# THE SYNTHESIS OF MESO-SUBSTITUTED PORPHYRINS

A Thesis

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Master of Science

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by

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CONTENTS

## SUMMARY

Three new ms-tetra-o-substitutedphenylporphyrins and their zinc complexes have been synthesized by the Rothemund reaction. Attempts to elucidate the mechanism of this reaction have been described and a possible intermediate or by-product isolated and identified. The electronic absorption spectra of the new compounds have been compared with two literature compounds and the nuclear magnetic resonance spectra of the free bases have been determined. The spectra have been discussed in relation to problems of porphyrin structure. Three porphyrins (in gm. quantities) have been sent to the Chester Beatty Research Institute, London, for testing for tumour inhibition.

McDonald's porphyrin synthesis has been modified to produce ms-disubstituted porphyrins and comparison of it with other syntheses for these compounds has shown it to be the best. The possibility of extending this synthesis to tri- and tetrasubstituted porphyrins has been envisaged.

Schotten-Baumann benzoylation of pyrroles has been shown to give 2-substituted derivatives and not the 1-isomers previously reported. An infrared study of the NH and CO stretching frequencies of 2-benzoylpyrroles and of the CO stretching frequencies of 1-benzoylpyrroles has been described.

## STATEMENT

The work described in this thesis incorporates no material previously submitted for a degree in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

(Robert L. Laslett)

## ACKNOWLEDGEMENTS

I would like to express my appreciation for the guidance and encouragement accorded me throughout the course of this work by Professor G. M. Badger, to whom the project owes its inception.

I am also indebted to Dr. R. A. Jones, for his generous assistance in the planning and execution of the work, particularly for his determination and interpretation of accurate infrared and electronic absorption spectra.

Many discussions with other members of the staff and research students have proved profitable, but I would especially thank Dr. T. M. Spotswood, who determined and interpreted the nuclear magnetic resonance spectra. For their patience and helpfulness, I should also like to thank Mr. R. J. Drewer, B.Sc., Mr. R. W. Guy, B.Sc., and my family. Thanks are also due to the kind people who supplied samples and whose names are recorded elsewhere.

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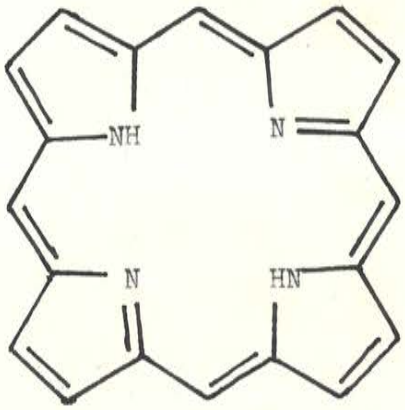
# CHAPTER I

## INTRODUCTION

### 1.1 Porphyrins and cancer

Porphyrins are substituted derivatives of porphin (I), the aromatic macrocycle formed when four pyrrole residues are linked via their α-positions.




I

These compounds are widespread in nature and are of fundamental biological importance since they form the basic skeleton of both haem and chlorophyll compounds. The haems are iron complexes of porphyrins while the chlorophylls are magnesium complexes of dihydroporphyrins.

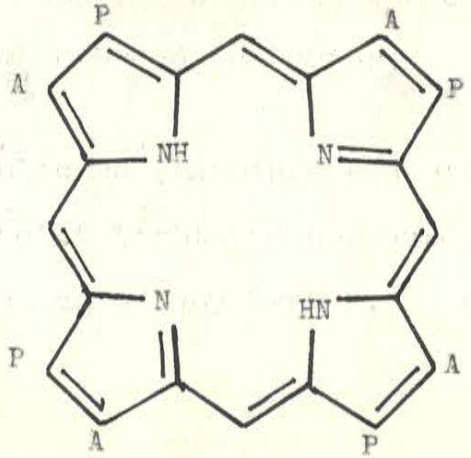
In 1924, Policard[1] examined experimental rat tumours under ultraviolet light and observed the characteristic strong fluorescence of porphyrins. However, it was

not until the 1940's[2] that the precise relation between porphyrins and cancer began to be thoroughly investigated. Since that time, experiments have followed four main trends:

(1) investigation of possible disturbances of the normal porphyrin metabolism as a result of the presence of tumour tissue;
(2) studies on the presence of porphyrins in tumour tissue;
(3) examination of the photosensitivity of tumours in the presence of porphyrins; and
(4) investigation of the ability of the neoplasm to accumulate porphyrins.

The last two methods were of interest to us since synthetic porphyrins could be used and these methods will therefore be discussed in greater detail.

Photosensitization of the skin[3] is a characteristic symptom of the disease, porphyria, which results from the presence of excess porphyrins, particularly uroporphyrin I (II).




A = Acetic Acid.

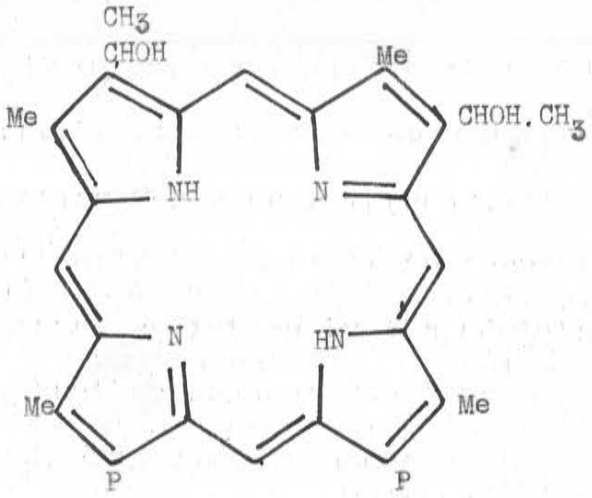
P = Propionic Acid.

II

In 1930, it was observed that this sensitivity extended to wavelengths in the X-ray range[4]. This appeared promising for cancer therapy, since it seemed likely that it would be possible to increase the tumouricidal effect of ionizing radiation by the administration of porphyrins. Further support for this view came from the fact that porphyrins could enhance radiosensitivity in normally radioresistant organisms, such as paramoecia[5].

The potential value of these observations was greatly increased when it was coupled with the fact that tumour tissue accumulates porphyrins. This latter property offered possibilities not only for cancer therapy, but also as an aid to diagnosis since it could permit external scintiscanning of radioactive derivatives. It was also recognized that the characteristic fluorescence of the porphyrins might be used to aid the surgeon during cancer operations. These possibilities have since been investigated with some success; but conflicting results have sometimes been obtained.

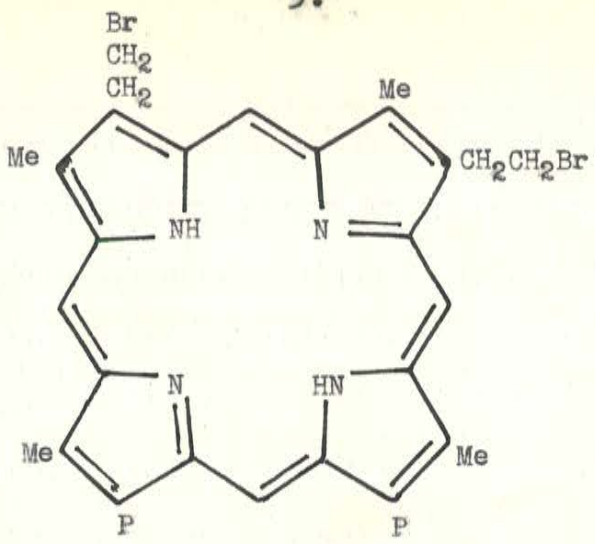
Auler and Banzer[6] first observed that haematoporphyrin (III, IX isomer) tends to accumulate in neoplastic tissue in men and animals. Figge and his coworkers[7] demonstrated that other naturally occurring porphyrins besides haematoporphyrin were localized and also that zinc




III

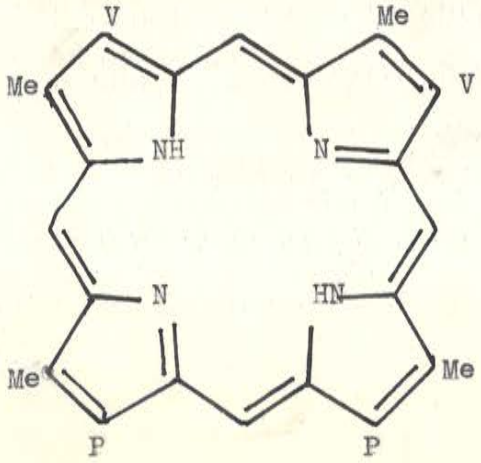
complexes of porphyrins, could accumulate in neoplastic, embryonic and traumatized tissue. They[8] also used large doses of haematoporphyrin in surgery of cancerous growths. However, Schwartz and his collaborators[9] have claimed that it was not haematoporphyrin, but rather an impurity in haematoporphyrin which was localized. In fact, they found as many as twenty different porphyrins in a sample of commercial haematoporphyrin. On the basis that the impurity was bis-(2-bromoethyl)-deuteroporphyrin (IV), Altman and Salomon[10] have found that the closely related, but more easily prepared, bis-(2-iodoethyl-$^{131}$I)-deuteroporphyrin becomes localized selectively in transplanted adenocarcinomata and in spontaneous mammary adenocarcinomata.

Lipson *et al.*[11] have found that the diacetyl derivative of haematoporphyrin is localized more effectively than haematoporphyrin itself. In the light of these




IV

successful experiments, the claim by Bases[12] that $^{64}Cu$-labelled copper complexes of porphyrins are not localized in human tumours but are in mouse tumours, seems rather surprising. Other workers[13] have concluded that haematoporphyrin is not only localized, but inhibits the development of Walker's adenocarcinoma in white rats. Working with a sample of haematoporphyrin, which had been carefully purified from protoporphyrin (V) and deuteroporphyrin (VI), Winkelman[14] made quantitative determinations of these three porphyrins in subcellular fractions of neoplastic tissue using fluorometric and spectrophotometric methods.

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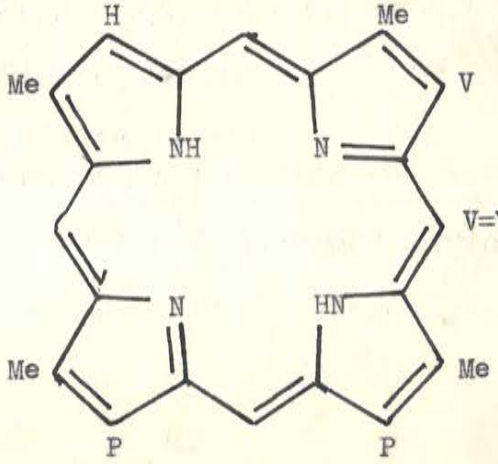
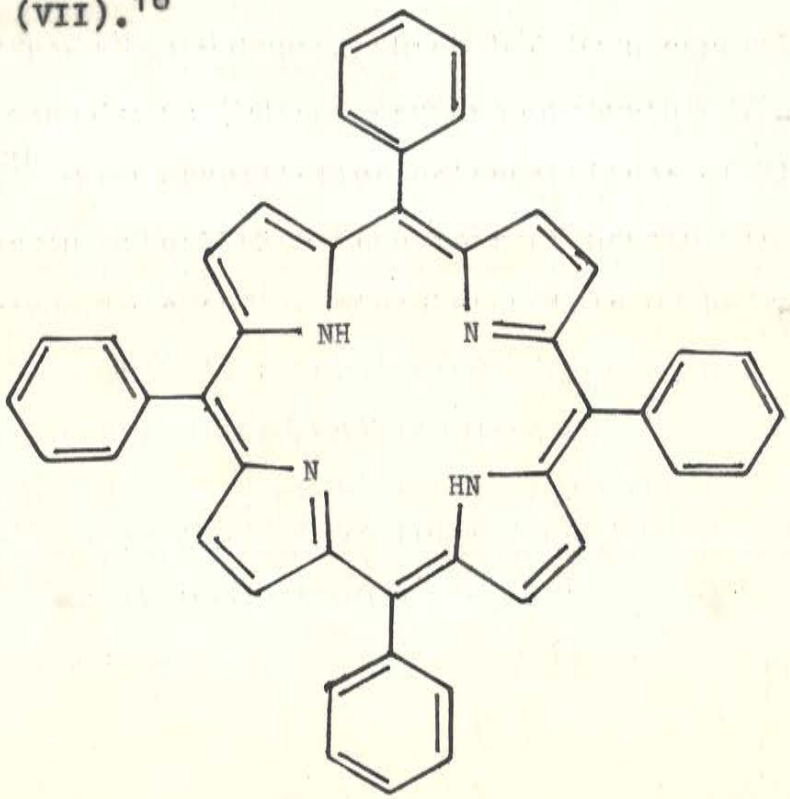



VI

V=Vinyl.

The site of origin of the protoporphyrin and deuteroporphyrin was not known. Some Japanese workers[15] have reported successes in the chemotherapy of malignant tumours using the disodium salt of the mercuric complex of haematoporphyrin. They believe the effectiveness of their therapy is based on the facts that the porphyrin forms a chelate complex with cuprous ion, thereby preventing the inhibition of enzymes containing the thiol group, and the mercuric ion, which is liberated, prevents the formation of non-protein thiols. An increase in cuprous ion and in non-protein thiols have been described as fundamental phenomena in tumour-bearing animals and cancer patients. The most recent successful experiments on the porphyrin-localizing property of tumours have been with sulphonic acid derivatives of tetraphenyl-porphyrin (VII).[16]




VII

The positions of the sulphonic acid groups are not known with certainty but, on the basis of the visible spectrum, they are believed to be in the phenyl rings and not on the $\beta$-positions of the pyrroles. The postulate[17] of the presence of a special phospholipid, 'malignolipin', in tumour tissue to explain the localizing property has been recently criticized.[18] From these studies, it seems that neoplastic tissue does possess the property of localizing a wide variety of porphyrins, but more needs to be known of the reasons for this.

