzene were still retained. Fractions

2 and 3 were similarly isolated (543.1 mg. and 112.8 mg.). An overall yield of 22.4% pigment was obtained, distributed in 11%, 73.5% and 15.5% in fractions 1, 2 and 3. For the tetra-(neo-pentyl)-tetrazaporphin isomic mixture: Found, C, 72.76; H, 8.61; N, 18.64. $C_{36}H_{50}N_8$ requires C, 72.70; H, 8.47; N, 18.84%.

The isomers showed minor, but significant, differences between their infra red spectra in the 'finger print' region. The fractions showed identical ultraviolet and visible absorption spectra, with corresponding extinction coefficients differing by less than 2%. $\lambda_{max.}$ in chloroform (average $\log_{10}\varepsilon$ values):
339.5 mμ ($\log_{10}\varepsilon$, 4.97); 551 mμ (4.73); 595 mμ (3.99); 623 mμ (4.94).

Rechromatography of fraction 3 (100 x 4 cm. column) produced no pure sample of isomer D but a fraction containing mainly isomer C with some isomer B could be obtained, the n.m.r. spectrum of which was reproduced, in part, in figure -7(c). In addition a small fraction of virtually pure, isomer C was obtained (2 mg.). This was used to enrich the above mixture of isomers B and C and the n.m.r. spectrum of the mixture was again recorded (figure -7(d)).

The residue remaining after steam distillation of the, crude, reaction product contained, both, pigment and neo-pentylsuccinamide. The pigment was extracted from this residue leaving the amide which could be crystallized from ethanol, and sublimed without melting above 270°. Found, C, 58.04; H, 9.80; N, 14.78. $C_9H_{18}N_2O_2$ requires C, 58.10; H, 9.75; N, 15.05%.

Magnesium Tetra-(neo-pentyl)-tetrazaporphin

Magnesium (1.5 g.) was caused to react with dry n-propanol (60 ml.) by addition of a crystal of iodine. Neo-Pentylsuccinonitrile (5 g.) was added and the mixture refluxed for 24 hours. The mixture was filtered and the filtrate evaporated over a steam-bath, under water pump vacuum. A dark oil remained from which the starting material (3.3 g.) could be distilled at 0.1 mm. pressure. The residue was dissolved in dry benzene and the solution passed down an alumina column (Spence 'H'). The pigment was strongly adsorbed at the top of the column, which was then eluted thoroughly with sodium-dried benzene. The pigment could then be eluted with 2% ethanol in benzene. The product so obtained was dried under vacuum (1 mm.) giving 406 mg. of magnesium pigment, contaminated with reduced pigment.

The product was ground and shaken with glacial acetic acid (5 ml.) for 1 hour. The suspension was diluted (to 50 ml.) with water and, after 1 hour, was filtered. The residue was washed with water, dried under vacuum, and chromatographed in benzene on alumina (30 x 2 cm.). In this way a 10.3% yield of tetra-(neo-pentyl)-tetrazaporphin (174 mg.) could be obtained.

Nickel Tetra-(neo-pentyl)-tetrazaporphin

Tetra-(neo-pentyl)-tetrazaporphin was refluxed for 6 hours in n-butanol with an excess of nickel chloride. The solvent was removed under reduced pressure, the residue was boiled with water 10 minutes, and the hot solution was filtered. The residue was then washed with a large volume of boiling water, to remove the last traces of nickel chloride: no trace of metal-free pigment could be detected, from the visible absorption spectrum of the product. $\lambda_{max.}$ in chloroform:
319 mμ ($\log_{10} \varepsilon$, 4.59); 342 mμ (4.60); 585 mμ (4.77).
Found, C, 66.44; H, 7.29; N, 16.75; Ni, 9.35.
$C_{36}H_{48}N_8Ni$ requires C, 66.38; H, 7.42; N, 17.22;
Ni, 8.98%.

Attempted Preparation of Dichlorosilicon Tetra-(neo-pentyl)-tetrazaporphin

Neo-Pentylsuccinimidine (330 mg.) was refluxed in dry chlorobenzene (15 ml.), for 5 hours, with nitrobenzene (3 ml.), silicon tetrachloride (0.3 ml.) and dry pyridine (0.84 ml.) [the latter two reagents being in the molar ratio 1:4]. A deep green solution was produced, which rapidly turned blue when attempts were made to isolate the product, presumably due to hydrolysis of the dichloro-silicon product to the corresponding dihydroxy form ($\lambda_{max.}$ = 585 mμ). Every effort had been made to remove all traces of metal from the starting materials.

No change occurred in the absorption spectrum after a portion of the product had been refluxed with n-butanol.

The product was isolated by filtering the reaction mixture, evaporating the filtrate to dryness and dissolving the pigment in benzene. The pigment was deposited on alumina (Spence 'H') from the benzene solution and was then eluted from the column with 10% methanol in benzene. From the eluate 8 mg. of pigment could be isolated.

Allylbenzene

Bromobenzene (242.7 g.; 1.55 moles) was added to magnesium (36 g.; 1.55 moles) in ether (700 ml.). Allyl

bromide (178 g.; 1.47 moles) was then added at such a rate as to maintain the reaction mixture at reflux. When the addition was complete the mixture was refluxed for a further 1.5 hours. Excess of water was added, and the magnesium salts produced were filtered off and washed with ether (3 x 25 ml.). The ether layer was separated, dried over sodium sulphate, and distilled through a 15 cm. vacuum-jacketed column (packed with Fenske helices). A 78% yield of product (135 g.; b.p. 153-154°) was obtained.

(γ-Phenylallyl)-succinic anhydride

Allylbenzene (52.5 g.) and maleic anhydride (43.4 g.) were refluxed in o-dichlorobenzene for 22 hours under nitrogen. The solvent was distilled off at 30 mm. pressure, up to 130°. Overnight the product solidified. It was dissolved in benzene (80 ml.) and the hot filtered solution was cooled to 5° for 3 hours. The product was filtered off, sucked dry and washed with petroleum ether (b.p.60-80°; 2 x 20 ml.). The product was dried for 2 hours at 55°/0.3 mm. (54 g., 55.2% yield).

γ-Phenylpropylsuccinimide

γ-Phenylpropylsuccinic acid (33 g.) was warmed with '880' ammonia (100 ml.) until the mixture became homogeneous.

The solution was then evaporated to dryness, and heated slowly during 30 minutes to 275°. The solid fused at 180°. The temperature was maintained at 270-275° for 1 hour. On cooling, the product could be crystallized from ethanol: yield 72.5% (22 g.). After recrystallization the m.p. was 79-80°.

Found, C, 72.20; H, 7.24; N, 6.46. $C_{13}H_{15}NO_2$ requires C, 71.86; H, 6.96; N, 6.45%.

γ-Phenylpropylsuccinamide

γ-Phenylpropylsuccinimide (15 g.) was heated with methanol (60 ml.) and liquid ammonia (30 ml.) in an enamel lined autoclave to 100° for 3 hours. Evaporation of the solution afforded the amide which was crystallized from ethanol.

Found, C, 64.84; H, 7.40; N, 11.92. $C_{13}H_{18}N_2O_2$ requires C, 66.62; H, 7.74; N, 11.96%.

CHAPTER 4

TETRAZAPORPHINS WITH CHARGED PERIPHERAL SUBSTITUENTS

Introduction

A powerful way of solublizing the tetrazaporphin system would be to attach a number of charged groups to the periphery of the ring system. This would serve the dual prupose of making the molecules attractive towards polar solvent molecules and causing the solute molecules, with like charges, to repel eaoh other. For reasons annotated in Chapter 1 tetrasubstituted tetrazaporphins, with substituents attached via methylene groups to the ring system (XXII) were considered advantageous. Quaternary ammonium salts ($R_1R_2R_3N^+ X^-$) and sulphonic acid salts ($R_1R_2R_3R_4N^+ \ 0.SO_2^-$) would be substituents which might render the corresponding tetrazaporphins (XXII; R ≡ $R_1R_2R_3N^+ X^-$ and $R_1R_2R_3R_4N^+ \ 0.SO_2^-$) soluble in methanol. Both systems could be prepared via the tetra-(halomethyl)-tetrazaporphin (XXII; R = Halogen), and the following synthetic processes were directed towards this tetrahalide.

Bromination of Tetramethyltetrazaporphin Derivatives

Tetramethyltetrazaporphin was prepared, as previously mentioned (Chapter 2), and this was treated with four equivalents of N-bromosuccinimide in refluxing carbon tetrachloride. When the formation of succinimide was complete (about 3 hours) the visible absorption spectrum of the product showed significant differences from that of tetramethyltetrazaporphin. The position of the longer wavelength band was virtually unchanged at 623 mμ compared with 624 mμ in the starting material. However, the other main visible band was shifted to 561 mμ (from 552 mμ) and became much broader and unsymmetrical. This suggested that the product was a mixture of compounds varying in their degree of bromination.

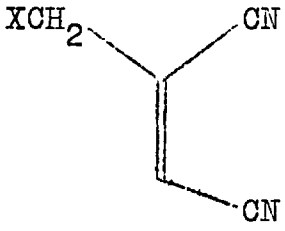
An equal volume of petroleum ether (b.p.60-80°) was added to cause precipitation of succinimide. Unfortunately on evaporation of the filtrate the pigment rapidly and completely decomposed.

Nickel tetramethyltetrazaporphin was similarly treated with various proportions of N-bromosuccinimide, up to 4 equivalents. Again this resulted in a slight bathochromic shift of the visible band (585 mμ) whilst the ultra violet band was virtually unaffected. More obvious was the marked broadening and decrease in symmetry of the visible

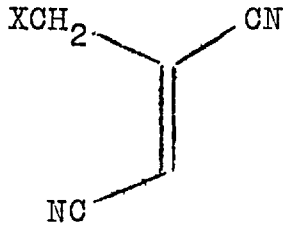
band. The apparent production of mixtures, although not altogether unexpected, led to the abandonment of this approach. It was, of course, essential to isolate a pure product of known structure in this investigation.

Halogenation of Citraconononitrile and Mesaconononitrile

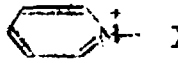
Attention was briefly turned to the synthesis of either halomethyl-maleonitrile XXXII or - fumaronitrile XXXIII from citraconononitrile and mesaconononitrile by allylic halogenation.



XXXII



XXXIII

It was hoped that conversion to acetate (XXXII or XXXIII; X ≡ OAc) or pyridinium halide (X ≡  X⁻), followed by reaction with magnesium alkoxide would yield the corresponding pigments.

However, neither citraconononitrile nor mesaconononitrile would react with an equivalent of N-bromosuccinimide (in the presence of 5% azo-bis-isopropylcyanide) in refluxing carbon tetrachloride. Citraconononitrile would not react at temperatures up to 120° without a solvent and with

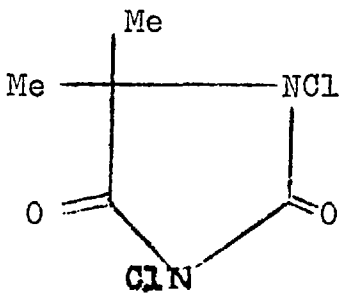
benzoyl peroxide. It also failed to react with the allylic chlorinating agent 1,3-dichloro-5,5-dimethylhydantoin XXXIV, using benzoyl peroxide and azo-bis-isopropylcyanide catalysts, or in the presence of strong light for extended periods. At reaction temperatures up to 160° substantial amounts of starting material could be recovered, whilst at higher temperatures there was decomposition. The recovered material could be identified by its various spectra, in particular the n.m.r. spectrum. This failed to give any evidence of cis-trans interconvertion occurring. [In carbon tetrachloride:-
Citraconononitrile: = CH, 4.10 τ (q), J = 2 c/s; CH_3, 7.79 τ(d)
Mesaconononitrile: = CH, 3.98 τ(q), J = 1.5 c/s; CH_3, 7.70 τ(d)]

It had not been anticipated that the above nitriles would fail to undergo the Wohl-Ziegler reaction. Bruylants[81] was able to brominate crotononitrile and iso-crotononitrile with N-bromosuccinimide although he isolated the products in only 34% and 27% yield after 2 hours at 110° and 118° respectively. The remaining unchanged nitriles were recovered.

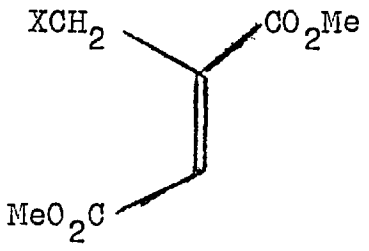
Bromination of Dimethyl-Citraconate and -Mesaconate

Dimethyl citraconate was brominated in the allylic position with N-bromosuccinimide in refluxing carbon

tetrachloride to give the trans product, dimethyl (bromomethyl)-fumarate XXXV (X ≡ Br).