Research on the combined effects of X-radiation and tumours have been more conflicting. Bases[19] felt that there was no evidence of a potentiating effect when haematoporphyrin was administered to eight X-irradiated patients with advanced cancers, but Schwartz[9], in a study of thirty-eight patients with diverse types of tumour, concluded that porphyrins enhanced the effect of X-irradiation in five patients. Other studies[20,21,22] seemed more promising and it was concluded that there was a significant difference in response between patients given the combined treatment and those treated by X-irradiation alone. Scanlon[23] has offered four reasons for the variability of these findings:

(1) variations in tumour dose;

(2) differences in interval between the administration of porphyrins and X-irradiation;

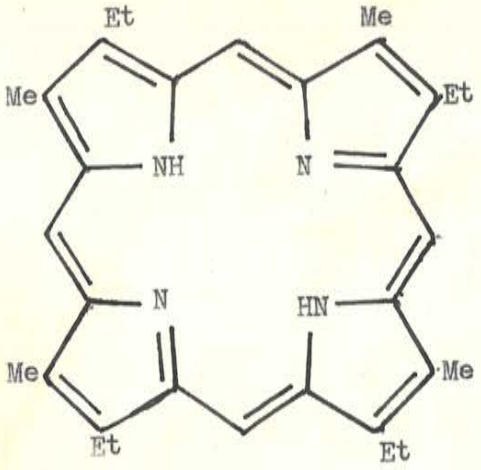
(3) differences in types of porphyrins used (particularly in purity); and

(4) differences in dosage of porphyrin administered.

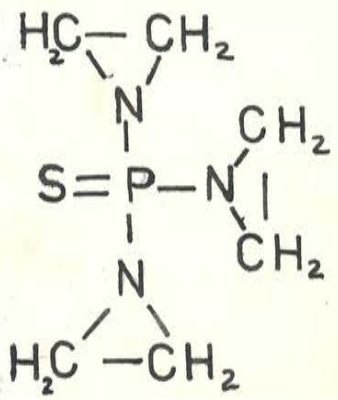
It seems that more work is needed on this promising combination, particularly with respect to the standardization of results so that difficulties in interpretation can be minimized.

The partial successes of the combined treatment of X-radiation and porphyrins has prompted investigations of the combined effect of porphyrins and the radiomimetic drugs, which are believed to have a mode of action on tumours similar to high energy radiation. Scanlon[23] and Calloway[24] have observed the effect on human and animal tumours of a combination of phyltone (a potassium salt of a derivative of etioporphyrin III (IX) ) and the biological alkylating agent, triethylenethiophosphoramide (X). Their conclusions were that this porphyrin was capable of favourably altering the therapeutic ratio of the radiomimetic drug towards some neoplasms.

The promise of the use of porphyrins as chemotherapeutic agents, like most others, is marred by certain




IX




X

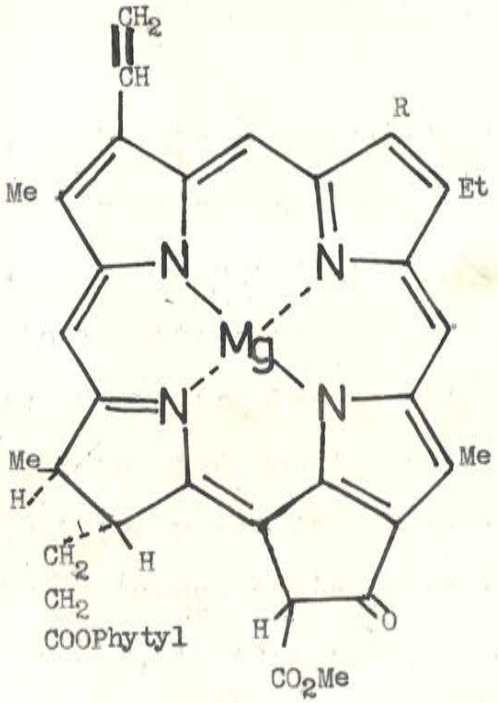
toxic side-effects. The photosensitivity has been mentioned above and, when large doses of porphyrin are injected[8], this must be considered. The report that the injection of haematoporphyrin into rabbits causes renal enlargement and Monckeburg arteriosclerosis is also of interest[25]. The other fact to be borne in mind for the intelligent use of porphyrins in cancer therapy and diagnosis is that they concentrate not only in tumour tissue, but in all tissues with a high mitotic index, that is in all growing tissues[26].

When our work was commenced, many of the above results had not been obtained, but the prospect of synthesizing pure porphyrins in gm. quantities for testing for tumour inhibition seemed most promising[27].

The Chester Beatty Research Institute in London kindly undertook to carry out the physiological part of the testing.

## 1.2 meso-Substituted Porphyrins

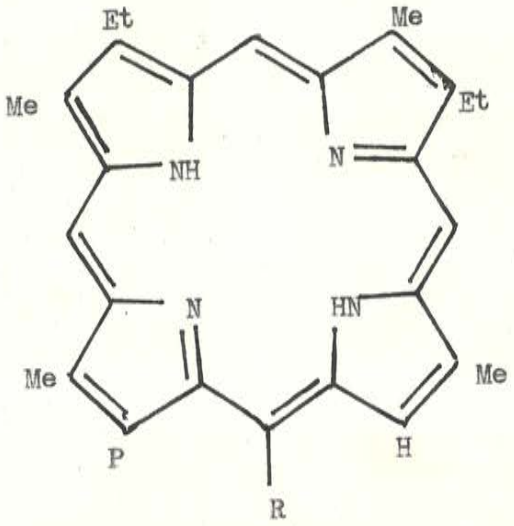
Porphyrins which have only one substituent in the ms-position have been studied because of their relation to the green plant pigments, chlorophyll a (XI, R = Me) and chlorophyll b (XI, R = CHO).




XI

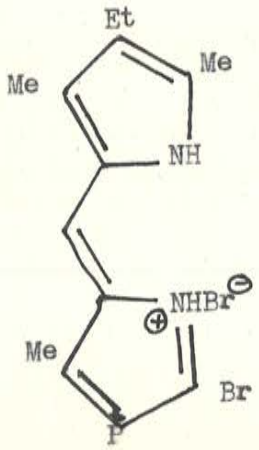
Chlorophyll, on vigorous treatment with alkali, gives rise to a mixture of phyllоporphyrin XV (XII, R = Me) and pyrroporphyrin XV (XII, R = H)[28], the latter presumably being formed by elimination of a methyl group from the

former as ms-methyl groups are known to eliminate under these conditions[29]. Phylloporphyrin has been the focal point of most of the studies on ms-monosubstituted porphyrins.

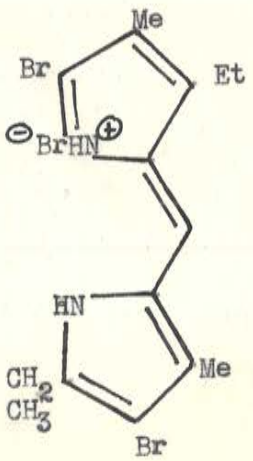



XII

Confirmation of phylloporphyrin as the $\gamma$-isomer rather than the $\alpha$, $\beta$ or $\delta$-isomers came from synthesis of the four isomers[30] and comparison of the synthetic products with the natural. Phylloporphyrin was prepared by condensation of the pyrromethenes (XIII) and (XIV).

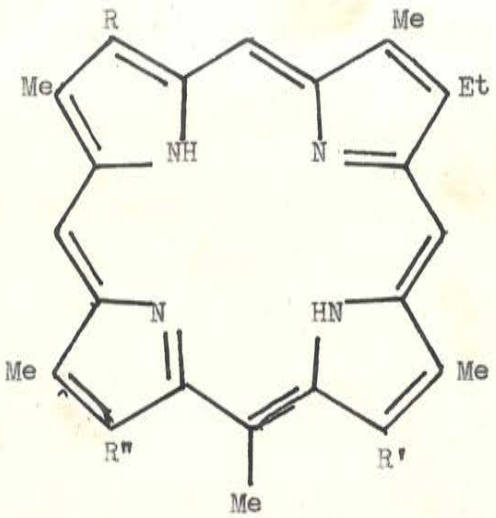



XIII

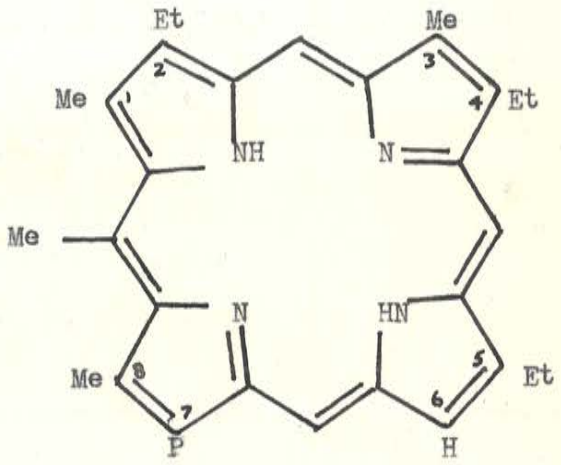



XIV

The product was a mixture of ten different porphyrins and they were separated on the basis of their different basicities. The best yield of the required γ-isomer was 3.5%, when (XIV) was brominated before the condensation. The condensation of 5-ethyl-5'-bromodipyrromethenes with 5-methyl-5'-bromodipyrromethenes was the basis of the synthesis of the α, β and δ-isomers of phylloporphyrin, and the syntheses of phylloetioporphyrin[31] (XV, R = Et, R' = H, R" = Et), 6-ethylphylloporphyrin[32] (XV, R = Et, R' = Et, R" = propionic acid), desethylphylloporphyrin[33] (XV, R = H, R' = H, R" = propionic acid), and even the recent synthesis of the δ-methyl derivative of the methyl ester of 1,3,8-trimethyl-2,4,5-triethylporphin-7-propionic acid (XVI)[34].

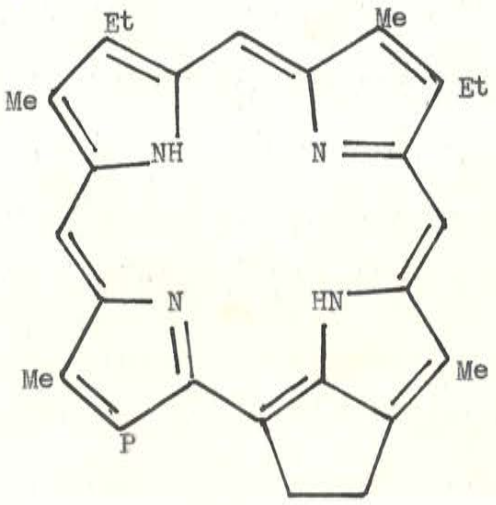



XV



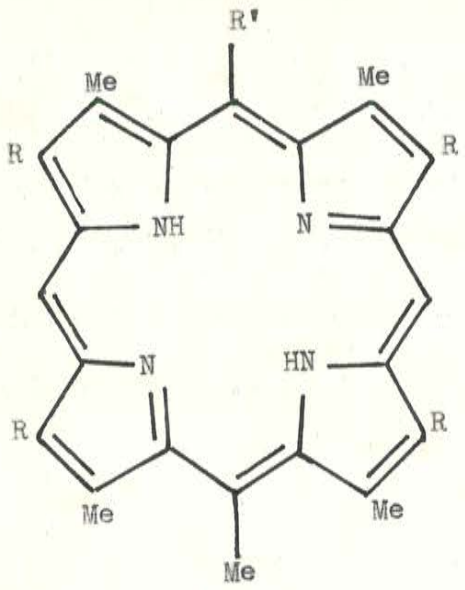

XVI

In all these syntheses, the products were mixtures and the yields were low. The ms-methyl group in phylloporphyrin has been used to produce derivatives of the important chlorophyll derivative, desoxyphyllocerythrin (XVII)[35,36,37] and has been the source of other porphyrins with different γ-substituents[38,39,40] (XII, R = CHO, $CH_2OH$ $CH_2Cl$ or COOH).

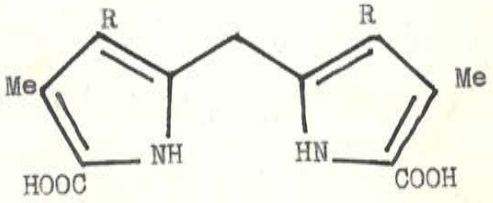



XVII

Recently, Kenner et al.[41] obtained ms-monomethyloctamethylporphyrin (XVIII, R = Me, R' = H) in 0.1% yield as a by-product in the synthesis of the ms-dimethyloctamethylporphyrin (XVIII, R = Me, R' = Me). Their method of synthesis was to heat an acetic acid solution of the diacid (XIX, R = Me) with acetyl chloride, and then to aerate the product.