XXXIV



XXXV

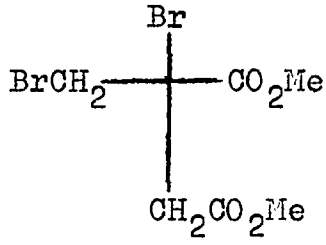
The same product was produced by bromination of dimethyl mesaconate. In both cases the n.m.r. spectrum of the crude product showed the reaction to have gone 90% to completion. [In carbon tetrachloride solution:— Br-CH_2, 5.32 τ (s), $=\overset{|}{C}H$, 3.31 τ (s); 2MeO, 6.14 τ (s) and 6.19 τ (s).

Unlike citraconononitrile and mesaconononitrile the vinyl proton was not coupled to the allylic methylene protons].

Bromine could be added to dimethyl itaconate and on distillation of the product XXXVI under reduced pressure hydrogen bromide was eliminated giving dimethyl (bromomethyl)-fumarate. It was necessary for the bromo group of dimethyl (bromomethyl)-fumarate to be converted into some other function before the ester groups could be transformed to amide groups, by reaction with ammonia. It was hoped that this amide might then be dehydrated to

the substituted fumaronitrile XXXIII, a possible pigment precursor. Possibilities were:

(a) Conversion of the bromide into a benzyl ether, which might be hydrolysed under mild conditions to the corresponding alcohol at a later stage. For instance, (hydroxymethyl)-fumaronitrile (XXXIII; X ≡ OH) might be generated by this method.

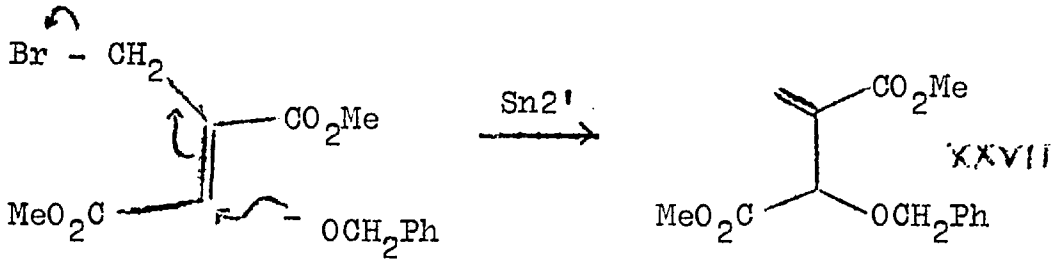


XXXVI

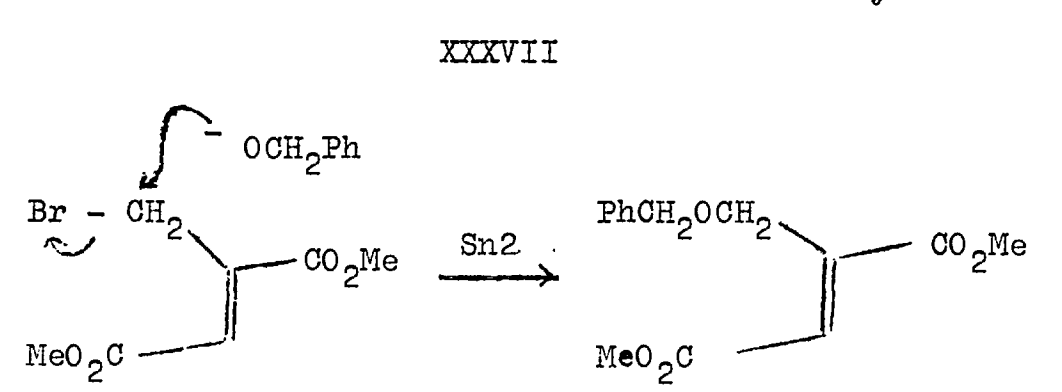
Sodium benzyloxide was prepared as a suspension in anisole by reaction of benzyl alcohol with sodium hydride. An equivalent of dimethyl (bromomethyl)-fumarate was then added and the mixture refluxed. Only a 30% yield of dimethyl (benzyloxymethyl)-fumarate (XXXV; X ≡ OPh) could be isolated. [N.m.r. spectrum in carbon tetrachloride: Phenyl-H, 2.92 τ (s); vinyl-H, masked by impurity; Benzyl methylene and allylic methylene-H, 6.11 τ or 6.21 τ; methoxyl-H, 6.40 and 6.44 τ (s)]. Possibly, material was lost by ester exchange:

$$PhCH_2O^- + MeO.CO.R \rightleftharpoons PhCH_2O.CO.R + MeO^-$$

It is also possible that bromide ion was displaced not in the desired Sn2 reaction, but in a competing Sn2' process:



XXXVII



XXXVIII

The product could then readily polymerize under the prevailing alkaline conditions.

Repetition of the reaction in refluxing benzene gave no definite product, and much starting material was recovered.

Attempted conversion of dimethyl (benzyloxymethyl)-fumarate into the corresponding diamide by a reaction

with '880' ammonia failed. After 2 days a dark brown oil was obtained and a trace of mesaconamide.

(b) By addition of bromine to dimethyl itaconate and then reaction with two equivalents of sodium benzyloxide in benzyl alcohol, dimethyl (benzyloxymethyl)-fumarate was obtained, rather than dimethyl γ-benzyloxyitaconate XXXVIII, as shown by the infra red absorption at 1120 $cm.^{-1}$. However, ester exchange appeared to have occurred and only an ester mixture was obtained.

(c) It was hoped to convert the bromide into a quaternary base, but reaction with pyridine produced only a dark oily product which could not be identified by spectral methods.

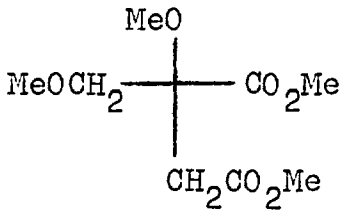
(d) The complication of Sn2' replacement of X groups in XXXV would be removed if the carbon-carbon double bond in dimethyl (bromomethyl)-fumarate could be reduced. But mild hydrogenation (over a 2% palladium on strontium carbonate catalyst at one atmosphere pressure of hydrogen) resulted in complete hydrogenolysis of the bromide to dimethyl mesaconate. A hydrogen transfer reduction, with cyclohexene as hydrogen source and 10% palladized charcoal catalyst,[82] followed the same course.

(e) By a route similar to Campbell and Hunt's[83] for diethyl (acetoxymethyl)-fumarate, the compound (XXXV; X ≡ OAc) was prepared. [N.m.r. spectrum in carbon

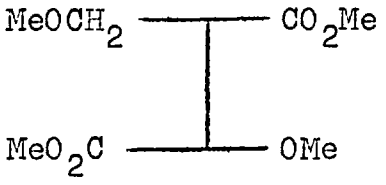
tetrachloride solution:
$= \overset{CH}{|}$, 3.15 τ(s); $-CH_2-$, 4.86 τ(s); acetate methyl -H, 2.00 τ(s); methyl ether H, 6.17 and 6.21 τ (s). This could not be converted into an amide, the acetoxy group in the allylic position being displaced. Attempts (similar to those in (d), above) were made to hydrogenate the carbon-carbon double bond but resulted in complete hydrogenolysis, to dimethyl mesaconate.

(f) It has been reported that simple aliphatic ethers can be completely cleaved with boron trifluoride etherate in acetic anhydride solution[84,85,86] to the corresponding acetates. This would allow alkyl ether functions to be used as protecting groups. If tetra-(methoxymethyl)-tetrazaporphin (XXII; R ≡ OMe) could be synthesized, four "reactive positions" could be generated by ether cleavage. The resultant tetra-(acetoxymethyl)-tetrazaporphin (XXII; R ≡ OAc) could be readily converted to the required tetra-(halomethyl)-tetrazaporphin intermediate.

In an attempt to synthesize the pigment precursor (methoxymethyl)-fumaronitrile, dimethyl (bromomethyl)-fumarate was treated with an equivalent of sodium methoxide in methanol. The product was not the expected dimethyl (methoxymethyl)-fumarate (XXXV; X ≡ OMe) but a saturated diester presumably XXXIX or XL, resulting from addition of methanol to the double bond.



XXXIX



XL

The n.m.r. spectrum was complex and could not be analysed. This would suggest the formation of XL, dimethyl α-methoxy-β-(methoxymethyl)-succinate, rather than XXXIX which would be expected to give six singlets, one for each of the methyl (4) and methylene (2) groups.

The product, with '880' ammonia readily gave a diamide which was assumed to be α-methoxy-β-(methoxymethyl)-succinamide.

Attempted Synthesis of Tetra-(alkoxymethyl)-tetrazaporphin

The feasibility of cleaving the alkyl ethers of a tetra-(alkoxymethyl)-tetrazaporphin by the method mentioned above was emphasized by the fact that tetramethyltetrazaporphin could be recovered from acetic anhydride solution containing boron trifluoride etherate after 60 hours at room temperature. This indicated the stability of the ring system under the reaction conditions.

The ether groups to be cleaved would be α to an aromatic system, hence methyl benzyl ether was used as a

model compound. This was synthesized by reaction of benzyl chloride with excess methanol in the presence of caustic soda. Youssefyeh and Mazur[84] used a lithium halide as an integral part of their cleavage reaction conditions. Attempts were therefore made to cleave methyl benzyl ether at room temperature with boron trifluoride etherate in acetic anhydride in the presence of lithium chloride. After 30 hours reaction the isolated product was found, spectrally, to be benzyl acetate with a trace of methyl benzyl ether.

Narayanan and Iyer[85,86] found lithium halides unnecessary and under these conditions the formation of benzyl acetate again was virtually complete. The use of acetyl chloride as a solvent[86] led to a mixture of benzyl chloride and benzyl acetate with sizeable quantities of benzyl alcohol, presumably produced by hydrolysis during working up.

Ethers have also been cleared to mixtures of halides and alcohols using halogens and diborane[68] or sodium borohydride[69] e.g. $ROR' + 2I_2 + NaBH_4 \longrightarrow 3RI + B(OR')_3 + NaI + 2H_2$

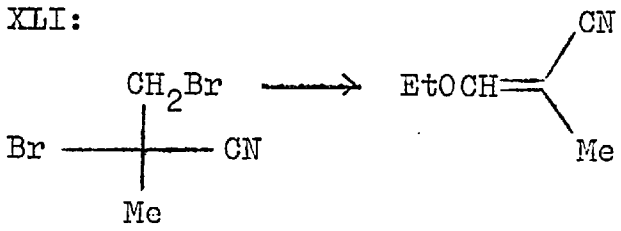
$$B(OR')_3 \xrightarrow[\text{Hydrolysis}]{} R'OH$$

Reaction of methyl benzyl ether with iodine and sodium

borohydride gave benzyl iodide but with substantial amounts of starting material. This reaction would be difficult to apply to tetrazaporphins which are known to halogenate[80] and reduce[36] readily.

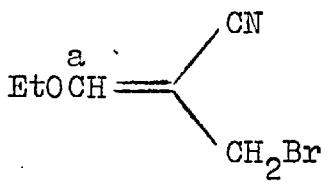
γ-Ethoxyitaconitrile (XLV)

As previously mentioned (Chapter 2) α-methyl-β-ethoxyacrylonitrile XLII could be prepared by reaction of sodium ethoxide on αβ-dibromo-α-methylpropionitrile XLI:

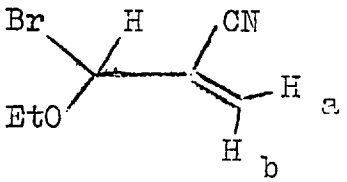


XLI

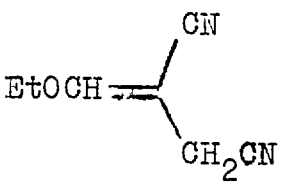
XLII



XLIII



XLIV



XLV

It was hoped that reaction with N-bromosuccinimide might give rise to α-bromomethyl-β-ethoxyacrylonitrile XLIII which with potassium cyanide could give the pigment precursor γ-ethoxyitaconononitrile XLV. However, reaction of N-bromosuccinimide in refluxing carbon tetrachloride

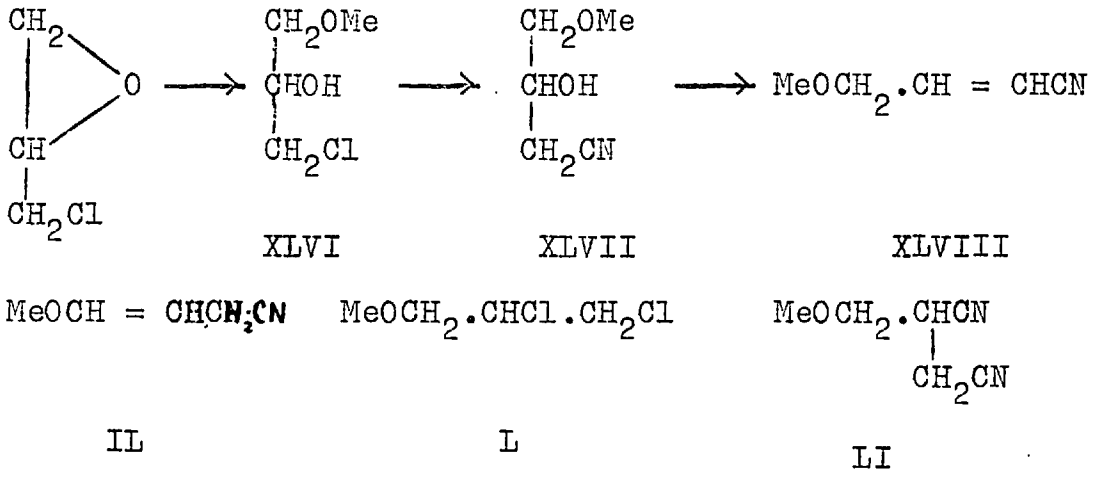
(for 12 hours with 1% azo-bis-isopropylcyanide) gave a product, which proved to be a powerful lachrymator, whose n.m.r. spectrum indicated it might be XLIII (mixture of cis and trans isomers) together with an equal amount of an impurity, possibly the isomer XLIV [N.m.r. in carbon tetrachloride:

XLIII cis a, 2.82 τ(s); trans a, 3.13 τ(s); XLIV a, 3.99 τ; b, 4.10 τ].

The mixture could not be separated by distillation and on reaction with potassium cyanide, in refluxing ethanol, no dinitrile could be isolated by distilling the product.

(Methoxymethyl)-succinonitrile (LI)

(Methoxymethyl)-succinonitrile LI has been prepared from epi-chlorohydrin,[81,55] as follows:



β-Hydroxy-γ-methoxybutyronitrile XLVII was prepared by this method. On attempting to dehydrate this material by slow distillation, from potassium carbonate,[81] a liquid was obtained. This had the boiling point reported for γ-methoxycrotononitrile XLVIII, but appeared (from its n.m.r. spectrum) to be a mixture of the required product and the isomeric γ-methoxyallyl cyanide IL. The mixture which appeared to contain both cis and trans forms of XLVIII and IL could not be separated by distillation. β-Acetoxy-γ-methoxybutyronitrile was also prepared by refluxing the alcohol with acetic anhydride.

An unsuccessful attempt to displace acetate in β-acetoxy-γ-methoxybutyronitrile was made with sodium cyanide in dimethyl sulphoxide (at 130°).

2,3-Dichloro-1-methoxypropane L (b.p.66-68°/60 mm.) was prepared from 1-chloro-3-methoxypropan-2-ol XLVI, by reaction with thionyl chloride. On reaction with sodium cyanide in dimethyl sulphoxide (at 130°) no (methoxymethyl)-succininitrile LI could be isolated.

β-Methoxypropionitrile was prepared by base catalysed addition of methanol to acrylonitrile. Attempts were then made to prepare (methoxymethyl)-succinonitrile, with no success, by condensing β-methoxypropionitrile with chloroacetonitrile using sodium methoxide in methanol and

sodium hydride in dimethyl sulphoxide - according to the conditions for condensing phenylacetonitrile with methyl 2-bromo-2-ethylbutyrate.[82]

β-Acetoxy-γ-methoxybutyronitrile was reported[81] to yield γ-methoxycrotononitrile on distillation with potassium acetate. On repetition of this reaction the product obtained, like that from β-hydroxy-γ-methoxybutyronitrile XLVII, contained the impurity IL in similar proportions. Using quinoline as catalyst, instead of potassium acetate, up to 200°, no elimination occurred. The G.L.C. of the olefinic product showed at least 3 fractions with similar retention times.

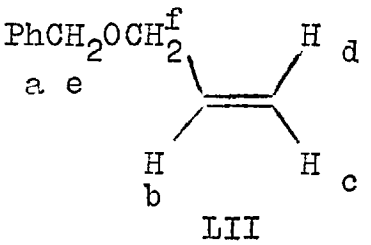
The olefinic mixture of XLVIII and IL, assumed by Kurtz[55] to be γ-methoxycrotononitrile (XLVIII), was treated with hydrogen cyanide under basic (potassium cyanide) conditions. About 60% of the starting mixture of vinyl and allyl ethers was recovered, but 10% of (methoxymethyl)-succinonitrile was finally isolated.

(Methoxymethyl)-succinimidine was prepared, as a yellow-brown solid, by reaction of (methoxymethyl)-succinonitrile with methanolic ammonia in a sealed tube (at 125-130° for 12 hours) in about 30% yield. This, however, would not give even a trace of pigment when refluxed in butanol or methanol with nitrobenzene (50% v/v).

A small amount of a magnesium pigment could be obtained by reaction of (methoxymethyl)-succinonitrile with magnesium n-propoxide in refluxing n-propanol. Simple self condensation of succinonitrile units would give rise to a tetrazaporphin in the hexahydro state, hence at some stage a dehydrogenation was required to yield the parent pigment. In the case of (methoxymethyl)-succinonitrile the pigment obtained may be produced by elimination of methanol, rather than dehydrogenation, the product would then be magnesium tetramethyltetrazaporphin. The magnesium pigment obtained showed a visible absorption band at 596 mμ (magnesium tetramethyltetrazaporphin 596 mμ).

(Benzyloxymethyl)-succinonitrile

The synthesis of (benzyloxymethyl)-succinonitrile was attempted in three steps. Firstly benzyl chloride was interacted with sodium allyloxide to give allyl benzyl ether.(83) Secondly, a reaction with sulphuryl chloride then gave a low yield of 1,2-dichloro-3-benzyloxypropane LIII. Chlorination of the benzylic methylene group occurred as a side reaction and benzaldehyde was detected on working up the reaction mixture.



LII

$PhCH_2OCH_2CHCl.CH_2Cl$

a b c d e

LIII

[N.m.r. spectra in carbon tetrachloride:
LII: a, 2.74 τ (s); b, 4.07 τ (s); c and d unresolved, 4.6-5.1 τ; e, 5.54 τ (s); f, 6.06 τ (d); J_{bc} = 9.5 c/s; J_{bd} = 17 c/s; J_{bf} = 5 c/s.
LIII: a, 2.53 τ (s); b, 5.50 τ (s); c, d and e unresolved, 5.8-6.7 τ.]

For the third step, the dichloride was treated with sodium cyanide in dimethyl sulphoxide (at 130° for 3 hours), but unfortunately no (benzoxymethyl)-succinonitrile, could be detected in the product.

1,2-Dibromo-3-benzyloxypropane appeared to be formed quantitatively by addition of bromine to benzyl allyl ether in carbon tetrachloride solution. This dibromide on reaction with sodium cyanide in dimethyl formamide (at 100° for 1 hour) produced a product from which only an unidentified benzyloxy substituted unsaturated acid could be isolated. This, presumably, was produced by hydrolysis of an unsaturated nitrilic product during work up. These results contrast markedly with the formation of neopentylsuccinonitrile (60% yield) from 1,2-dichloro-4,4-dimethylpentane (Chapter 3). The above reactions exemplify the inertness towards substitution of halogens β to an ether grouping.

EXPERIMENTAL

Dimethyl (bromomethyl)-fumarate

(a) Dimethyl citraconate (40.4 g.), recrystallized N-bromosuccinimide (40.4 g.) and benzoyl peroxide (2 g.) were mixed in carbon tetrachloride (250 ml.) and the mixture was refluxed for 6 hours. Petroleum ether (b.p. 60-80°; 100 ml.) was added to precipitate the succinimide and the mixture was filtered. The filtrate was distilled to yield dimethyl (bromomethyl)-fumarate (43.3 g.; 71%) b.p.76-78°/0.15 mm. (or (99°/1.5 mm.):
Found C, 35.32; H, 4.03; Br, 33.99. $C_7H_9BrO_4$ requires C, 35.46; H, 3.83; Br, 33.71%.

(b) Bromine (6.3 g.) in chloroform (5 ml.) was added, dropwise, to a rapidly stirred solution of dimethyl itaconate (5 g.) in chloroform (20 ml.), over 1 hour. The mixture was stirred overnight and distilled. The product (5.5 g.; 73.4%) distilled at 78-80°/0.2 mm.

Dimethyl (Benzyloxymethyl)-fumarate

Dry benzyl alcohol (13.7 g.) (freed from benzoic acid and benzaldehyde) was treated with an equivalent of sodium hydride (5.8 g.) (as a 53.3% suspension in mineral oil) in boiling, dry anisole (300 ml.) under nitrogen. The

mixture was then refluxed for 2 hours, and the solvent removed under reduced pressure ($59^{\circ}/33$ mm.). The sticky solid remaining was shaken with water (100 ml.) and the mixture was extracted with ether (3 x 50 ml.). The extract was dried over sodium sulphate and distilled. The product distilled out $152-159^{\circ}/0.2$ mm. (10 g.; 30%) and contained a little mineral oil (from the sodium hydride suspension) which could not be removed by fractionation (through a 6 inch column packed with Fenske helices).

Dimethyl (Acetoxymethyl)-fumarate

Dimethyl (bromomethyl)-fumarate (10 g.) was heated in refluxing absolute ethanol (50 ml.) with anhydrous potassium acetate (5 g.) for 1 hour. The ethanol was taken off under reduced pressure and the residue was taken up in benzene (50 ml.). The solution was filtered and distillation when the product was obtained in 76.3% yield (6.8 g.; b.p.$84-86^{\circ}/0.1$ mm.; n_D^{20} 1.4585).

Dimethyl α-Methoxy-β-(methoxymethyl)-fumarate (XXXIX)

Dimethyl (bromomethyl)-fumarate (16 g.) was added during 10 minutes to a stirred solution of an equivalent of sodium methoxide (from 1.55 g. of sodium) in methanol (25 ml.). An exothermic reaction occurred and stirring was continued overnight at room temperature. The solvent

was taken off under reduced pressure, water (10 ml.) was added and the product was extracted with ether (3 x 10 ml.). The ether extract was dried over sodium sulphate and distilled, giving a 70% yield of product (10.4 g.; b.p.82°/ 0.7 mm.).

α-Methoxy-β-(methoxymethyl)-fumaramide

Dimethyl α-methoxy-β-(methoxymethyl)fumarate (4.5 g.) was allowed to stand overnight at 0° with '880' ammonia (7.5 ml.) containing a few drops of methanol. The product (2.57 g .; 66%) was filtered off, washed with water and crystallized from aqueous ethanol to give a solid m.p.205-206°. The product could also be purified (less readily) by sublimation at 1 mm. Sublimation at 20 mm., however, gave a mixture of amide and imide.
Found C, 44.4; H, 7.37; N, 14.67. $C_7H_{14}N_2O_4$ requires C, 44.21; H, 7.22; N, 14.73%.

Methyl Benzyl Ether

Methanol (380 g.) and sodium hydroxide (69 g.) were heated to boiling, the source of heat was removed, and benzyl chloride (151 g.) was added so as to maintain reflux. The mixture was then refluxed overnight. Finally, the methanol was taken off under reduced pressure, water (250 ml.) was added, and the product extracted with ether

(3 x 10 ml.). The ether extract was dried over sodium sulphate and distilled. A yield of 99.8 g . (75.3%; b.p. 170-171°) was obtained.

Cleavage of Methyl Benzyl Ether

(a) Methyl benzyl ether (1 g.) was kept overnight at 0°, with boron trifluoride etherate (2.1 ml.) in acetic anhydride (12 ml.). The mixture was poured onto ice and allowed to stand for 2 hours so that the acetic anhydride underwent hydrolysis. The product was extracted with ether (20 ml.), the organic layer was washed free from acid with saturated aqueous sodium bicarbonate, dried over sodium sulphate, and evaporated by warming gently under reduced pressure. Benzyl acetate remained, it was identified by its n.m.r. spectrum.

(b) Methyl benzyl ether (5 g.) in chloroform (10 ml.) was mixed with sodium borohydride (0.25 g.) under nitrogen, and iodine (5.2 g.) was added. The mixture was allowed to stand for 12 hours with occasional agitation. The chloroform solution was washed with water, dried over calcium chloride and the solvent was taken off under reduced pressure. to give the high boiling benzyl-containing products. The composition of the product was estimated from its n.m.r. spectrum.

1-Chloro-3-methoxypropan-2-ol (XLVI)[81]

Epi-chlorohydrin (300 g.) was added to a stirred, hot mixture of methanol (440 ml.) and concentrated sulphuric acid (11 g.) at such a rate that gentle refluxing was maintained. The mixture was stirred for 4 hours, sodium carbonate (14 g.) was added, and the stirring was continued overnight. Most of the methanol was removed by distillation (steam bath) and the product was filtered. Fractionation of the filtrate under reduced pressure through a 6 inch column of Fenske helices gave a 68.1% yield of compound XLVI (275 g.; b.p.75-77°/19 mm.; n_D^{25} 1.4463). The high and low boiling fractions were refractionated to give a further 5% yield of product (20 g.).