XVIII

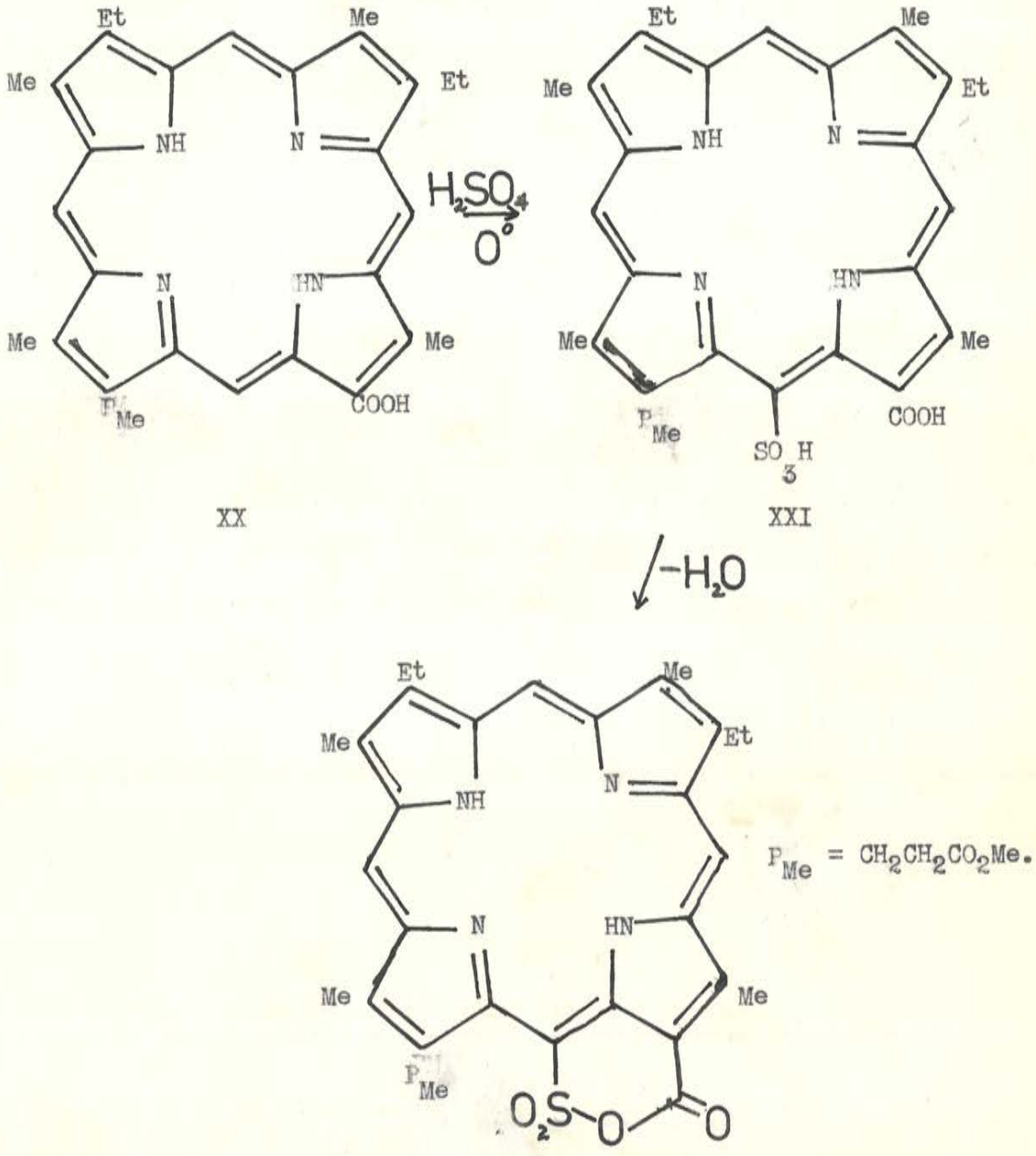



XIX

In a similar experiment, but using the diacid (XIX, R = Et), they obtained a 1% yield of a mixture of two ms-monosubstitutedetioporphyrins (XVIII, R = Et, R' = H). The mixture was separated using countercurrent distribution, but it was not possible to infer the precise structure of the two isomers. It appears that the monosubstituted porphyrins (which incidentally have not been characterized by analysis) must have been formed by fission of the dipyrrylmethane fragments, followed by recombination of the individual pyrrole units with formaldehyde (or its equivalent) formed from the methane bridges. However, apart from methyl substituents and their derivatives, no other ms-monosubstituted porphyrins have been investigated.

A porphyrin with a sulphonic acid group in the $\gamma$-position (XXI) has been postulated in the formation of

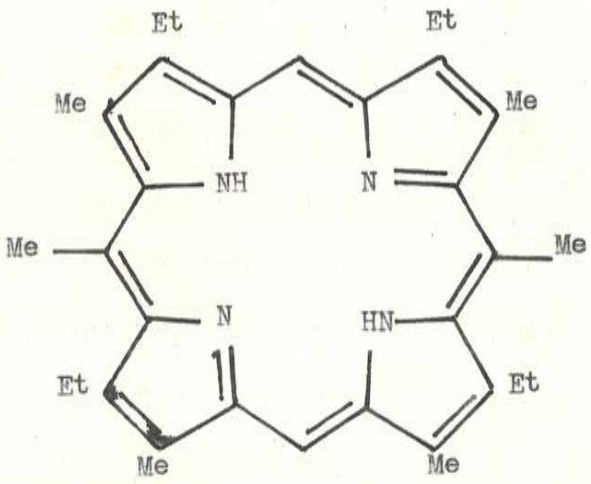
rhodoporphyrin-methylester-6, γ-carbosulphoanhydride (XXII) by the action of oleum on rhodoporphyrin methyl ester (XX) but was not isolated[39].



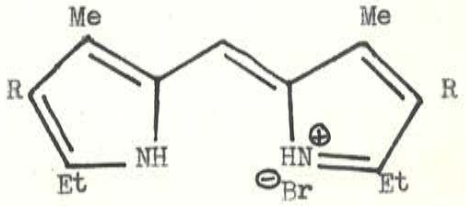

XX XXI XXII

Although visible spectra have been reported for most of the porphyrins above, no systematic study with modern instruments has been undertaken.

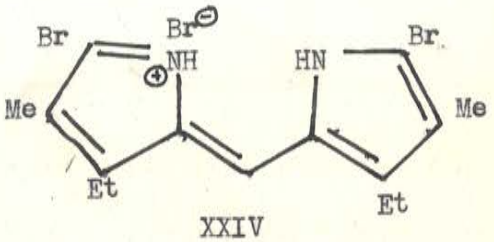
The chemistry of ms-disubstituted porphyrins has been investigated still less. In 1931, Fischer and Kurzinger[42] obtained $\beta$, $\delta$-dimethyletioporphyrin IV (XXIII)* in meagre yield by the condensation of methenes (XXV, R = Et) and (XXIV) and subsequent oxidation.




XXIII




XXV




XXIV

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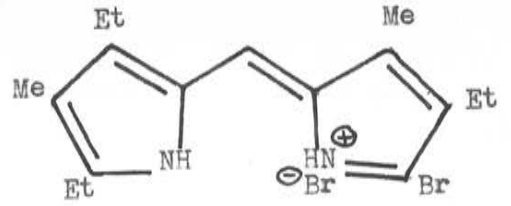
* Nomenclature
This compound was labelled $\alpha$, $\gamma$-dimethyletioporphyrin IV by Fischer, presumably in order to make it easier to relate to chlorophyll. The nomenclature with the $\alpha$-carbon atom between the 2 and 3 carbon atoms will be used throughout this thesis.

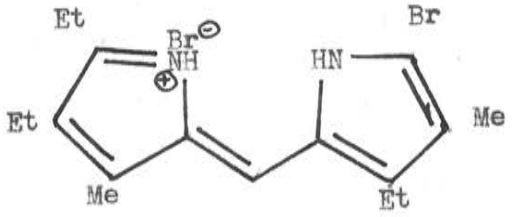
A similar condensation with methenes (XXV, R = H) and (XXIV) did not produce a ms-disubstituted porphyrin. In both these reactions, mixtures of porphyrins were obtained.

ms-Disubstituted porphyrins were amongst the mixtures of products reported from the synthesis of all four isomers of phylloporphyrin[30]. Presumably they arose by self-condensation of the pyrromethene fragments which contained the ethyl group in the 5(5')-position. Thus, α, γ-dimethyletioporphyrin I (XXVI, R = Me) was obtained from the dipyrromethenes(XXVII) and (XXVIII), α, γ-dimethylmesoporphyrin V(XXX) from the dipyrromethene (XXIX), and β, δ-dimethyldeuteroetioporphyrin II (XXXII)[31] from the dipyrromethenes (XXXI) and (XXXIII). The yields were of the order of 1%. The structures indicated have not been assigned on the basis of unambiguous synthesis, but they are probably correct because the corresponding porphyrins without ms-substituents were also obtained in each case. If fission and recombination had occurred, it is unlikely that this would have been so.

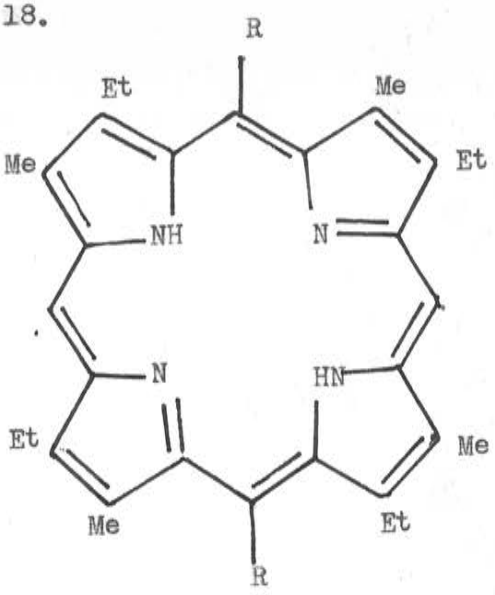
Other ms-disubstituted porphyrins reported were ms-dimethyloctamethylporphyrin (XVIII, R = Me, R' = Me) and ms-dimethyletioporphyrin II (XVIII, R = Et, R' = Me), obtained in poor yield in the synthesis by Kenner[41] mentioned above. The only substituents involved in disubstitution



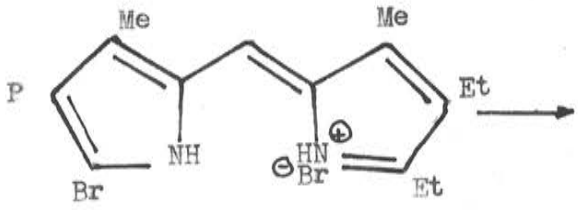
XXVII



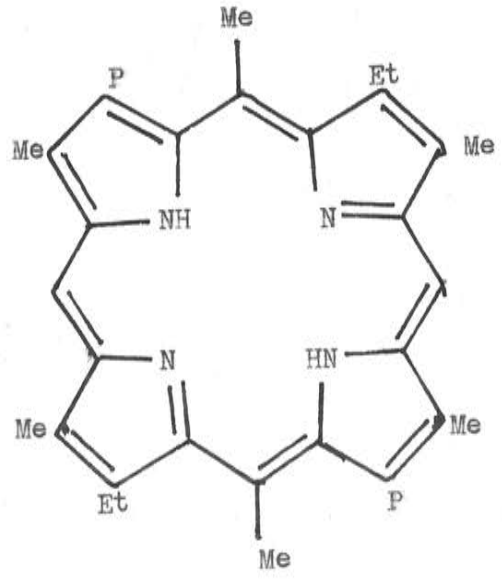
XXVIII



XXVI



XXIX



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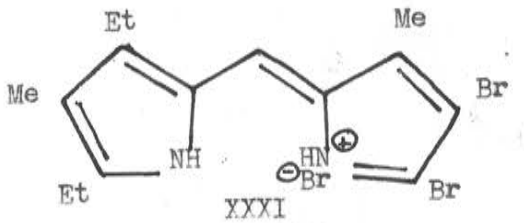
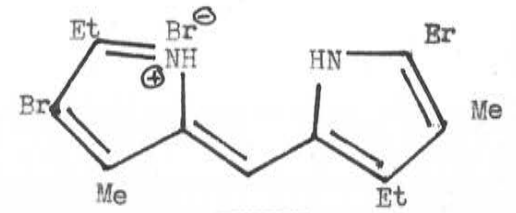
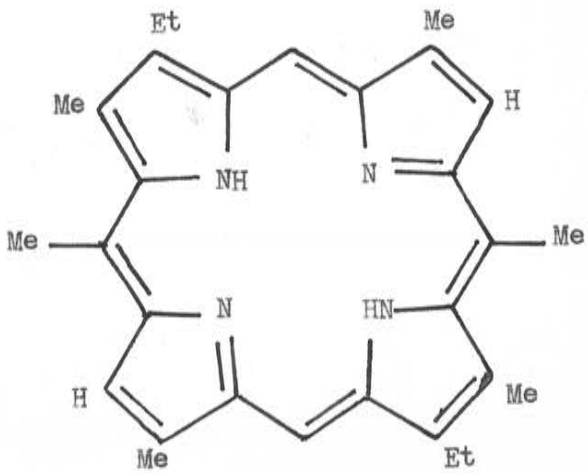


XXXI



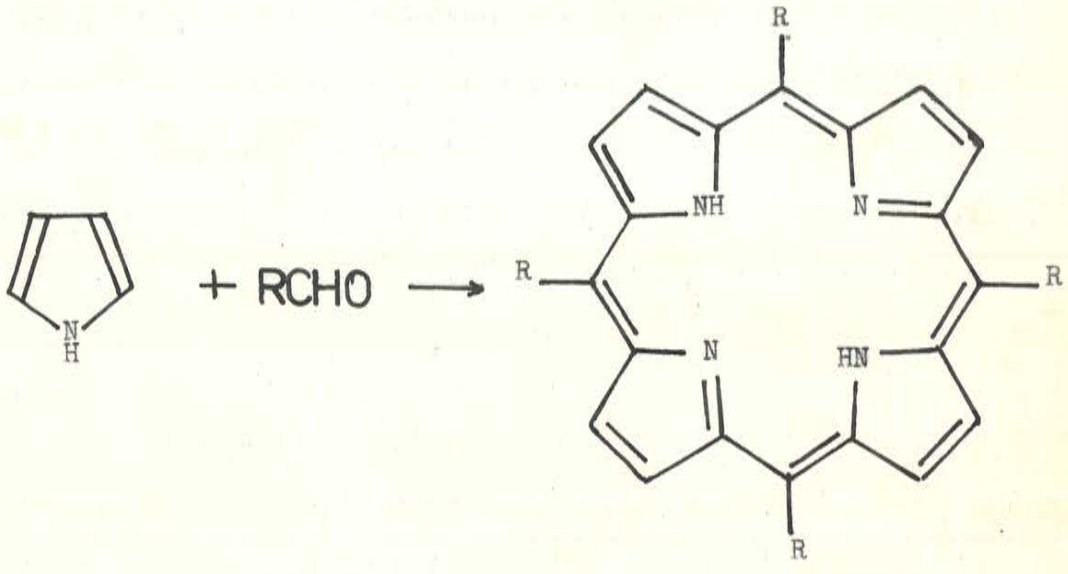
XXXIII



XXXII

have been methyl and halogen groups, and no porphyrins with an $\alpha,\beta$-type of substitution pattern have been reported. ms-Dichloroetioporphyrin I (XXVI, R = Cl) was obtained from the corresponding tetrasubstituted derivative by the action of pyridine, but the precise position of the ms-substituents is unknown[43].