β-Hydroxy-γ-methoxybutyronitrile (XLVII)[81]

Powdered sodium cyanide (117 g.) was stirred rapidly with water (115 ml.) for 10 minutes and 1-chloro-3-methoxypropan-2-ol (275 g.) was added. The mixture was maintained at 45-50° for 3 hours and then stirred overnight at room temperature. The mixture was neutralized carefully with concentrated hydrochloric acid and most of the methanol was distilled off (steam bath). The mixture was filtered, the residue washed with methanol (2 x 10 ml.), and the filtrate and washings were fractionated yield, 81.8% (207.8 g.; b.p.80-84°/0.5 mm.).

β-Acetoxy-γ-methoxybutyronitrile[81]

β-Hydroxy-γ-methoxybutyronitrile (207.8 g.) was refluxed with acetic anhydride (210 g.) for 30 minutes and the mixture was then fractionated under reduced pressure. A 92.8% yield (263.7 g.) of product was obtained (b.p. 72-76°/0.3 mm.; n_D^{24} 1.4296).

Dehydration of β-Hydroxy-γ-methoxybutyronitrile (XLVIII)

β-Hydroxy-γ-methoxybutyronitrile (90 g.) was slowly distilled from anhydrous potassium carbonate (4 g.) until the still-head temperature reached 185°. More potassium carbonate (1 g.) was added to the residue and the distillation operation was repeated. A further quantity of β-hydroxy-γ-methoxybutyronitrile (92.8 g.) was similarly treated. The combined distillate comprising unsaturated nitrile and water was saturated with potassium carbonate. The organic layer was separated and fractionated and the product collected between 175 and 185° (66% yield; 101.8 g.).

Deacetoxylation of β-Acetoxy-γ-methoxybutyronitrile

Anhydrous potassium acetate (0.4 g.) was added to β-acetoxy-γ-methoxybutyronitrile (10 g.) which was distilled through a 3 inch Vigreaux column: the fraction b.p. 110-190° was collected. Refractionation gave product b.p.175-180°, in 59.8% yield (3.69 g.). Fractions of

b.p. 120-175° and 180-200° were combined and redistilled to produce further amounts of product, 14.6% (0.9 g.) which was freed from acetic acid by treatment with solid potassium carbonate.

(Methoxymethyl)-succinonitrile (LI)[55]

The mixture of γ-methoxycrotononitrile and γ-methoxyallyl cyanide (39 g .), from the deacetoxylation of β-acetoxy-γ-methoxybutyronitrile, was warmed with liquid hydrogen cyanide (16.9 ml.) and potassium cyanide (0.5 g.) under reflux. The temperature of the mixture was raised to 65° during 1 hour and maintained at 65-70° for 4 hours. The mixture was stirred overnight, excess hydrogen cyanide was taken off at 40° under reduced pressure, and ether (50 ml.) was added to the cooled mixture which was then filtered. The filtrate was washed with saturated aqueous sodium chloride (3 x 20 ml.) and the extracts were back extracted with ether (20 ml.). The combined ether solution was dried over sodium sulphate and distilled. A considerable quantity of starting material was recovered (61.5%; 24 g.); the product distilled at 110-112°/0.3 mm. in 10.1% yield (5 g.). On redistillation the material boiled at 88-90°/0.05 mm.

(Methoxymethyl)-succinimidine

(Methoxymethyl)-succinonitrile (0.43 g.) was heated in a sealed tube with a 40% solution of anhydrous ammonia in methanol (3 ml.) at 125-130° for 12 hours. The solvent was evaporated off under reduced pressure and the oily product was triturated with dry ethyl acetate, giving a 30% yield of a yellow-brown solid product (150 mg.).

Benzyl Allyl Ether (LII)

Sodium (72.7 g.) was dissolved in allyl alcohol (480 g.). Benzyl chloride (400 g.) was added over 1 hour and the mixture was refluxed for a further hour. The mixture was cooled and water (600 ml.) and ether (200 ml.) were added. The ether layer was separated and the aqueous layer was washed with ether (200 ml.). The ether solutions were combined, washed with water (3 x 200 ml.) and dried over calcium chloride. The product was then fractionally distilled (through a 9 inch Vigreaux column), the product being collected at 84-86°/10 mm. in 90.1% yield (421.8 g.; $n_D^{23.5}$ 1.5075).

1,2-Dichloro-3-benzyloxypropane (LIII)

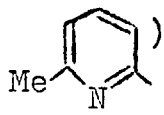
Redistilled sulphuryl chloride (18.2 g.) in carbon tetrachloride (30 g.) was added during 2 hours to a stirred solution of benzyl allyl ether (20 g.) in carbon tetra-

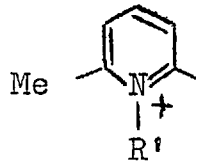
chloride (30 g.). The mixture was then refluxed for 1 hour. The product was fractionated (through a 6 inch column packed with Fenske helices): the required material distilled at 84-86°/0.5 mm. (23% yield; 6.8 g.).

CHAPTER 5

Side Chain Aminated Tetrazaporphins

One aim of the work described in the previous Chapter was to synthesize a tetrazaporphin with four side chains containing quaternary ammonium groups. The key intermediate was a tetra-(halomethyl)-tetrazaporphin. An alternative route involved the synthesis of a pigment containing aminated side chains which would then be quaternized with alkyl halides. Exploratory work in this direction is reported here.

It was hoped to synthesize a tetrasubstituted tetrazaporphin with pyridine groups attached to the side chains. A suitable compound was tetra-(6-methyl-2-pyridylmethyl)-tetrazaporphin (XXII; R ≡ ) which appeared

accessible by the sequence shown in figure 15. The product might then have been converted into a methanol-soluble pigment (XXII; R ≡  X^-)

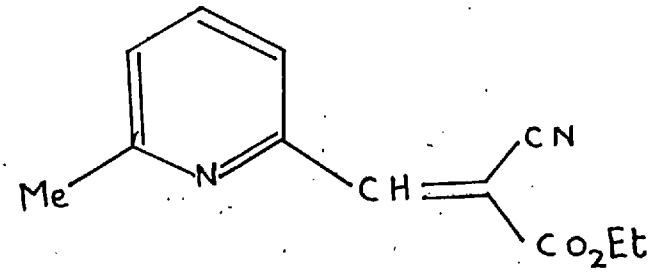
by quaternizing the pyridine nitrogens with an alkyl halide.

6-Methylpyridine-2-aldehyde was chosen as the starting material as, having no free α-pyridyl positions, it would lead to a product with a simple n.m.r. spectrum. There would be no risk that the signals from the tetrazaporphin ring protons would be masked.

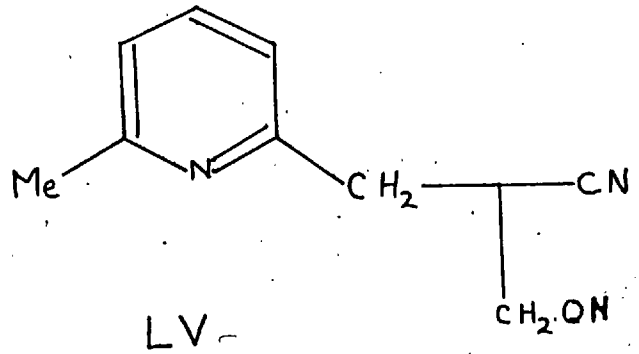
6-Methyl-2-formylpyridine (Koch-Light Ltd.) was shown to be free of α-unsubstituted pyridine by its n.m.r. spectrum which showed no absorption in the 0 to 2 τ region. [N.m.r. spectrum in deuterochloroform: aldehyde proton, -0.05 τ (s); aromatic protons, 2.1 to 2.8 τ; CH_3, 7.33 τ (s).]

6-Methylpyridine-2-aldehyde condensed readily with ethyl cyanoacetate in the presence of a trace of piperidine to give ethyl α-cyano-β-(6-methylpyridine-2)-acrylate LIV. The n.m.r. spectrum of the product was consistent with the product being only one of the two geometrical isomers of structure LIV.

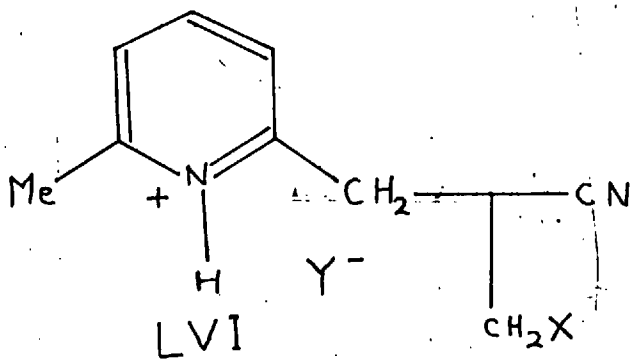
[N.m.r. spectrum in deuterochloroform: olefinic proton, 1.73 τ (s); aromatic protons, 2.1 to 2.9 τ; ester methylene protons, 5.58 τ (q), J = 7.1 c/s; pyridine methyl protons, 7.34 τ (s); ester methyl protons, 8.57 τ (t).]



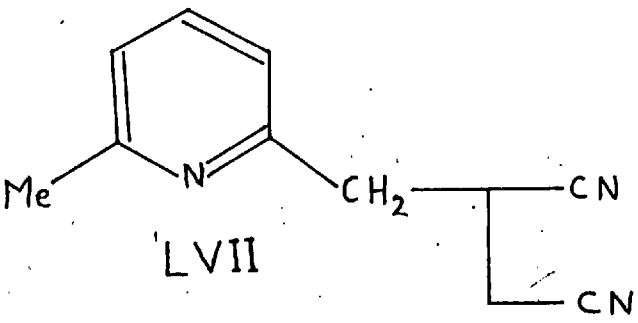
LIV



LV



LVI



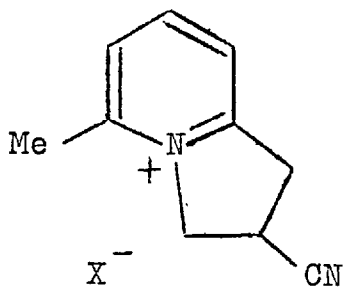
LVII → XXII

Figure 15

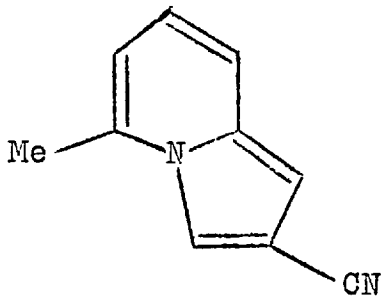
Substituted α-cyanoacrylates have been reduced with sodium borohydride in iso-propanol to β-cyano-alcohols.[94] Under these conditions ethyl α-cyano-β-(6-methylpyridine-2)-acrylate LIV gave 2-(γ-hydroxy-β-cyanopropyl)-6-methyl-pyridine LV. The infrared spectrum of the product showed no trace of any ester C = O, olefinic C = C or conjugated C ≡ N stretching absorptions, but absorption characteristic of hydroxyl (3210; 1085 cm^{-1}) and non-conjugated C ≡ N (2230 cm^{-1}) appeared, and the pyridine C ⩵ C, C ⩵ N stretching absorptions were clearly discernible (1598; 1580 cm^{-1}). The n.m.r. spectrum also agreed with structure LV, although the spectrum was too complex for a complete analysis. [Spectrum in deuterochloroform: a, 2.39 τ (approx.t) J_{ab} = 7.7 c/s; b, 2.91 τ (approx.d); c, ca. 5.2 τ (broad - s); d, ca. 6.2 τ (approx.d) J = 5.7 c/s; e, ca. 6.8 τ (approx. s); f, masked by e; g, 7.47 τ (s).] The product was separated as a pale yellow solid which melted near room temperature and could not be satisfactorily recrystallized. The scale of this reaction was limited by the fact that the starting material (LIV) was only soluble to about 3% in iso-propanol. Similar reductions have been conducted in dry diglyme.[94] Compound LIV was indeed more soluble (about 10%) in

diglyme but the reaction was too rapid and exothermic, and a reduced yield of product was isolated. However, dioxane was satisfactory.

As indicated above, it was hoped to replace the hydroxyl group of LV with a group, X, which might be displaced by cyanide ion to produce the required (6-methyl-2-pyridylmethyl)-succinonitrile (LVII). It was envisaged that the group X might be a halide or tosylate group. It was anticipated that simple replacement of the hydroxyl group of LV with a good leaving group would probably cause the molecule to cyclize by an S_Ni process to LVIII,[95] which in the presence of an oxidizing agent would afford the conjugated system LIX.[96] It can be seen, therefore, that it was necessary to convert the amine function to its hydrochloride or quaternary salt to prevent such a reaction occurring.



LVIII



LIX

It was hoped that reaction of the alcohol LV, with thionyl chloride, would yield the corresponding chloride, as the pyridine hydrochloride (LVI, X ≡ Y ≡ Cl). Although rapid reaction did occur only a dark intractable product was obtained. This showed only a comparatively weak nitrile absorption in the infra red. Attempted sublimation under vacuum produced only sulphur-containing products (soluble in organic solvents) and ammonium chloride, presumably produced by breakdown of the molecule. On gently warming the alcohol LV with phosphorus pentachloride, only a similar product resulted. Hence the hydrochloride of 2-(γ-hydroxy-β-cyanopropyl)-6-methylpyridine (LV) was prepared (pyridine C = C, C = N stretching absorption 1626; 1646 cm^{-1}): this, like the parent base, was difficult to crystallize, because it tended to form supersaturated solutions.[N.m.r. spectrum in deuterium oxide: a, 1.51 τ (t), J_{ab} = 7.9 c/s; b, 2.15 τ (approx. d); d, ca. 6.1 τ (m); e, ca. 6.5 τ (m); f, masked by e; g, 7.19 τ (s).]

In an attempt to prepare the tosylate LVI (X ≡ OT_s; Y ≡ Cl), the above hydrochloride was heated with an equivalent of tosyl chloride at 70-100° for 2 hours under nitrogen. The product was refluxed with a little ethanol to convert any excess of tosyl chloride to ethyl tosylate,

which was removed by washing with ether. The product could not be crystallized and lacked strong sulphonic ester absorption in the infra red region (1350 to 1400 cm^{-1}). This and the presence of hydroxyl absorption suggested the material was mainly unchanged. The crude material was heated for 3 hours with sodium cyanide in dimethyl formamide and the product (67%), isolated by distillation, was recovered (LV). The n.m.r. spectrum of the product showed a disproportionately large absorption in the 6.4 to 7.3 τ region, the region in which the methylene and methine protons of the product LVII would be expected to absorb. This suggested that some dinitrile may have been formed: however, no separation of this could be achieved.

In other attempts to make the tosylate, dimethyl formamide was used as solvent and an equivalent of pyridine was added to the reaction mixture, but again the tosylate was not apparently obtained.

Attempts were made to quaternize the pyridine group of 2-(γ-hydroxy-β-cyanopropyl)-6-methylpyridine (LV). No reaction was detected with ethyl bromide or methyl tosylate in refluxing benzene, containing 10% methanol, after 24 hours. No product could be isolated after LV had been heated in an autoclave with ethyl bromide to 100°, for 3 hours. Ethyl tosylate was then heated with

LV until ethanol was evolved ($\sim 160^{\circ}$), but the product could not be crystallized, and it set to a glass on standing. The pyridine C = C, C = N stretching absorptions confirmed the presence of a quaternized species, and the lack of strong absorption in the 1350 to 1400 cm^{-1} region of the infra red spectrum suggested the absence of a sulphonate ester. This, together with the lack of hydroxyl absorption, suggested that the product was the bicyclic species LVIII (X ≡ OTs). The pyridine methyl proton signal (7.30 τ) in the n.m.r. spectrum, in deuterium oxide, differed significantly from that previously observed for the protonated pyridine species (7.18 τ).

Faced with these synthetic difficulties this approach was abandoned.

EXPERIMENTAL SECTION

Ethyl α-Cyano-β-(6-methylpyridine-2)-acrylate (LIV)

6-Methylpyridine-2-aldehyde (86.5 g.; m.p.30-32°) was mixed with 'AnalaR' ethyl cyanoacetate (80.8 g.) in dioxane (45 ml.) under nitrogen. The stirred mixture was cooled to 10° and piperidine (1 ml.) was added. An exothermic reaction occurred and the mixture was then kept overnight. The product was pressed on to a filter pad, sucked dry and washed with 50% aqueous ethanol (3 x 25 ml.). The product was dried at 40-50°/3 mm. for 6 hours, to afford a 90% yield (138.7 g.) of a pale yellow crystalline solid. The product (m.p.85°) was recrystallized from ethanol.

Found, C, 66.75; H, 5.54; N, 12.81. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.58; N, 12.96%.

2-(γ-Hydroxy-β-cyanopropyl)-6-methylpyridine (LV)

Ethyl α-cyano-β-(6-methylpyridine-2)-acrylate LIV (86 g.) was dissolved in dry dioxane (220 ml.). The solution was then added dropwise, during 30 minutes and under nitrogen, to a stirred suspension of sodium borohydride (43 g.) in dioxane (50 ml.) cooled in ice. The mixture was then stirred at room temperature overnight.

Water (50 ml.) was added and the mixture was stirred for a further 24 hours. The product was filtered and the residue was washed with chloroform (50 ml.). The total filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in chloroform, dried over calcium chloride and evaporated to dryness. The remaining oil was boiled with petroleum ether (b.p. 60-80°; 100 ml.) and when the mixture was kept overnight at 0°, the product solidified and was collected (56 g.; 80% yield). The product could be distilled at 136-138°/0.7 mm.

CHAPTER 6

Iron Tetrazaporphins

Introduction

The condensation of phthalonitrile and substituted phthalonitriles with various iron salts leads to iron (II) rather than iron (III) phthalocyanines.[40,97] These have been converted by both Lever and Sammes[40] to dipotassium dicyano-iron (II) phthalocyanines which proved to be remarkably soluble in methanol. It was hoped that if tetrazaporphin iron (II) compounds could be prepared then these might analogously be converted into soluble dipotassium dicyano-iron (II) complexes, for n.m.r. spectral studies.

Iron Tetramethyltetrazaporphins

Magnesium tetramethyltetrazaporphin was prepared by reaction of citraconononitrile with magnesium n-propoxide,[35] it was hoped that, by addition of an anhydrous iron salt to the reaction mixture, tetramethyltetrazaporphin iron (II) would be formed.

Anhydrous ferric chloride was added to excess magnesium n-propoxide in refluxing n-propanol and citraconononitrile was added slowly. Initially a purple coloration

appeared, but this soon disappeared after addition was complete. Reduction of ferric chloride with chlorobenzene produced anhydrous ferrous chloride.[98] When this was used, instead of ferric chloride, a persistent purple-blue coloration was produced. If the reaction was stopped by pouring the mixture into water, a blue species could be extracted into chloroform. This showed strong absorption at 606 mμ and there were weak absorption bands at 679 and 551 mμ. The main absorption band was broad, and at an unusually long wavelength for a divalent transition derivative of tetramethyltetrazaporphin. Thus nickel- and copper-tetramethyltetrazaporphins show a strong sharp band at 585 mμ.[35]

When a similar preparative mixture was evaporated to dryness under anhydrous conditions a dull purple material was extracted from the residue, with chlorobenzene. This material showed visible absorption bands at 679 and 551 mμ, and the material absorbing at 606 mμ was present as a minor product.

The blue species, species 1, could be isolated from either reaction product by chromatography in benzene on a sodium sulphate column, whilst the dull purple species, species 2, was exclusively eluted with benzene from a tartaric acid column. However, both purified species

in benzene solution, on standing for a few days, reverted to mixtures of the two species.

Both species produced identical purple solutions in pyridine showing the characteristic spectrum (λ_{max} = 584; 328 mμ) of a divalent transition metal tetrazaporphin.

Species 1

The elementary analysis suggested that the compound was tetramethyltetrazaporphin-hydroxyl iron (III) or -aquoiron (II). [The word "hydroxyl" is used generally in this context, to denote an OH function bound to the metal concerned by either an ionic- or covalent-bond. The covalent form is indicated by use of the prefix "hydroxy" and the ionic form is indicated by use of the word "hydroxide".] The found C/H ratio (14.28) corresponded more closely to that required by the iron (III) species (14.02) than the iron (II) species (13.13).

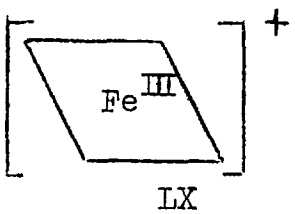
Reaction with pyridine: When a pyridine solution of species 1 was evaporated to dryness under reduced pressure a dark solid with a strong reflex remained, which in carbon tetrachloride solution showed the spectrum expected for the iron (II) compound (λ_{max} = 584 mμ). After being dried, at 60°/0.1 mm. overnight, the solid appeared to

lose its reflex, and in carbon tetrachloride it then showed a spectrum identical with that of species 1. The elementary analysis of the product suggested two possible structures:

1. Tetramethyltetrazaporphin aquo-dipyridine-iron (II). As the iron (II) atom in the tetrazaporphin can only accommodate two co-ordinated solvent molecules, this structure would necessitate the third solvent molecule (pyridine or water) being only loosely bound in the lattice. Such a pigment species seemed unlikely to survive heating at 60°/0.1 mm. and so this constitution for the pigment was hardly acceptable.

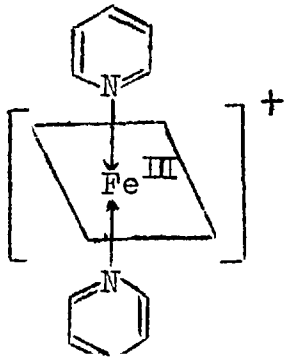
2. The ionic species, tetramethyltetrazaporphin dipyridine-iron (III) hydroxide. This would seem the most likely structure.

The found $^{C}/_{H}$ ratio (13.55) favoured the iron (III) species (12.77). The similarity between the visible and ultra violet spectra of the dipyridate and species 1 suggested that the latter was also an ionic species, that is, tetramethyltetrazaporphin iron (III) hydroxide, represented by LX.



LX

OH^-

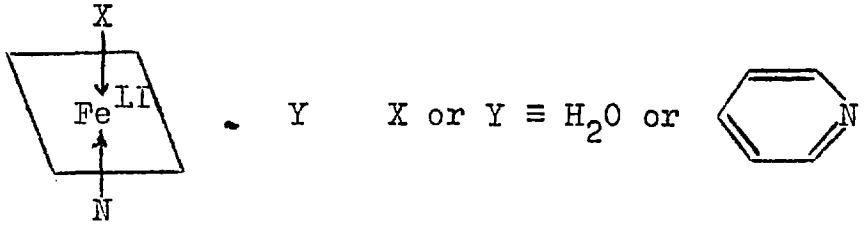


OH^-

LXI

Neither species 1 nor the dipyridinate LXI were sufficiently soluble in any common solvent to give an n.m.r. spectrum, but when either species was dissolved in benzene, the benzene n.m.r. signal was significantly broadened, as was the tetramethylsilane internal reference signal. This observation was in accord with these species being paramagnetic, containing trivalent iron.

It therefore appeared that on dissolving tetramethyltetrazaporphin iron (III) hydroxide (LX) in pyridine the iron was reduced, immediately and completely, to the iron (II) state by pyridine, or impurities in it. The material isolated from pyridine solution was an iron (II) complex solvated with pyridine as in LXII. Only two solvent molecules can be co-ordinated to the metal, so the third molecule, of water or pyridine, per iron atom must evidently be held in the crystal lattice. Compound LXII rearranged and oxidized on heating under vacuum to LXI.



LXII

A similar reduction effected by pyridine has been reported for chlorohaemin.[18] In chloroform solution the complex had a magnetic moment of 5.94 Bohr magnetons but in pyridine solution, over a period of days, the magnetic moment decreased to between 2 and 3 Bohr magnetons.[105] Use of purified pyridine slowed the change drastically. It appeared therefore that some impurity in the pyridine reduced the metal to the iron (II) state.

Aetioporphyrin chloroiron (III) has also been reduced photochemically to the iron (II) species in pyridine solution, under nitrogen. The product was then reoxidized to an iron (III) form on exposure to air.[106]

In methanol tetramethyltetrazaporphin iron (III) hydroxide was slowly reduced to an iron (II) species. However, when the iron (III) hydroxide species was heated with potassium cyanide in refluxing methanol no soluble species was produced.

The iron (III) hydroxide species was unaffected by the presence of diethylamine or triethylamine, but when a solution of the pigment was shaken with aqueous ammonia a purple solution was produced. This showed a visible absorption band at 594 mμ (minor peak 492 mμ) with an ultra violet spectrum characteristic of an iron (II) pigment (λ_{max} = 331 mμ).

Species 2

Species 1 (LX) and its dipyridinate (LXI) were instantaneously converted by acid into the dull purple species 2 (λ_{max} = 679; 551 mμ). Iron (II) species were similarly converted to species 2, but more slowly. Species 2 was best prepared from species 1 by reaction with acetic acid or liquid hydrogen cyanide. The respective products, after being dried, showed no acetate or cyanide absorption in the infra red region. Hence the effect of these acids seemed merely to be catalytic.

The unusual nature of the visible and ultra violet spectra of species 2 suggested that its formation involved a fundamental change in the state of the absorbing aromatic ring electrons. However, the ready interconversion with tetramethyltetrazaporphin iron (III) hydroxide (species 1), and the similarity of the infra red spectra of the two substances, suggested a close structural relation between them. The following possibilities for the structure of species 2 were considered:

1. The material was an iron tetrahydro-pigment. This seemed unlikely because of the similarity of the infra red spectrum to that of the iron (III) hydroxide species. The found $^{C}/_{H}$ ratio (13.01) did not correspond to either of the most likely possibilities, tetrahydrotetramethyltetrazaporphin iron (III) hydroxide (11.35) or

tetrahydrotetramethyltetrazaporphin iron (II) (11.92).