Although ms-trisubstituted porphyrins have not been reported, the ms-tetrasubstituted compounds have been comprehensively investigated, presumably because of their ready preparation. They were first prepared by Rothemund[44] in 1935, when he heated a mixture of pyrrole, an appropriate aldehyde (XXXIV, R = H, Me) and pyridine in a sealed tube to 85-90°. (Fig. 1).

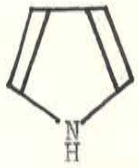



XXXIV XXXV

Fig. 1.

A wide variety of aldehydes[45,46] has since been employed at higher temperatures, but most investigations have concentrated on ms-tetraphenylporphyrin[47-50] (XXXV, R = $C_6H_5$), its derivatives and metal complexes[51-53], which not only can be prepared in large amounts, but also have found commercial application as photosensitizers in photoxidation reactions, particularly of olefin compounds[54-59]. Ball, Dorough and Calvin[60] increased the yields of ms-tetraphenylporphyrin by adding zinc acetate but a very recent paper[58] has criticized the original conditions of the Rothemund reaction, claiming 90% yields of ms-tetra-substututedporphyrin in the absence of pyridine. The mechanism of this useful reaction is not known.

The other method employed for the synthesis of ms-tetrasubstituted porphyrins was developed by Eisner[61]. He synthesized ms-tetramethylporphyrin (XXXV, R = Me) from the Mannich base (XXXVI).

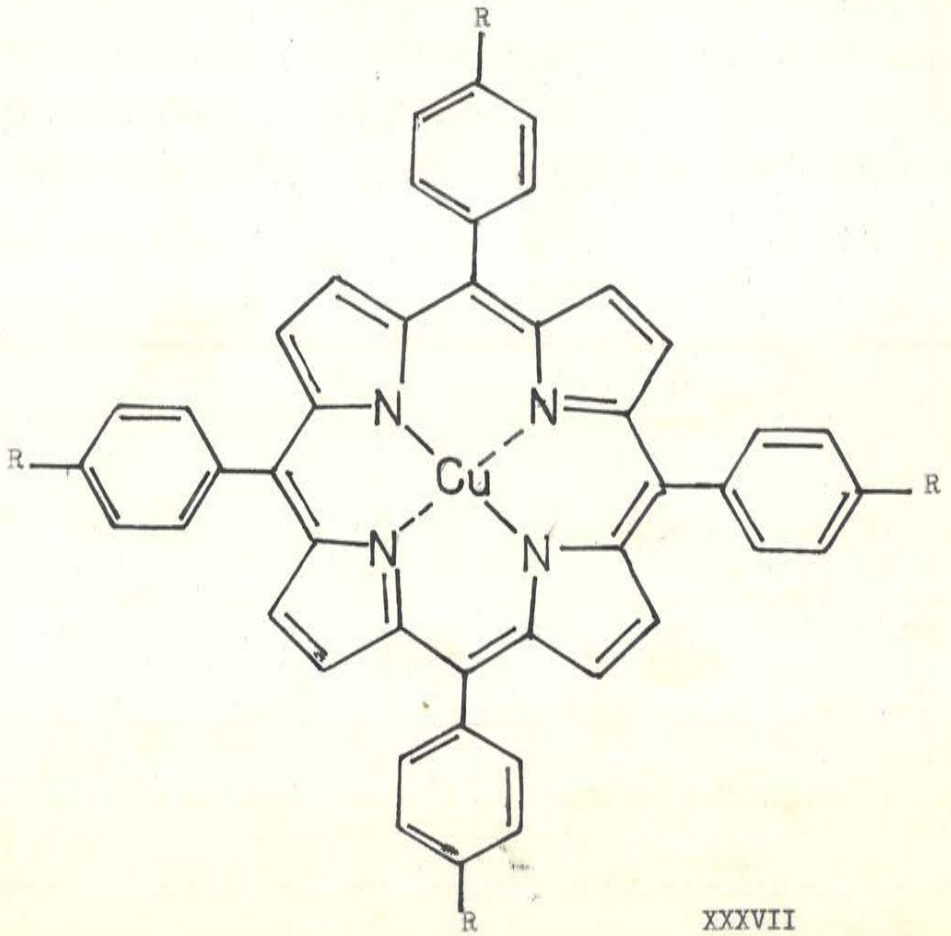


CHMe.N.$C_5H_{10}$.

XXXVI

The yield was not estimated because of spectroscopic difficulties.

Like the Rothemund reaction, the properties of ms-tetrasubstituted porphyrins have been extensively investigated. The visible, ultraviolet and infrared spectra of the ms-tetrasubstituted porphyrins and their metal chelates have been thoroughly investigated, both for the information they give about porphyrin structure, and for testing theories of chelate formation[62-71]. Paramagnetic resonance studies[72,73] on copper ms-tetraphenylporphyrin (XXXVII, R = H) and copper ms-tetra-p-chlorophenylporphyrin (XXVII, R = Cl) have demonstrated long range nuclear interactions; and similar spectral studies[41] on ms-tetraphenylporphyrin itself have been used to elaborate the relation of the phenyl rings to the porphyrin macrocycle.




XXXVII

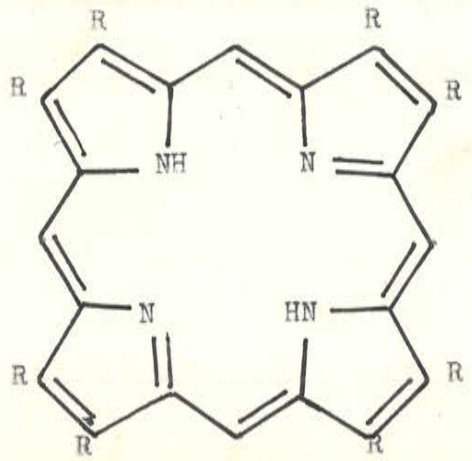
The copper salt of tetraphenylporphyrin has been subjected to X-ray analysis[74] and the metal-free compound to dipole moment measurements[75]. The relationship between ms-tetrasubstituted porphyrins and the corresponding di- and tetrahydro derivatives has been examined photochemically, both by oxidation[76-78] and reduction[79-81] experiments. The stability of ms-tetraphenylporphyrins to γ-irradiation has also been investigated[82-84].

Summarizing the studies on ms-substituted porphyrins, we can see that those with less than four substituents have undergone limited synthetic investigation and their physical properties have not been comprehensively studied with the aid of modern instruments. On the other hand, the tetrasubstituted compounds have been fairly extensively studied. However, a recent nuclear magnetic resonance study[41] has indicated that a wider variety of ms-substituted porphyrins could be profitably investigated. With these investigations in mind, it was decided to undertake a comprehensive study of the synthesis of ms-substituted porphyrins. It was hoped that this study would provide suitable porphyrins for testing for cancer inhibition.

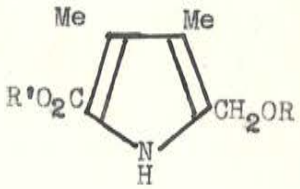
## 1.3 Porphyrin syntheses

The yields in porphyrin syntheses are notoriously low[85], and very complicated mixtures are often obtained. However, as many avenues of synthesis have been employed and no radically new synthesis was envisaged, it was necessary to review the literature in order to see which were the most likely methods of obtaining meso-substituted porphyrins and satisfying the dual criteria of yield and purity. All porphyrin syntheses begin from simple pyrrole units (or their precursors), but there is a diversity of methods for obtaining the aromatic macrocycles, depending on whether the key components are mono-, di- or tetrapyrrolic units.

Polymerization of simple pyrrole units under thermal, or acidic conditions, was the method developed by Siedel and Winkler[86]. They reported a 47% yield of octamethylporphyrin (XXXVIII, R = Me) from the thermal cyclization of the hydroxymethylpyrrole (XXXIX, R = R' = H).

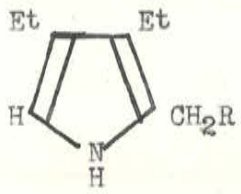



XXXVIII




XXXIX

Later workers[87] have criticized their experiments, stating that the hydroxymethylpyrrole was, in fact, an acetoxy derivative (XXXIX, R' = H, R = $COCH_3$). Nevertheless, Treibs[88] has demonstrated that hydroxymethylpyrroles are suitable porphyrin precursors. Johnson *et al.*[87,89] have simplified the procedure by using the *t*-butyl ester (XXXIX, R' = $Bu^t$, R = $COCH_3$), and have improved the yield by carrying out the condensation in the presence of cobaltous chloride. A similar reaction[90], which gave high yields, but unfortunately was not completely reproducible, was the thermal polymerization of the Mannich base (XL, R = $NC_5H_{10}$) to octaethylporphyrin (XXXVIII, R = Et). Successful porphyrin syntheses from simple pyrrole units have also been developed in this department[91].




XL

The Rothemund reaction, mentioned above was another promising synthesis from a monopyrrolic unit.

The classical syntheses of porphyrins, developed by Fischer and his school, have involved the fusion of two dipyrromethene units, the best yields being obtained in

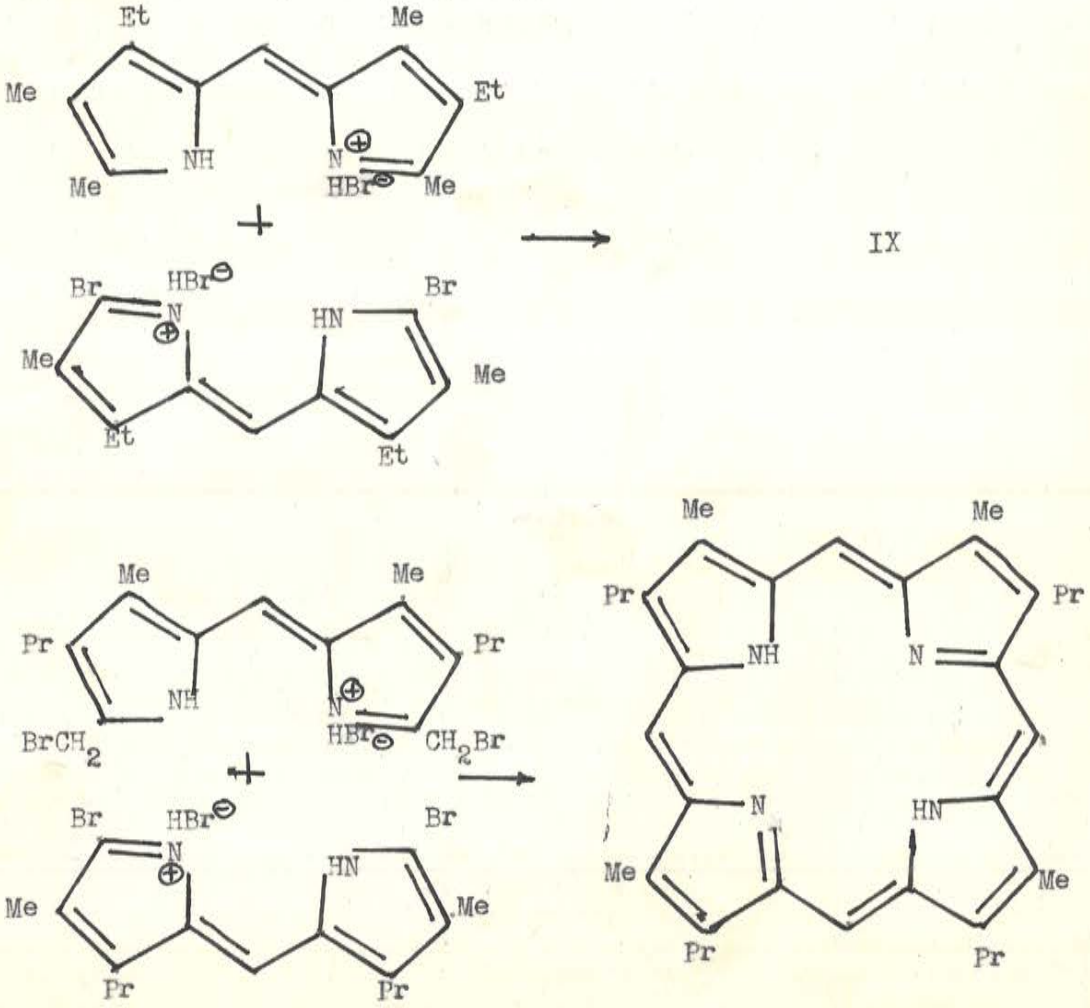
a high melting acid, like succinic acid. There have been three main combinations employed:

(1) a 5,5'-dimethyldipyrromethene with a 5,5'-dibromodipyrromethene[92];

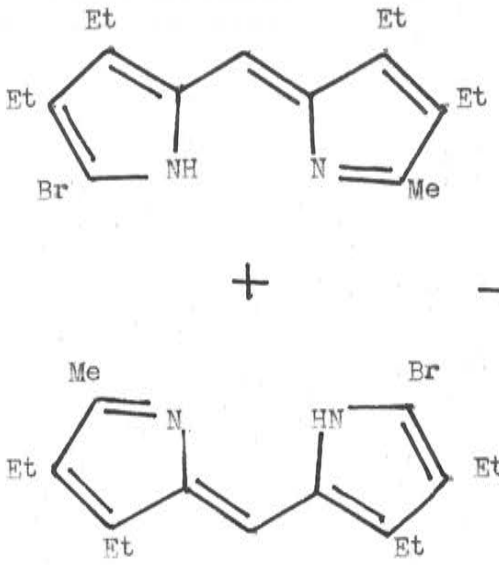
(2) a 5,5'-dibromomethyldipyrromethene with a 5,5'-dibromodipyrromethene[93]; and

(3) a 5-methyl-5'-bromodipyrromethene with itself[94].

The reactions which have produced the highest yields are given as examples (Fig. 2).

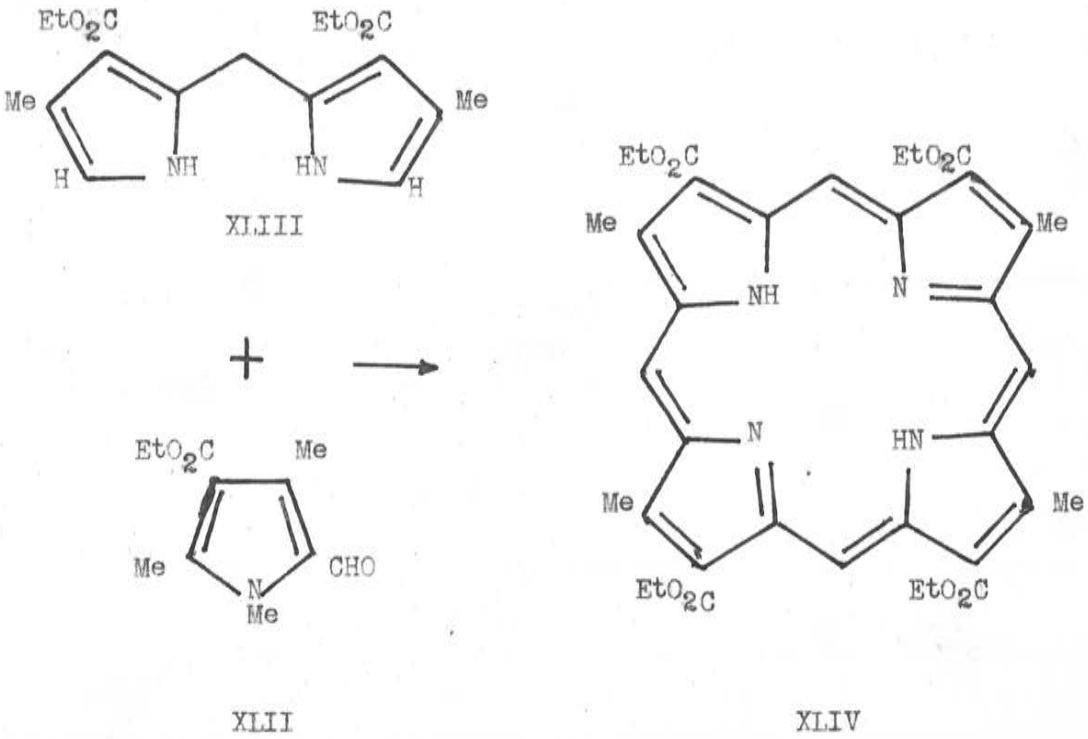



Pr = Propyl.




XXXVIII , R = Et.

Fig. 2.



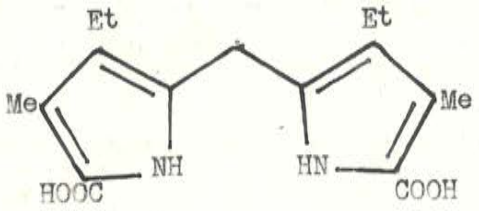

XLIII

XLII

XLIV

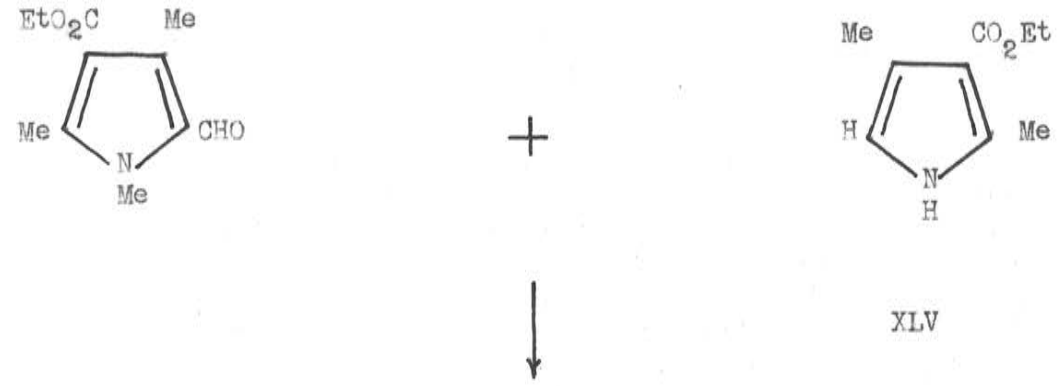
Fig. 3.

Another synthesis, which involved dipyrryl units, was the decarboxylative cyclization of dipyrromethane diacids in formic acid at 37°. The best yield for this reaction was obtained by Fischer and Halbig[95], who cyclized the dipyrromethane diacid (XLI) to etioporphyrin II (IX) in 67% yield.

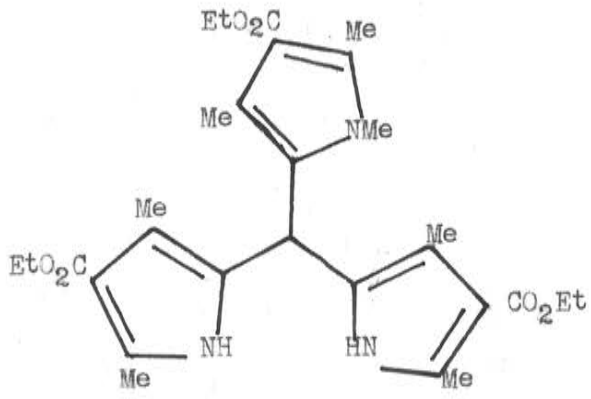



XLI

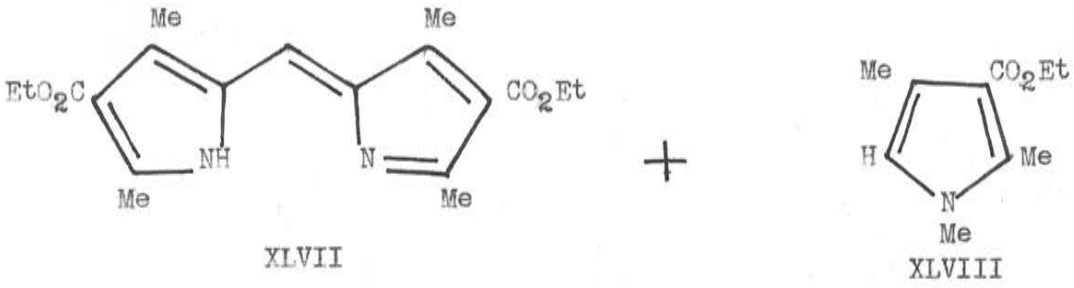
For synthetic purposes, the observation by Fischer and Riedl[96] that dipyrromethanes undergo cleavage at the methane bridge when treated with acid is obviously important. An interesting analogous reaction was employed by Andrews, Corwin, and Sharp[97] when they used an N-methylpyrrole (XLII) to provide the bridge carbon atoms instead of formic acid (Fig. 3) and obtained the porphyrin (XLIV) in 40% yield. The dipyrromethane component was a 5,5'-unsubstituted dipyrromethane (XLIII), instead of a diacid. The rationale of the use of the N-methylpyrrolealdehyde was based on the fact that the aldehyde condenses with two molecules of a pyrrole with an unsubstituted $\alpha$-position (XLV) to form a tripyrrylmethane intermediate which subsequently cleaves to




XLV




XLVI




XLVII XLVIII

Fig. 4.

give a symmetrical dipyrrylmethene (XLVII) and an N-methylpyrrole (XLVIII). (Fig. 4).

The preparation of 5,5'-unsubstituted dipyrromethanes without stabilizing substituents in the β-positions (XLIX, R,R' = alkyl) paved the way for a convenient porphyrin synthesis[98]. (Fig. 5). The reactive dipyrromethanes condensed with dipyrromethane dialdehydes (L, R,R' = acetic or propionic acid residues) in the presence of hydriodic acid catalyst to yield dihydroporphyrins which were readily oxidized to the corresponding porphyrins. The overall yield was 55 - 65%.

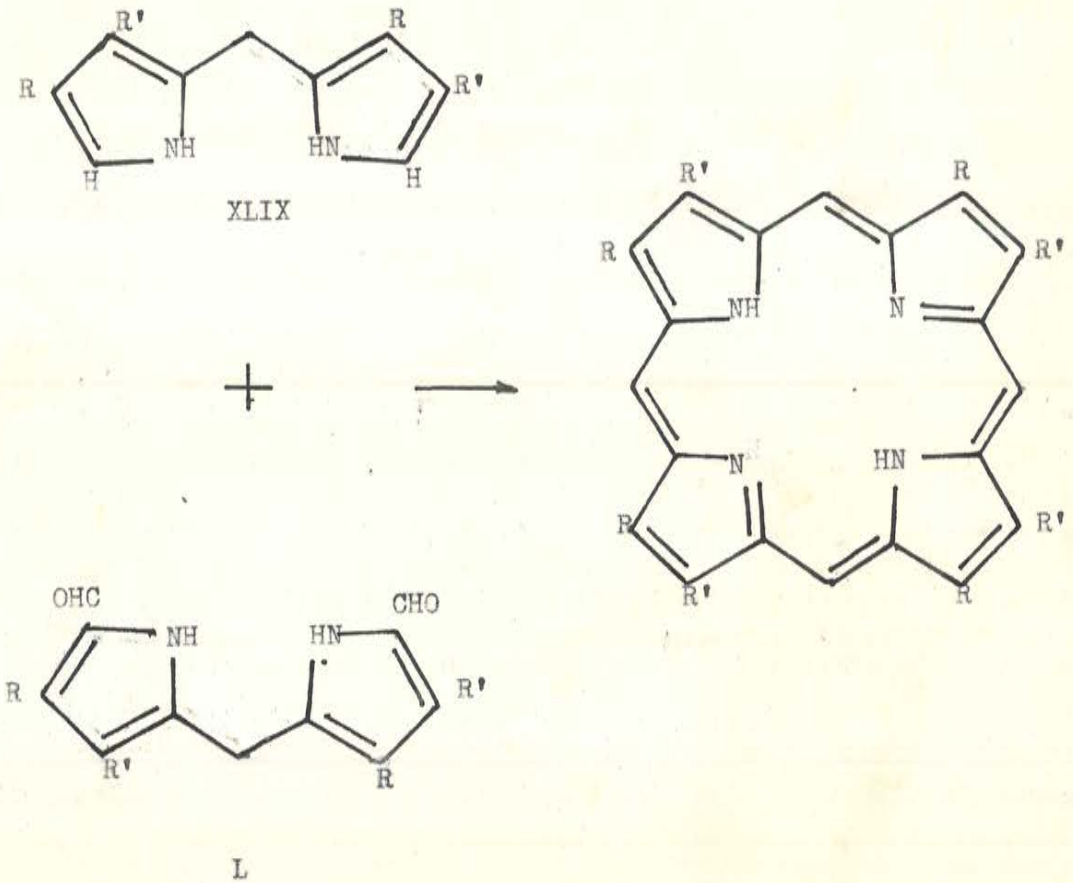
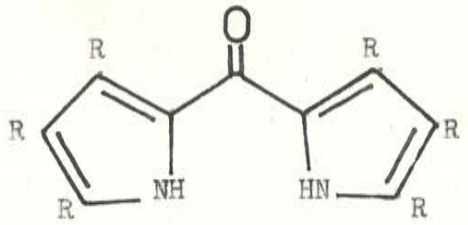


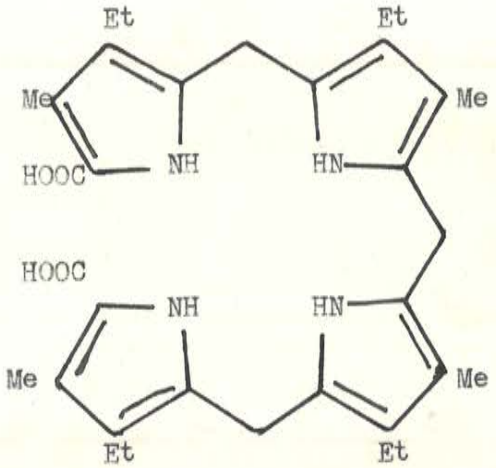

Fig. 5.