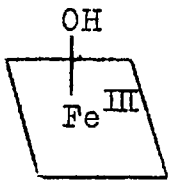
2. It was a form with the ring system protonated. This also seemed unlikely because both the iron (III)- and iron (II)- species were converted into the same unidentified species. This was shown by the absorption spectral changes caused by addition of 5% of glacial acetic acid to the chloroform solutions. In contrast, the spectrum of nickel tetramethyltetrazaporphin in 20% glacial acetic acid in chloroform was indistinguishable from that in pure chloroform.

Since 1963 a number of detailed X-ray crystallographic structural determinations of porphyrins have been reported.[18] (99-102) It became immediately obvious that, unlike phthalocyanines,[5] porphyrins were not rigidly planar.[99] To accommodate large metal atoms the system is able to buckle, by projecting alternate nitrogens up and down with respect to the average molecular plane. The central "hole" can be expanded, so that the radius to the N atom is about 2.06 Å,[18] without effecting the distance of the meso bridging carbons from the centre of the macrocycle. Iron prophyrins were found to have Fe-N distances larger than 2.06 Å and this was made possible by a displacement of the iron atom out of the average plane of the molecule.[100]

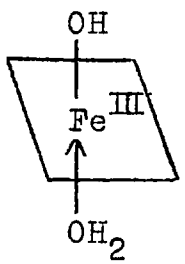
The crystal structures of the dimethyl ester of meso-porphyrin methoxyiron (III) and chlorohaemin have been reported.[18] In these compounds the iron is 0.455 Å and 0.475 Å, respectively, out of the plane formed by the four nitrogens. As a result the porphyrin ring system exists in a "domed" configuration. The resulting decrease in planarity would be expected to increase, relatively, the energy of the ground state of the molecule. A change in the electronic absorption spectrum of the material was therefore to be expected. The crystal structure of meso-tetraphenylporphyrin aquo-hydroxy iron (III) has also been reported.[101] In this compound the iron atom is displaced 0.2 Å out of the plane of the macrocyclic nitrogens, although the iron is, formally, in an octahedral environment. The iron-(hydroxyl) oxygen distance (2.18 Å) is considerably shorter than the iron-(water) oxygen distance (2.95 Å). Magnetic moment determinations show that these compounds are partially spin paired. Low spin iron atoms would be sufficiently small for a coplanar configuration of the complex. Such an iron (II) compound would show the absorption spectrum of a typical divalent transition metal porphyrin. In low spin iron (III) compounds, where the

iron is covalently linked to an oxygen, the tendency for the iron atom to be situated in the plane of the macrocycle would be opposed by steric repulsions arising from the fact that in a planar structure the N-O distance would be less than the sum of the O and N van der Waals' radii. In such a case the steric strain (ca. 10 Kcal/mole[18]) could easily be removed by ionization of the Fe-O bond.

By analogy with porphyrins it seemed likely that the tetramethyltetrazaporphin iron species 2 was tetramethyltetrazaporphin hydroxyiron (III) LXIII, the covalent form of species 1 (LX). The elementary analysis suggested that the compound existed as the hydrate LXIV.



LXIII

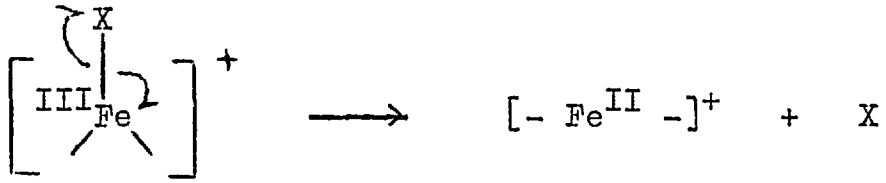


LXIV

The enforced "doming" of the tetrazaporphin ring system in such compounds might explain the unusual nature of the absorption spectrum of species 2.

Mass Spectra

Shannon and Swan[103] reported observing ion fragmentations in mass spectra of the form:



Such a dissociation could only occur if the X group was covalently bound to the iron atom. In the hope that the nature of the hydroxyl-iron bonds in species 1, its dipyridinate, and species 2 might be determined in this manner, mass spectral measurements were made. Unfortunately all three species showed a parent ion at $^{m}/e$ = 524 corresponding to the simple iron (II) species. No trace of an ion of $^{m}/e$ at 524 + OH = 541, or of a metastable peak for the dissociation 541 $\longrightarrow$ 524, was observed. Under certain circumstances the dipyridine-iron (III) hydroxide compound showed only the spectrum of the pyridine ligands.

Iron Tetra-(neo-pentyl)-tetrazaporphins

An iron pigment was produced by heating neo-pentyl-succinimidine and ferrous chloride in a boiling 2:1 mixture of chlorobenzene and nitrobenzene. The solvents were

removed under reduced pressure and the residue, in benzene, appeared (from its visible absorption spectrum) to be a mixture of hydroxyiron (III) and iron (III) hydroxide species. Like the tetramethyltetrazaporphin iron pigments, chromatography of the mixture in benzene on tartaric acid gave exclusively the covalent species, whilst chromatography on sodium sulphate produced the ionic species. However, the species so produced, in benzene solution, rapidly reverted to mixtures of the two forms. An equilibrium appeared to exist in solution and the position of equilibrium was dependent on the solvent used, and on the concentration. The covalent species was increasingly favoured on dilution.

After chromatography on tartaric acid or sodium sulphate the material still contained considerable impurity (the infra red spectrum showed strong carbonyl absorptions). The material was purified by refluxing it with N caustic soda, in the presence of a little ethanol. This tended to hydrolyse impurities to water soluble materials. After the residue had been filtered and washed with hot water the pigment was extracted from the remaining solid with benzene. On evaporating the benzene solution a dark solid, with a purple reflex, was obtained. The infra red spectrum of the product showed it to contain

only traces of carbonyl containing impurity (probably neo-pentylsuccinimide). The product gave an elementary analysis which (apart from the nitrogen determination) was in agreement with the material being the hydroxyl iron III compound. The magnetic moment was found, by the Gouy method, to be 3.80 Bohr magnetons. The magnetic susceptibility was independent of magnetic field strength, showing the product to be free from ferromagnetic material. The magnetic moment, hence, indicated the compound to be partially spin paired.

The colour of this hydroxyl iron (III) compound in solution depended on the solvent used, e.g. it appeared turquiose-green in chloroform and dull purple in glacial acetic acid. In methanol and pyridine solutions it existed as an iron (II) species and this appeared bright purple in methanol and reddish-purple in pyridine. From the pyridine solution a purple solid, with a strong reflex, was isolated. This was dried at room temperature/10^{-5}mm. and was found to be diamagnetic (by the Gouy method). The elementary analysis suggested the material to be tetra-(neo-pentyl)-tetrazaporphin aquo-dipyridine-iron (II). Dissolution of the material in chloroform gave, initially, a purple solution (i.e. an iron (II) species) but this rapidly oxidized to a solution of hydroxyiron

(III) and iron (III) hydroxide species. When the aquo-dipyridine-iron (II) species was heated under vacuum the solid showed no physical change until 140°, the material then lost its lustre. The substance that remained appeared identical to the hydroxyl iron (III) pigment.

Tetra-(neo-pentyl)-tetrazaporphin Chloroiron (III)

Fischer and Endermann[8] prepared a "haemin" of tetramethyltetraethyltetrazaporphin by reaction of the metal-free pigment with ferrous acetate and excess sodium chloride, in refluxing aqueous formic acid. They reported only the absorption spectrum of the product in pyridine, where the material existed as an iron (II) species.

By a similar preparative method, using ferrous chloride instead of ferrous acetate, tetra-(neo-pentyl)-tetrazaporphin chloroiron (III) was made. The product contained, variously, between 1 and 5% of the metal free pigment (estimated from the visible absorption spectra). The product was, however, free from ferromagnetic material and had a magnetic moment of 4.92 Bohr magnetons. This indicated it to be a high spin iron (III) species. It appeared to exist, in inert solvents, exclusively as the covalent form, as shown by its electronic absorption spectrum which was very similar to that of the hydroxyiron (III) compounds.

The chloroiron (III) species, like other iron (III) species, was reduced immediately by pyridine to the iron (II) form. This form was sufficiently soluble in pyridine to give an n.m.r. spectrum. The spectrum showed two singlets, at 5.95 τ and 8.63 τ, (ca. 6% w/v solution) corresponding to the methylene and t-butyl protons. The aromatic proton signal was masked by the pyridine proton absorption. Although the pigment was expected to be a mixture of substitutional isomers, these isomers appeared indistinguishable. This observation was not unexpected as the solute molecules were likely to be planar, due to solvent molecules co-ordinating to the iron atoms, in solution. The n.m.r. spectral measurements of tetra-(neo-pentyl)-tetrazaporphin (Chapter 3) indicated that in a planar configuration substitutional isomers were indistinguishable.

Attempted Preparation of Tetra-(neo-pentyl)-tetrazaporphin n-Propoxyiron (III)

The reaction of citraconononitrile with magnesium n-propoxide and ferrous chloride probably produced tetramethyltetrazaporphin n-propoxyiron (III) which then hydrolysed to the hydroxyl iron (III) compounds isolated. Fischer et al.[104] prepared methoxy- and ethoxy-aetiohaemin by reacting aetiohaemin with sodium-methoxide

and -ethoxide in the appropriate alcohol.

It was hence hoped that tetra-(neo-pentyl)-tetrazaporphin n-propoxyiron (III), the analog of the above n-propoxyiron (III) tetrazaporphin, might be prepared from the chloroiron (III) pigment. However, reaction of tetra-(neo-pentyl)-tetrazaporphin chloroiron (III) with sodium n-propoxide, under nitrogen, produced only an unidentified diamagnetic iron (II) pigment (λ_{max} = 616; 602; 550; 321 mμ, in chloroform).

Tetra-(neo-pentyl)-tetrazaporphin Bromoiron (III)

This was prepared in a similar manner to the chloroiron (III) compound, using ferrous bromide. The product had an electronic absorption spectrum identical with that of the chloroiron (III) compound. Its elementary analysis suggested that it retained, about one molecule of hydrogen bromide per molecule of pigment.

Dipotassium Dicyanoiron (II) Tetra-(neo-pentyl)-tetrazaporphin

This was prepared by reaction of the aquo-dipyridine-iron (II) pigment with potassium cyanide in ethanol. The product, after isolation and drying, gave a n.m.r. spectrum in methanol. This showed a singlet at 6.72 γ, corresponding to the t-butyl protons, the aromatic proton

signal was masked by traces of pyridine (ca. 6% w/v solution). On diluting the solution the t-butyl proton signal appeared to become a closely spaced multiplet. This change may be due to traces of acid, in the methanol used, causing the complex to dissociate to other iron (II) species.

When an attempt was made to dissolve the complex in chloroform, potassium cyanide was liberated and the simple iron (II) species passed into solution.

EXPERIMENTAL SECTION

Relevant electronic absorption spectra are tabulated and reproduced in Chapter 7.

Tetramethyltetrazaporphin Iron (III) Hydroxide (LX)

Magnesium turnings (2.8 g., 1.15 g.atoms) were reacted with dry boiling n-propanol (80 ml., reaction catalysed by a crystal of iodine), ferrous chloride (5 g., 0.4 moles) was added followed by citraconononitrile (3.5 g., 0.38 moles) in n-propanol (20 ml.), the latter solution being added during 25 minutes. The mixture was refluxed for a further 30 minutes after which the mixture was poured into water. The residue was filtered off and dried under vacuum, overnight. It was then ground up

and extracted continuously with hot chlorobenzene (200 ml.) for 3 hours. The extract was filtered, while still warm, and evaporated to dryness. The residue was dissolved in benzene and chromatographed on a column (4 x 30 cm.) of powdered sodium sulphate (dried at 130° overnight). A fast moving band was eluted, the resultant solution was evaporated to dryness, and the residue was crushed up under ether (10 ml.) and quickly filtered off. The product, tetramethyltetrazaporphin iron (III) hydroxide, was dried at 40°/0.1 mm. overnight, resulting in a 7.3% yield (306.2 mg.).

Found: C, 54.98; H, 3.85; N, 25.54; Fe, 11.98.
$C_{20}H_{17}N_8FeO$ requires C, 54.45; H, 3.89; N, 25.41; Fe, 12.66%.

Tetramethyltetrazaporphin Aquo-hydroxyiron (III) [LXIV]

(a) Tetramethyltetrazaporphin iron (III) hydroxide was dissolved in chloroform and glacial acetic acid was added (to 10% v/v concentration). The mixture was shaken for 5 minutes and evaporated to dryness under reduced pressure to yield the product, which was dried at 40°/0.1 mm. overnight.

(b) Tetramethyltetrazaporphin iron (III) hydroxide (100 mg.) was refluxed in liquid hydrogen cyanide (10 ml.) for 1

hour then the solution was evaporated to dryness and the residue was dried to the required product.
Found: C, 52.05; H, 4.00; N, 26.3, 21.31; Fe, 11.74%. $^{C}/_{H}$, 13.01. $C_{20}H_{19}N_8FeO_2$ requires C, 52.30, H, 4.17; N, 24.40; Fe, 12.16%. $^{C}/_{H}$ 12.55.