The possibility of another synthesis from dipyrryl units was suggested by McDonald. Dipyrroketones (LI) were postulated as suitable porphyrin precursors, but these have not yet been successfully employed.



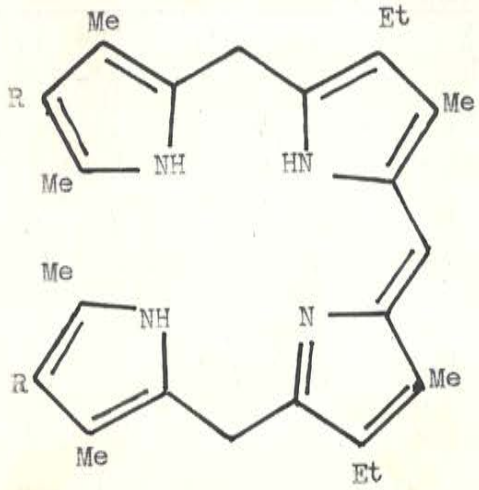

LI

By a method analogous to that employed in the dipyrromethane diacid decarboxylative reaction, Corwin[99] has carried out an oxidative cyclization in formic acid of the bilane diacid (LII) to etioporphyrin II (IX) in 40% yield.

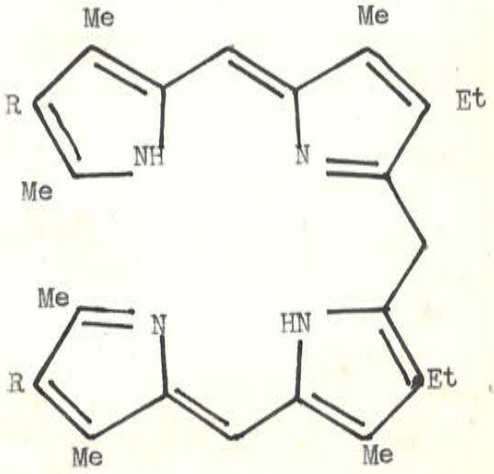



LII

Another synthesis from tetrapyrrole precursors was the oxidative cyclization by copper acetate of the terminal methyl groups of the bilenes (LIII) and biladienes (LIV) to the corresponding porphyrins[100]. The yields were only 20%.




LIII




LIV

One of the major problems in porphyrin synthesis has been the mixture of isomers resulting from working with pyrrole compounds which had different substituents in the $\beta$-position[101a]. It was decided early in our work that this problem could be avoided by using pyrrole precursors which had the same $\beta$-substituents. Consequently, the discussion above has deliberately neglected the isomer problems arising from some of the syntheses.

After consideration of these synthetic methods and in view of the other synthetic investigations of

porphyrins from monopyrrole[91] and tetrapyrrole[102] precursors in this department, it was decided to attempt to modify the above syntheses from dipyrryl units in order to produce mono-, di-, tri- and tetra-ms-substituted porphyrins. Furthermore, because of the high yields reported and the fact that no mechanism had been proposed, it was decided to investigate further the synthesis of ms-tetrasubstituted porphyrins by the Rothemund reaction.

# CHAPTER 2

## THE ROTHEMUND REACTION

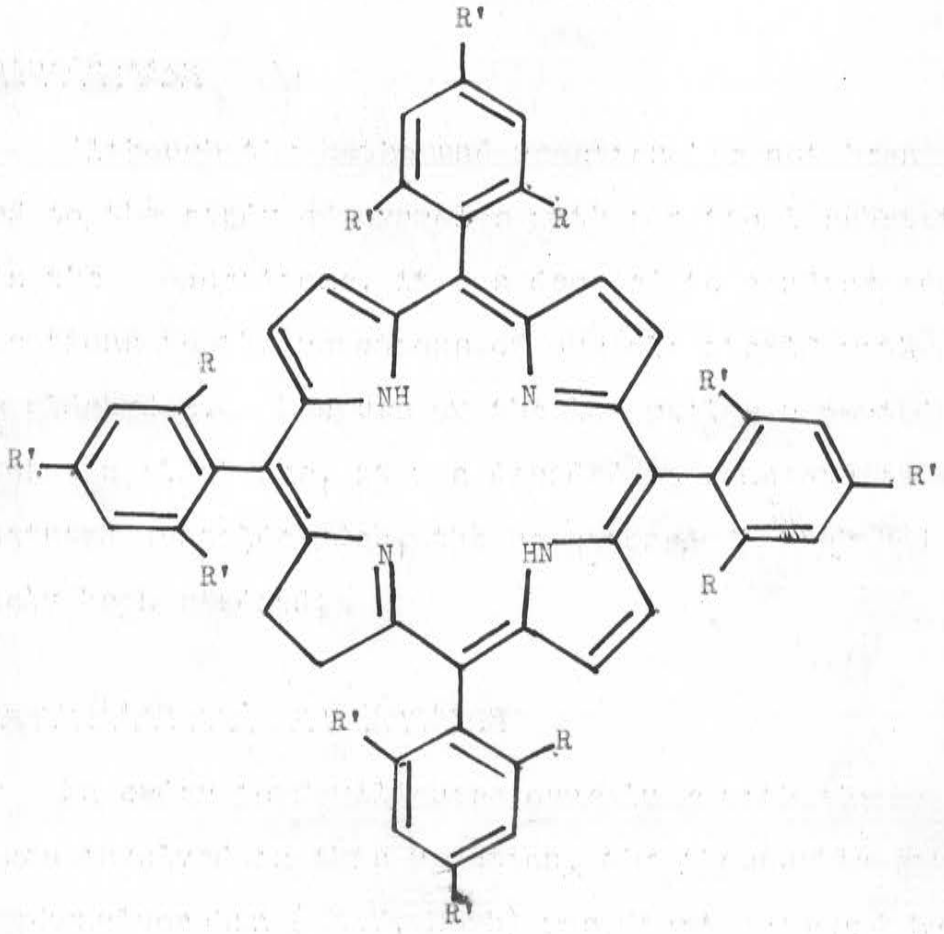
### 2.1 Introduction

Although the Rothemund reaction has not been extended to the study of pyrroles with identical substituents in the $\beta$-positions, it was decided to confine our investigations to the reactions of pyrrole itself with various aldehydes. Because of the low yields reported for aliphatic aldehydes, it was decided to concentrate on o-substituted benzaldehydes, the reactions of which had not previously been studied.

### 2.2 Preparation and Purification

In order to familiarise ourselves with the techniques involved in this reaction, the thoroughly-studied ms-tetraphenylporphin (XXXV, R=Ph) was first prepared by the method of Ball, Dorough and Calvin.[60] The work-up procedure employed involved separation of the purple crystals of zinc complex from contaminating "tar" by washing with acetone and then further purification by chromatography on talc in trichloroethylene. Although the initial product contained variable amounts of the zinc complex of ms-tetraphenylchlorin (LV, R=R'=H), the impurity was removed during the chromatographic procedure. The pure zinc

complex was readily converted to the free base with mineral acid. The yield in this reaction was slightly higher than

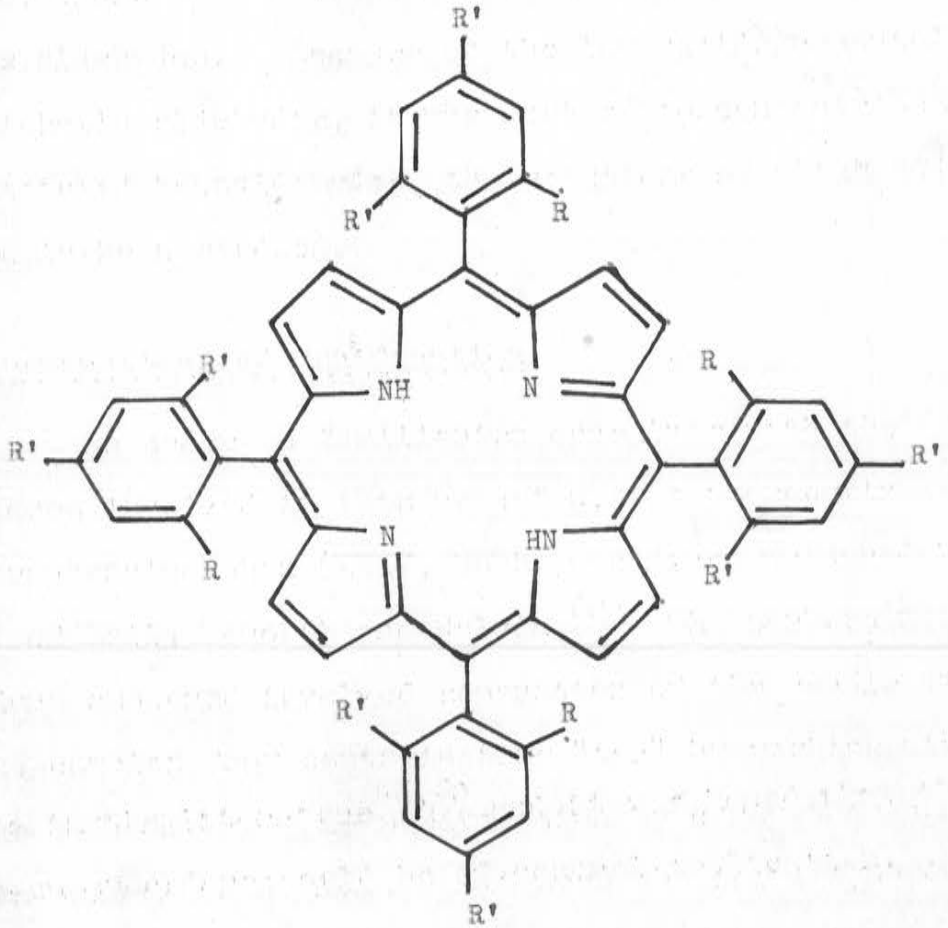



LV

those in the literature[46,60] and it was hoped that this work-up procedure would be of general application.

The Rothemund reaction of pyrrole with mesitaldehyde, o-chlorobenzaldehyde and o-methoxybenzaldehyde was next investigated. The same work-up procedure was used,

but the results were not satisfactory. In the mesitaldehyde reaction, purple crystals of zinc ms-tetramesitylporphin were obtained on acetone-washing, and these readily gave ms-tetramesitylporphin (LVI, R=R'=Me) but the products were contaminated with a high percentage of ms-tetramesitylchlorin (LV, R=R'=Me) and its zinc complex, which talc chromatography did not remove. No crystalline products were obtained from




LVI

the o-chloro- and o-methoxybenzaldehyde reactions, although the solutions did exhibit a strong red fluorescence. Attempts to isolate ms-tetra(o-chlorophenyl)porphin (LVI, R=Cl,R'=H) and ms-tetra(o-methoxyphenyl)porphin (LVI, R=OMe,R'=H) by talc chromatography were unsuccessful.

There were, thus, two main problems to be overcome in the preparation of the substituted tetraphenylporphyrins:

(1) separation of the porphyrins from the tarry reaction products;

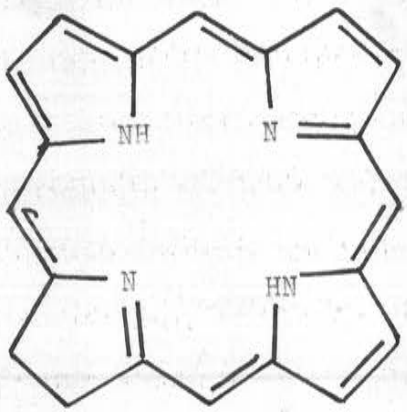
(2) removal of their contaminating chlorins.

The talc chromatography procedure which had been used successfully for similar compounds,[46] was abandoned in favour of a pyrolytic technique. Porphyrins are very stable compounds to heat and it was hoped that pyrolysis of the crude reaction product would cause decomposition of the impurities, while leaving the porphyrins intact. A series of relatively pure porphyrins was heated to 400° under nitrogen, but decomposition occurred and this procedure was not further investigated.

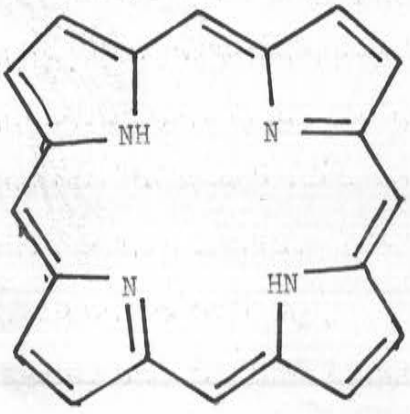
However, in the above experiments it was observed that the porphyrins sublimed and sublimation under reduced pressure was therefore investigated as a purification technique. Apart from zinc ms-tetra(o-chlorophenyl)porphin,

the semipurified porphyrins sublimed satisfactorily but, unfortunately, this procedure was not successful for the elimination of chlorin impurities.

Meanwhile, investigations were being carried out on the oxidation of chlorins, for it was hoped not only to remove the chlorins but also to increase the yield of porphyrins. Quinones had successfully been employed by Eisner and Linstead[103] for the oxidation of chlorins, but they did report that only 70% of chlorin (LVII) was converted to porphin (LVIII). In our experiments, we used the

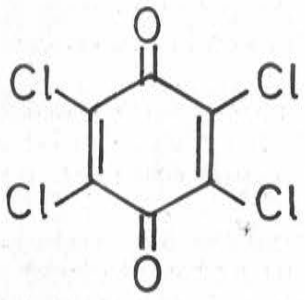



LVII




LVIII

quinone, chloranil (LIX), but evidently it was not active enough for the amounts of chlorin in our porphyrins were unchanged.