Tetra-(neo-pentyl)-tetrazaporphin Hydroxyl Iron (III)

Neo-Pentylsuccinimidine (5 g.) and ferrous chloride (1.1 g.) were heated to boiling in a mixture of chlorobenzene (100 ml.) and nitrobenzene (50 ml.) during 30 minutes, under nitrogen. The mixture became blue, then purple-blue and finally dull purple. It was then refluxed overnight. The mixture was evaporated to dryness under reduced pressure and the residue was refluxed with N caustic soda (50 ml.) and ethanol (10 ml.) for 1 hour. The warm suspension was filtered, and the residue, after being washed with hot water, was boiled with water (50 ml.) for 10 minutes. The solid was filtered off and again washed, and then dissolved in benzene, dried over calcium chloride, and filtered. The solution was evaporated to dryness and on drying at $60^{o}/1$ mm. (12 hours) the residue represented a 46.6% yield of product (2.32 g.).
Found: C, 64.58; H, 7.02; Fe, 8.18. $C_{36}H_{49}N_8FeO$ requires C, 64.95; H, 7.42; Fe, 8.39%.

Tetra-(neo-pentyl)-tetrazaporphin Aquo-dipyridine-iron (II)

Tetra-(neo-pentyl)-tetrazaporphin hydroxyl iron (III) (300 mg.) was dissolved in pyridine (10 ml.) by warming gently. The solution was evaporated to dryness under reduced pressure below 30°. The residue was broken up and dried at room temperature/10^{-5} mm. for 6 hours.

Found: C, 67.37; H, 7.24; Fe, 6.77. $C_{46}H_{60}N_{10}FeO$ requires C, 67.4; H, 7.33; Fe, 6.5%.

Tetra-(neo-pentyl)-tetrazaporphin Chloroiron (III)

Finely ground tetra-(neo-pentyl)-tetrazaporphin (106 mg.), sodium chloride (500 mg.) and 100% formic acid (15 ml.) were mixed, and to the rapidly stirred solution was added saturated aqueous ferrous chloride (0.5 ml.). The whole was refluxed for 15 minutes. The cooled mixture was then filtered and the residue was thoroughly washed with warm water. The product was dried at 60°/0.1 mm. overnight, giving a 92.8% yield (113.2 mg.).

Found: C, 63.25; H, 6.85; Cl, 5.07; Fe, 6.38. $C_{36}H_{48}N_8FeCl$ requires C, 63.20; H, 7.07; Cl, 5.18; Fe, 8.16%.

Tetra-(neo-pentyl)-tetrazaporphin Bromoiron (III)

This was prepared in a similar manner to the chloro-iron compound.

Found: C, 54·33 51.46; H, 5·85 6.28; N, 14.26; Br, 20.47; Fe, 5.60 7.47. $C_{36}H_{49}N_8FeBr_2$ requires C, 53.4; H, 6.12; N, 13.85; Br, 19.78; Fe, 6.9%.

Dipotassium Dicyanoiron (II) Tetra-(neo-pentyl)-tetrazaporphin

Tetra-(neo-pentyl)-tetrazaporphin aquo-dipyridine-iron (II) (102 mg.) was heated with potassium cyanide (25 mg.) in boiling absolute ethanol (5 ml.) for 4 hours. The cooled mixture was filtered and evaporated to dryness under reduced pressure. The product was dissolved in dry n-propanol (10 ml.) and the solution was filtered and evaporated to dryness under reduced pressure. The solid was then transferred to a sample tube and dried at 30°/0.1 mm. for 6 hours, yielding 97 mg. of product (89% yield).

CHAPTER 7

Electronic Absorption Spectral Data

The wavelengths are quoted in millimicrons and the extinction coefficients are given in terms of $\log_{10}\varepsilon$, in brackets.

Tetra-(neo-pentyl)-tetrazaporphins

(a) Metal free pigment in chloroform (spectrum 1).

339.5;	551;	595;	623.
(4.97)	(4.73)	(3.99)	(4.94)

(b) Nickel pigment in chloroform (spectrum 2).

319;	342;	585.
(4.59)	(4.60)	(4.77)

(c) Chloroiron (III) pigment in chloroform.

321;	363;	436;	554;	673.
(4.65)	(4.38)	(4.07)	(4.24)	(4.20)

(d) Hydroxyl iron (III) pigment in glacial acetic acid (spectrum 3).

318;	363;	432;	556;	670.
(4.46)	(4.30)	(4.05)	(4.11)	(4.09)

(e) "Hydroxyl iron (III)" pigment in pyridine (i.e. iron (II) species present - spectrum 4).

332;	440;	537;	583.
(4.50)	(3.95)	(4.16)	(4.62)

Tetramethyltetrazaporphin

(a) Iron (III) hydroxide pigment in carbon tetrachloride (spectrum 5).

302;	341;		606.
(4.56)	(4.58)		(4.45)

(b) Hydroxyiron (III) pigment in carbon tetrachloride with 5% v/v glacial acetic acid.

315;	356;	426;	552;	670
(4.64)	(4.50)	(4.19)	(4.28)	(4.31)

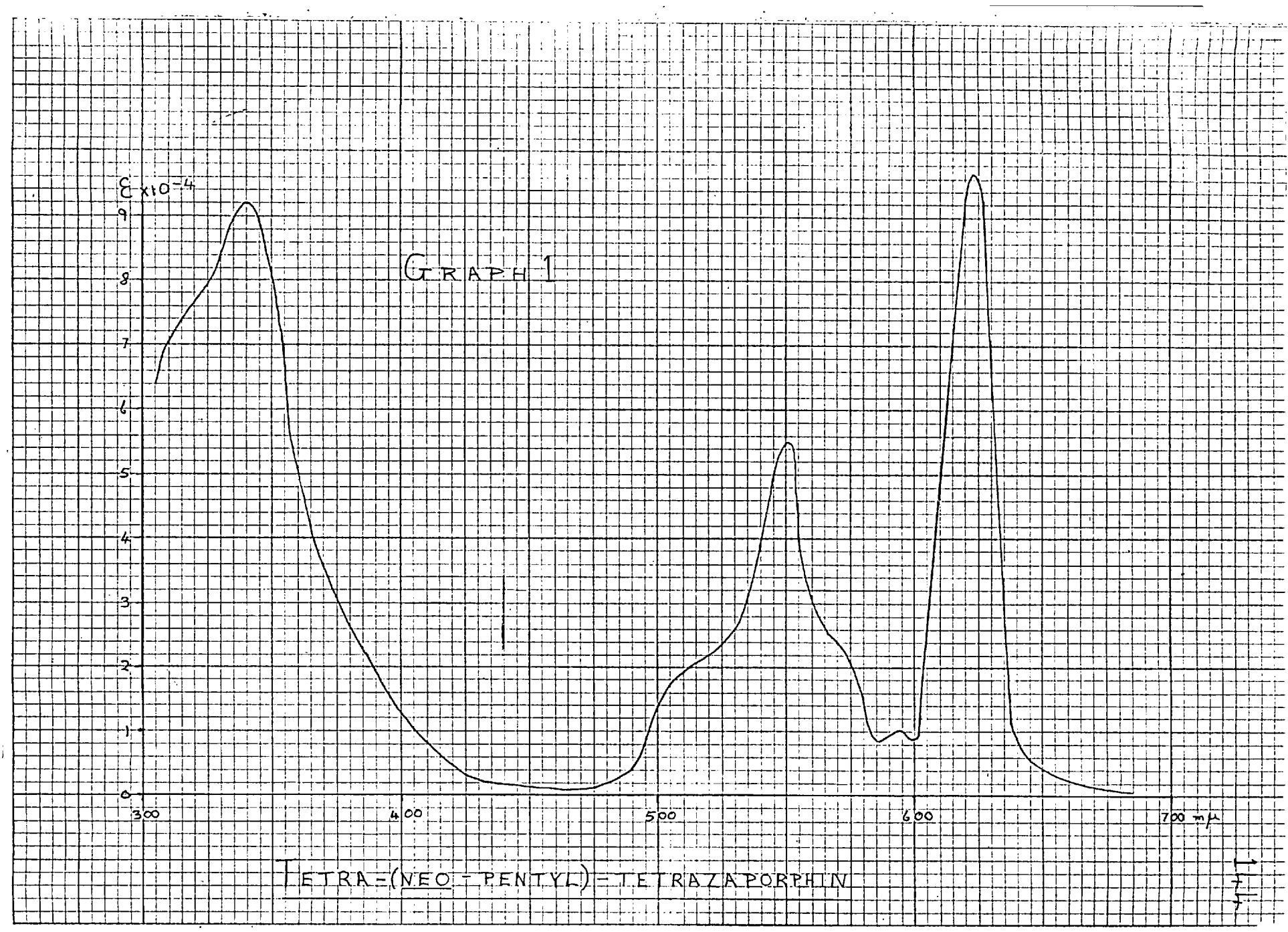
(c) "Iron (III) hydroxide" pigment in 50:50 pyridine-carbon tetrachloride (i.e. iron (II) species present).

328;	444;	537;	583.
(4.71)	(4.16)	(4.35)	(4.86)

Spectra

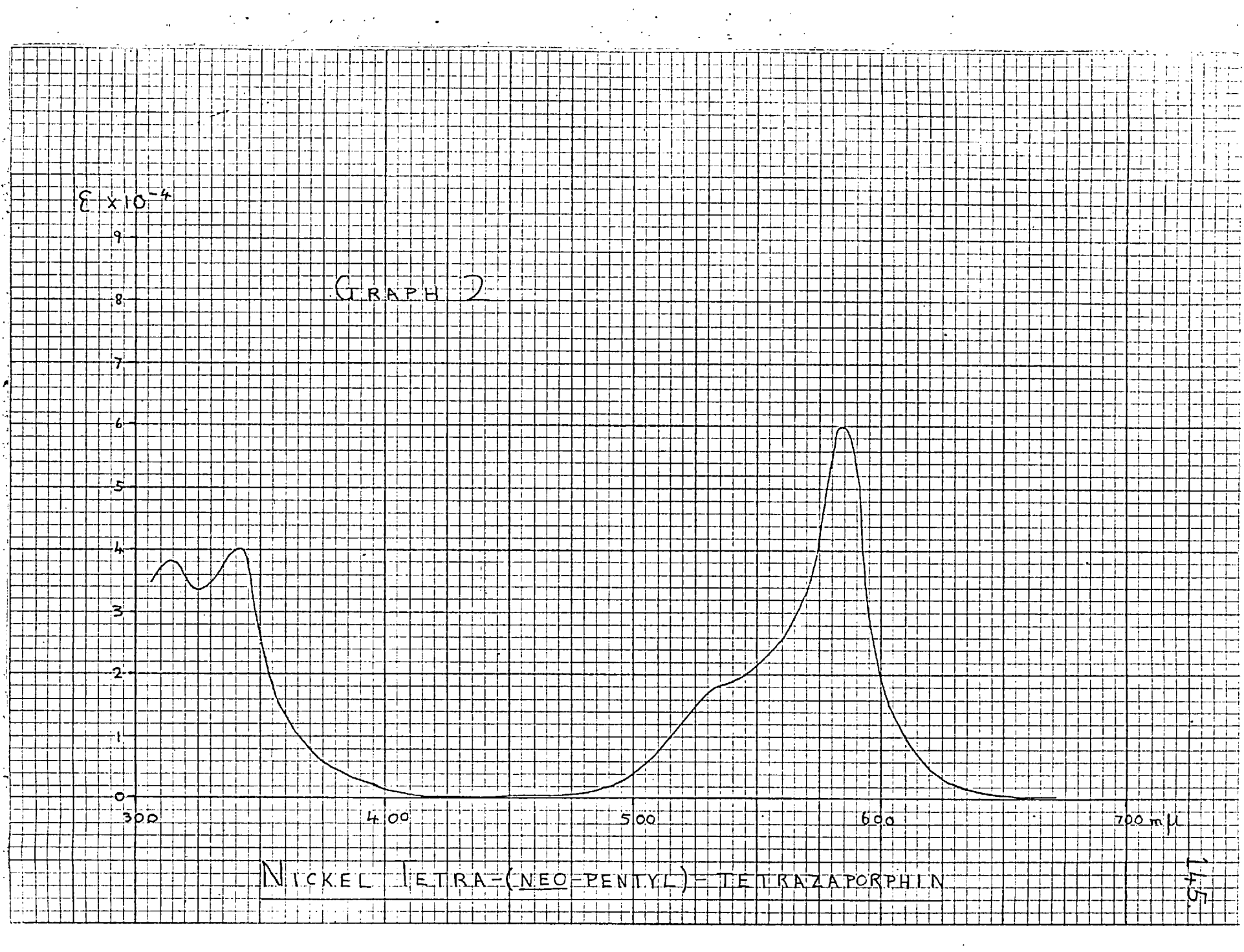
1. Tetra-(neo-pentyl)-tetrazaporphin in chloroform.
2. Tetra-(neo-pentyl)-tetrazaporphin nickel in chloroform.
3. Tetra-(neo-pentyl)-tetrazaporphin hydroxyl iron (III) in glacial acetic acid.

4. Tetra-(neo-pentyl)-tetrazaporphin iron (II) in pyridine (produced by dissolving the hydroxyl iron (III) pigment).
5. Tetra-(neo-pentyl)-tetrazaporphin hydroxyl iron (III) in chloroform.
6. Tetramethyltetrazaporphin iron (III) hydroxide in carbon tetrachloride.



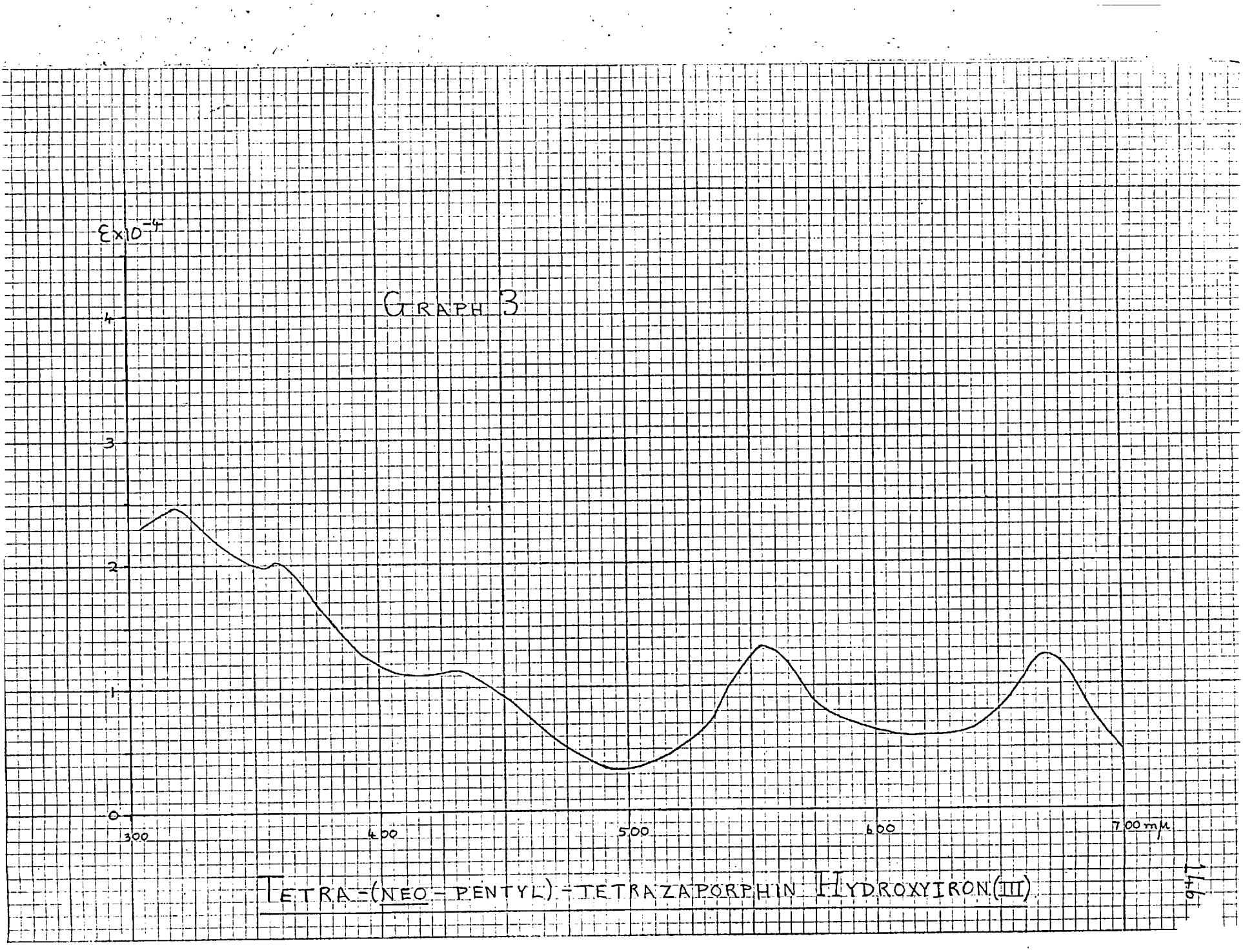
GRAPH 1

TETRA=(NEO-PENTYL)=TETRAZAPORPHIN



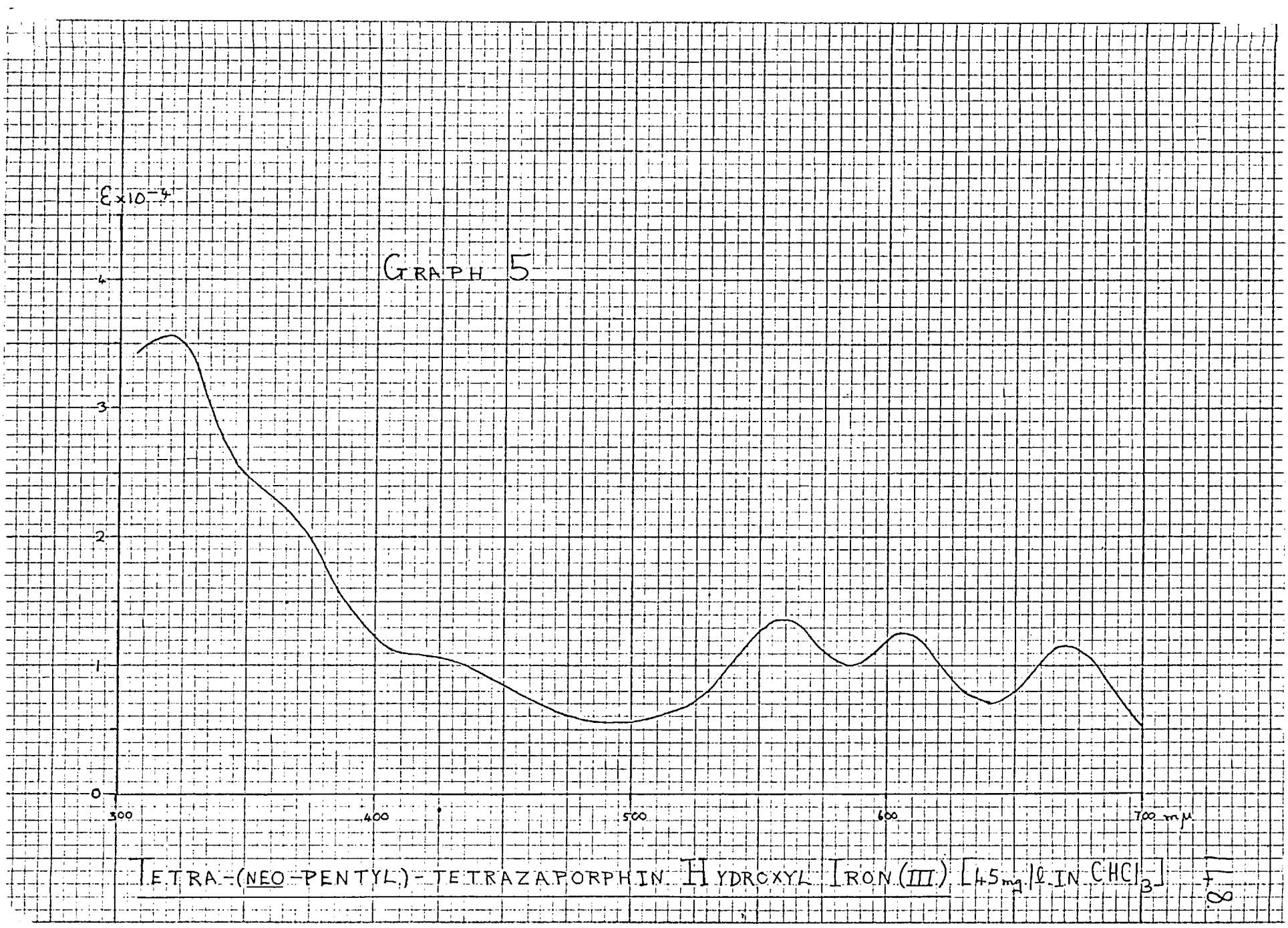
GRAPH 2

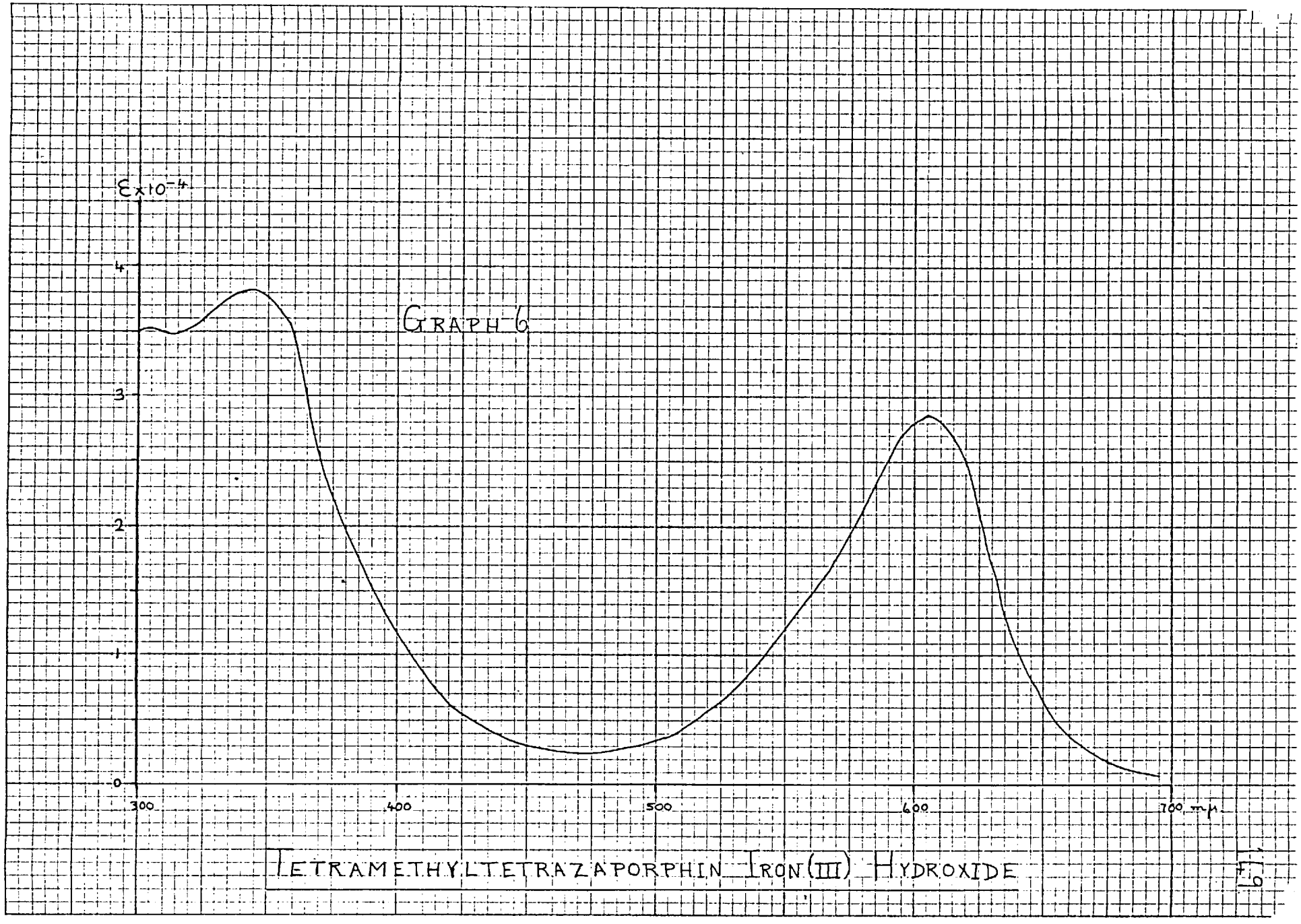
NICKEL TETRA-(NEO-PENTYL)-TETRAZAPORPHIN


ε x 10⁻⁴
GRAPH 3
4
3
2
1
0
300
400
500
600
700 mμ
TETRA-(NEO-PENTYL)-TETRAZAPORPHIN HYDROXYIRON(III)

GRAPH II

TETRA-(NEO-PENTYL)-TETRAZAPORPHIN. IRON(II)


ε x 10⁻⁴
GRAPH 5
4
3
2
1
0
300
400
500
600
700 mμ
TETRA-(NEO-PENTYL)-TETRAZAPORPHIN HYDROXYL IRON (III) [45 mg/l IN CHCl3]
f ∞



GRAPH 6

TETRAMETHYLTETRAZAPORPHIN IRON(III) HYDROXIDE

Fig. 6

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