LIX

The first problem, viz. separation of the porphyrins from "tar" was overcome by precipitating the crude porphyrin from a pyridine solution of "tar" with methanol, and purification of the solid obtained by chromatography on alumina in benzene. This procedure enabled ms-tetra(o-chlorophenyl)porphin (LVI, R=Cl,R'=H) and ms-tetra(o-methoxyphenyl)porphin (LVI, R=OMe,R'=H) to be prepared, but the products were still contaminated with the corresponding chlorins.

It has not been possible to free the free base porphyrins from their chlorin impurities directly, but a method for obtaining pure zinc complexes has at least been achieved. Dorough and Huennekens[63] found that benzene was a very good solvent for catalysing the photo-oxidative decomposition of zinc chlorins. However, they found that the corresponding zinc porphyrin was not the only product. We found that our chlorin-contaminated zinc porphyrins were purified after standing for 12 hr. in benzene, and then

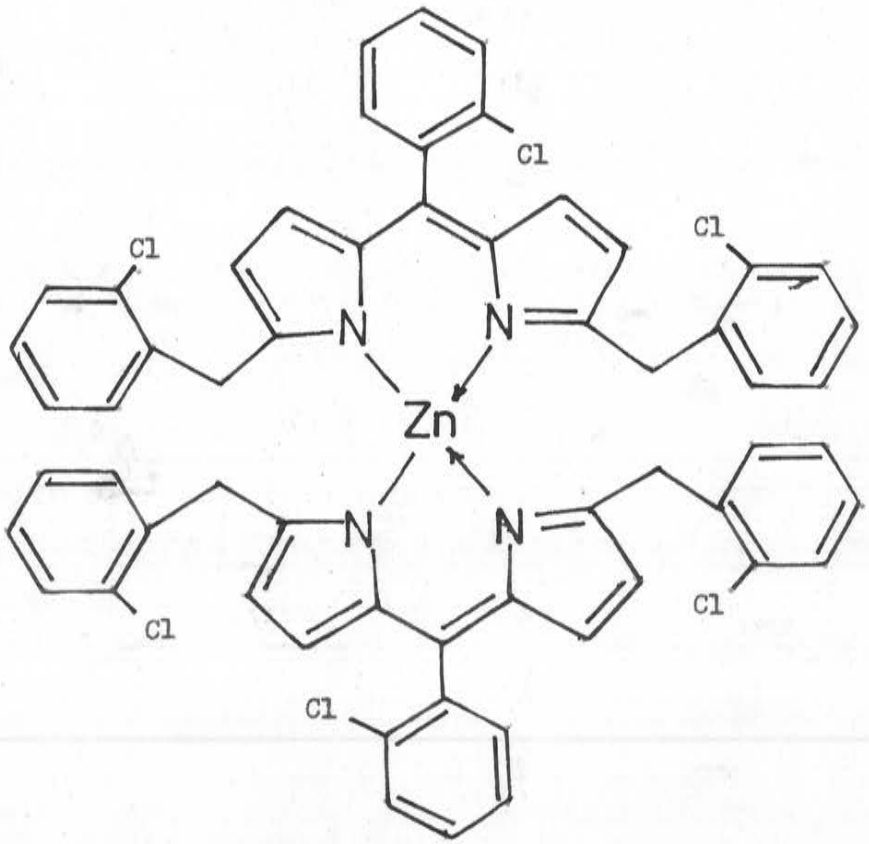
rechromatographed. Chlorin-free ms-tetramesityl-, ms-tetraphenyl-, ms-tetra(o-chlorophenyl)- and ms-tetra (o-methoxyphenyl) porphins were thus prepared.

However, a further problem was encountered after these had been overcome, for difficulty in obtaining good analytical figures for the various porphyrins was experienced. The porphyrins are notoriously difficult to analyse and Thomas and Martell[46] record the synthesis of ms-tetra(p-nitrophenyl)porphin despite the fact the found figure for the carbon analysis was 4½% lower than the calculated value, and the found figure for the nitrogen analysis was 3% low. They attribute their poor analyses to the stability of the porphyrin ring. Our most inaccurate analysis, viz. ms-tetramesitylporphin was 3% low in carbon and 0.6% in nitrogen.

Because of the problems mentioned above, not as much about the mechanism of the Rothemund reaction was discovered as we had hoped; but some information was obtained. For instance, distillation of the "tar" from the o-chlorobenzaldehyde reaction indicated the presence of pyrrolic materials, but these were inseparable from the pyridine with which they were associated and thus they were not identified.

A more profitable result was observed in alumina

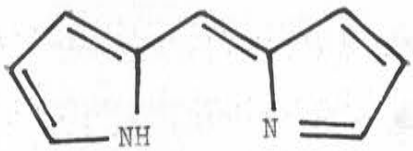
chromatography of the crude porphyrin from the o-chlorobenzaldehyde reaction. Zinc ms-o-chlorophenyl-5,5'-di-o-chlorobenzyldipyrromethene (LX), which is either an intermediate in the formation of the zinc ms-tetra(o-chlorophenyl) porphin or else a by-product, was isolated from the initial fractions.




LX

The evidence for structure (LX) was as follows. The analytical figures clearly demonstrated a ratio of chlorine atoms to nitrogen atoms of 3 to 2, and agreed with

the structure assigned. The ultraviolet and visible spectrum showed an intense peak at 500 mμ, which is characteristic of zinc pyrromethenes[104] and the infrared spectrum did not contradict the above structure. It was observed that there were no bands due to NH or OH groups and no band above 1600 cm.$^{-1}$, which could be assigned to a carbonyl. There was, however, a strong band at 1554 cm.$^{-1}$, which is characteristic of dipyrromethenes.[105,106] There was also a band at 1013 cm.$^{-1}$, which could be assigned to a C-Cl vibration of a chlorine atom attached to an aromatic ring,[107] and bands at 1160, 1125, 1040, 946 and 843 cm.$^{-1}$, which could be characteristic of an o-disubstituted benzene ring.[108] Furthermore, the proton magnetic resonance spectrum indicated a doublet at τ 6.07 assigned to the benzyl protons; this would mean that if two or more benzylic groups were present in the molecule, then they must be in identical environments. The only piece of evidence conflicting with the structure proposed was the molecular weight determination, and this was ignored because of the weight of the other evidence. Compound (LX) represents one of the most simply substituted dipyrromethenes known, for dipyrromethene itself (LXI) and its simpler substitution products are still unknown.[101b] (LX) is stabilized by the metal atom for the free base is unstable.




LXI

Slight evidence for zinc pyrromethenes was obtained in the mesitaldehyde and o-methoxybenzaldehyde cases as well. In both cases, orange solutions with green fluorescences were obtained and their electronic absorption spectra were indicative of zinc pyrromethenes. However, the products were not obtained crystalline and it can only be assumed that they are similar in nature to (LX). No evidence for such an "intermediate" was obtained in the benzaldehyde reaction and presumably this was because the reaction was carried out on a smaller scale. The fact that no such products were isolated following reactions with the p-substituted benzaldehydes, investigated by Thomas and Martell, can perhaps be explained by the different work-up procedure employed.

One gram quantities of carefully purified ms-tetraphenylporphin, ms-tetra(o-chlorophenyl)porphin, and zinc ms-tetraphenylporphin were sent to London for testing for tumour inhibition, but the results of these tests are still awaited.

## 2.3 Spectral Studies

The proton magnetic resonance spectra of ms-tetraphenylporphin and its o-chloro, o-methoxyl, p-methoxyl and 2,4,6-trimethyl derivatives were determined as free bases and the assignments of the chemical shift are shown in Table Ia. ms-Tetraphenylporphin is the only compound in the above series whose spectrum has been determined previously,[41] but this was as its dication. The spectrum of the free base ms-tetraphenylporphin was slightly different, but readily interpreted. The peaks at $\tau$ 1.80, 2.27 and 2.67 can confidently be assigned to the ortho, meta, and para hydrogens of the phenyl ring and occurred at slightly higher field than those in the dication. The peaks ascribed to the $\beta$-hydrogens occurred at the same position in both.

In the spectrum of the p-methoxyl derivative, the signals at $\tau$ 1.87 and 2.65 could be assigned to the ortho and meta hydrogens respectively, but the assignment of the peaks in the aromatic region of the o-substituted phenylporphyrins was much more complicated. The peak at $\tau$ 2.0 in the o-methoxyl derivative was the only one to be confidently assigned and this was attributed to the m-hydrogen adjacent to the methoxyl group. The low position of the phenyl resonances in all these compounds has been

## TABLE I

Chemical shifts in proton magnetic resonance spectra of ms-tetra-substituted porphyrins

(a) Solutions in deuterochloroform.

| Substituent | NH | β-H | Benzenoid aromatic | o-Me | p-Me | MeO | Others |
|---|---|---|---|---|---|---|---|
| Phenyl | | 1.15 | 1.80,2.27 2.67 | | | | |
| p-Methoxy-phenyl | | 1.13 | 1.87,2.65 | | | 5.91 | |
| o-Methoxy-phenyl | | 1.22 | 2.0,2.28, 2.38,2.58, 2.7. | | | 6.45 | |
| o-Chloro-phenyl | 12.60 | 1.31 | 1.87,2.23 | | | | |
| Mesityl | | 1.38 | 2.21 | 8.15 | 7.37 | | 8.73 |

(b) Solutions in trifluoroacetic acid.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Phenyl[a] | 12.07 | 1.15 | 1.41,1.92 | | | | |
| o-Chloro-phenyl | 12.10 | 2.07 | 2.47,2.75 | | | | 3.4,4.2 |
| p-Methoxy-phenyl | | 2.68 | 2.33,2.50 | | | 5.77 | 3.3,4.3 |

---

a. Ref. 41.

ascribed by Kenner[41] to the effect of the current in the porphyrin ring.

The sharp peak at τ 8.73 in the spectrum of ms-tetramesitylporphin is of unknown origin. The NH peaks in the free bases were very broad and of low intensity and, except for ms-tetra(o-chlorophenyl)porphin, they occurred at approximately τ 9.0.

As the size and number of substituents in the ortho-positions of the phenyl rings increase, the signals due to the protons in the β-positions of the pyrrole rings shift to higher field. This is evidently caused by twisting of the phenyl rings relative to the macrocycle. Hoard et al.[109] in a recent X-ray crystallographic study of ms-tetraphenylporphin have shown that the phenyl group is inclined at 81.5° to the "plane" of the porphyrin ring, and also that the porphyrin ring can buckle. This would mean that the angle between the β-hydrogen atoms and the phenyl ring could be quite different from 81.5°. The observed changes in the chemical shift then could arise from two possible reasons. The twisting of the phenyl ring could cause the β-hydrogen to lie in the shielded region of the aromatic nucleus or it could cause further buckling of the macrocycle, which would decrease the macrocyclic ring current. Both these effects would result in shifts to higher field.

The proton magnetic resonance spectra of the dications of ms-tetra(o-chlorophenyl)porphin and ms-tetra (p-methoxyphenyl)porphin were determined in trifluoroacetic acid and compared with the results obtained by Kenner[41] for the dication of ms-tetraphenylporphin in the same solvent. The proposed assignment for the chemical shifts are shown in Table I(b). In the case of the dications, the shift in signals of $\beta$-protons is much more marked, but it does not correspond to the simple steric relationship determined for the free bases. This is possibly caused by protonation of the methoxy groups since the methoxy signal occurred at lower field than for the free base and was very broad. The breadth of the signal could possibly be caused by the rate of exchange between the protonated and non-protonated forms. The unassigned bands at $\tau$ 3.3 and 4.3 in our samples were probably due to solvent impurities.

The electronic absorption spectra of ms-tetraphenylporphin and the other four free base porphyrins were determined in benzene and compared with the results obtained by Thomas and Martell with ms-tetraphenylporphin and its p-substituted derivatives. The results are shown in Table II. The spectra were typical of porphyrins showing an intense (Soret) peak at approximately 420 mμ and characteristic bands in the region 510-650 mμ. The

## TABLE II

### Electronic absorption maxima of ms-Tetrasubstituted Porphyrins

(i) Free bases in benzene.

| Substituent | IV | | III | | II | | I | |
|---|---|---|---|---|---|---|---|---|
| | mμ | $\epsilon \times 10^{-3}$ | mμ | $\epsilon \times 10^{-3}$ | mμ | $\epsilon \times 10^{-3}$ | mμ | $\epsilon \times 10^{-3}$ |
| Phenyl | 419 | 470 | 485 | 3.4 | 514 | 18.7 | 549 | 7.7 | 591 | 5.4 | 647 | 3.4 |
| Phenyl[a] | 419 | 478 | 485 | 3.4 | 515 | 18.7 | 548 | 8.1 | 592 | 5.3 | 647 | 3.4 |
| o-Chlorophenyl | 418 | 371 | 478 | 3.1 | 513 | 16.4 | 543 | 3.8 | 589 | 6.1 | 645 | 1.1 |
| p-Chlorophenyl[a] | 421 | 515 | 485 | 4.0 | 515 | 21.0 | 550 | 9.0 | 592 | 6.0 | 647 | 3.7 |
| o-Methoxyphenyl | 420 | 349 | - | - | 513 | 15.2 | 546 | 4.6 | 590 | 4.2 | 647 | 1.5 |
| p-Methoxyphenyl | 424 | 408 | 488 | 3.4 | 518 | 13.5 | 556 | 8.9 | 595 | 4.0 | 652 | 3.7 |
| p-Methoxyphenyl[a] | 424 | 485 | 488 | 4.3 | 519 | 17.0 | 555 | 11.9 | 595 | 5.5 | 653 | 4.5 |
| Mesityl | 420 | 368 | 483 | 2.8 | 515 | 15.4 | 548 | 5.3 | 593 | 3.8 | 649 | 2.3 |

a. Ref. 66.

## TABLE III

Electronic absorption maxima of ms-Tetrasubstituted Porphyrins

(ii) Zinc complexes in benzene.

| Substituent | mμ | $\epsilon x10^{-3}$ | mμ | $\epsilon x10^{-3}$ | mμ | $\epsilon x10^{-3}$ | mμ | $\epsilon x10^{-3}$ |
|---|---|---|---|---|---|---|---|---|
| Phenyl | 424 | 564 | 514 | 3.3 | 550 | 22 | 590 | 4.1 |
| Phenyl[a] | | | 513 | 3.3 | 550 | 22 | 590 | 3.8 |
| o-Chlorophenyl | 424 | 407 | 512 | 5.9 | 549 | 16.5 | 588 | 2.1 |
| o-Methoxyphenyl | 424 | 520 | 513 | 2.9 | 550 | 22 | 588 | 2.1 |
| p-Methoxyphenyl | 427 | 446 | 515 | 3.3 | 553 | 19 | 592 | 5.6 |
| Mesityl | 424 | 607 | 512 | 2.5 | 547 | 21 | 587 | 1.8 |

a. Ref. 110

bands at approximately 480 mμ are believed to be due to impurities. In all cases except for ms-tetra(o-chlorophenyl) porphin, the spectra were of the etio type (I<II<III<IV). The intensities of bands I and III are particularly sensitive to the nature, position and number of substituents in the porphyrin nucleus,[111] and the steric or electronic effects of the o-chlorophenyl group may have caused the observed result.

Comparison of the results for the corresponding ortho- and para-substituted porphyrins with those of ms-tetraphenylporphin shows that the steric effect of the ortho substituents acts in the opposite direction to their electronic effect, assuming that the electronic effects in the ortho and para positions are identical, for the bathochromic shift initially observed by comparing the p-substituted porphyrins with the unsubstituted is effectively nullified by placing the same substituents in the ortho position. The effect is most marked with ms-tetra(o-methoxyphenyl) but is observable in the chlorinated compounds. The steric effect of the ortho-groups may also explain why the intensities of the o-substituted compounds are lower than those with no steric problems.

The electronic spectra of the zinc complexes of the above porphyrins were determined in benzene and their

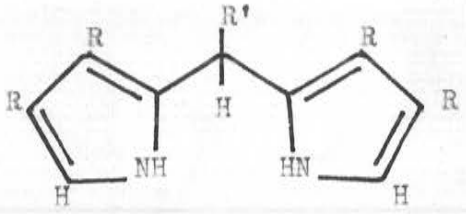
results are listed in Table III. As in the free base spectra, the p-methoxy derivative is the only one to differ significantly from the rest as it shows a distinct bathochromic shift that can readily be explained from the electronic effect of the methoxy substituent. Also, as in the free base, the extra steric effect of placing the methoxy group in the ortho-position nullifies the bathochromic shift.

# CHAPTER 3

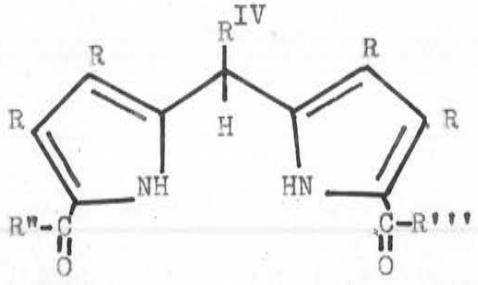
## THE STEPWISE SYNTHESIS

### 3.1 Introduction

Because the McDonald synthesis[98] of porphyrins from a dipyrromethanedialdehyde and an $a$, $a'$-unsubstituted dipyrromethane seemed capable of high yields and ready modification, it was chosen as the basis for our stepwise synthesis. In theory, it appeared that the synthesis could be modified by substituting the hydrogens in the meso-positions and by replacing the aldehyde groups by ketones. Thus, all the possible combinations of mono-, di-, tri-, and tetra-substituted porphyrins could be formed from the dipyrromethane units (LXII and LXIII). The



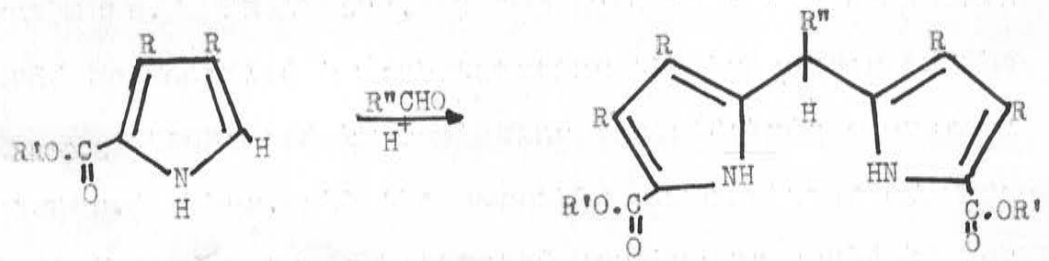

LXII




LXIII

$a$, $a'$-unsubstituted compounds (LXII) were the key intermediates since a variety of acylation procedures would give the diacyl derivatives (LXIII) from them. Direct synthesis of the $a$, $a'$-unsubstituted compounds is not feasible, but their synthesis seemed possible from the

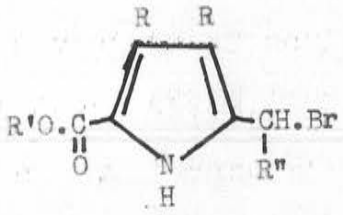
corresponding diacids, the synthesis of which is readily achieved from their esters. ms-Substituted dipyrromethanes with ester groups in the 5 and 5' positions (LXIV) have not been previously prepared, but analogous reactions with Knorr pyrrole derivatives[111-115] suggested that condensations of appropriate pyrrole esters (LXV) with suitable aldehydes would be successful. (Fig. 6) The other possible dipyrromethane synthesis from a substituted bromomethyl-




LXV LXIV

Fig. 6.

pyrrole (LXVI) and an $\alpha$-unsubstituted pyrrole (LXV) did not seem as practicable because of the well-known deactivating effect of an $\alpha$-ethoxycarbonyl group on the other $\alpha$-position of the pyrrole.

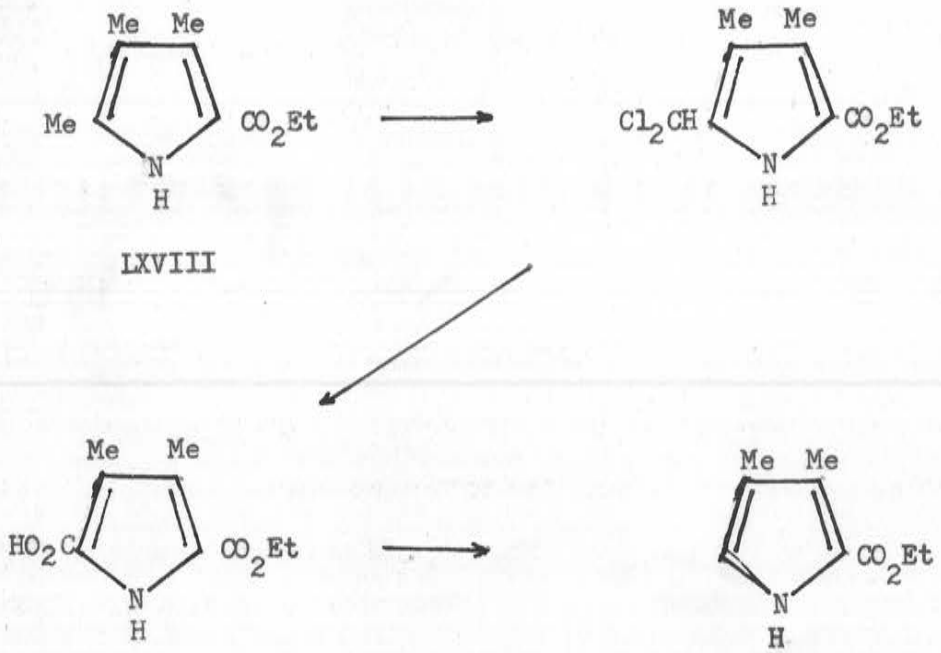



LXVI

Our proposed stepwise synthesis begins with the pyrrole (LXV) and proceeds *via* various pyrromethane derivatives to the desired porphyrins.

## 3.2 Pyrroles

Ethyl 3,4-dimethylpyrrole-2-carboxylate (LXVII) was chosen as the starting pyrrole for our synthesis. The first attempt at its synthesis was by sulphuryl chloride oxidation of ethyl 2,3,4-trimethylpyrrole-5-carboxylate (LXVIII), subsequent hydrolysis, and decarboxylation (Fig. 7). Fischer and Hierneis[116] reported low yields in their




LXVIII

LXVII

Fig. 7.

preparation of the acid and similar results were obtained for both the ethyl and the t-butyl esters. This pathway was abandoned in favour of a more direct route, which unfortunately also went in low yield. Kleinspehn's ring synthesis[117] from 3-methylpentan-2,4-dione (LXIX, R=Me) and diethyloximinomalonate (LXX) in slightly modified form was the synthesis eventually employed (Fig. 8)

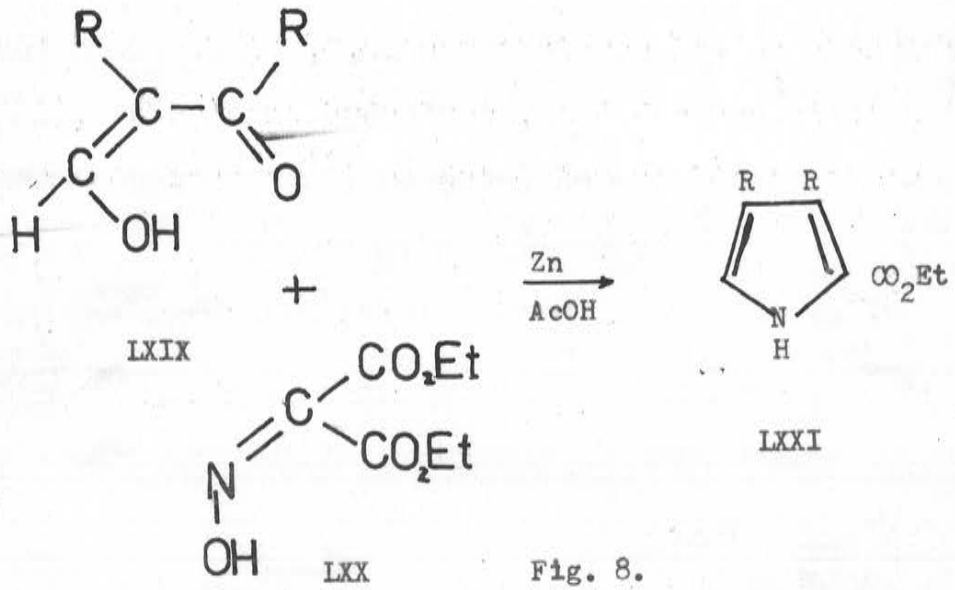
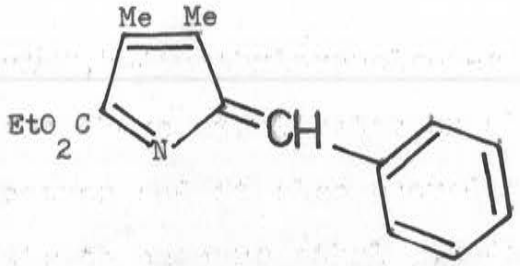



Fig. 8.

Benzyl 3,4-dimethylpyrrole-2-carboxylate was readily prepared from the above ethyl ester by alkoxide-catalysed trans-esterification and it also proved a useful intermediate. However, attempts to prepare ethyl 3,4-diphenylpyrrole-2-carboxylate (LXXI, R=Ph) by a method analogous to that used for the $\beta$, $\beta$-dimethyl compound, were unsuccessful. Under the conditions employed, the hydroxymethylene ketone of desoxybenzoin (LXIX, R=Ph) was reduced to desoxybenzoin.

## 3.3 Dipyrromethanes and Dipyrromethenes

As anticipated, the proposed synthesis of the meso-substituted dipyrromethane diesters (LXIV, R=Me, R'=Et, R"=Me,Ph) from the pyrrole (LXVII) and the appropriate aldehyde proceeded smoothly in good yields. It was found, however, that acetaldehyde had to be used in excess (because of its volatility) in order to obtain good yields; but benzaldehyde, on the other hand, had to be used in strict stoichiometric quantities, otherwise greatly reduced yields of crude products were obtained. On the basis of studies on similar compounds by Shinohara et al.,[115] we assumed that excess benzaldehyde had caused conversion of the ms-substituted methane to the 2H-pyrrole derivative (LXXII), although this was not isolated. Because of the




LXXII

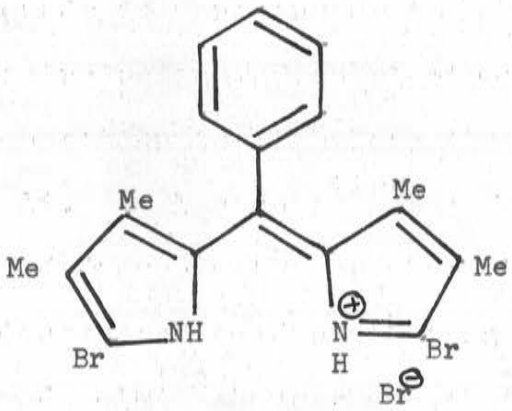
success of the trans-esterification reactions with pyrrole esters, it was decided to extend the reaction to dipyrromethanes. The benzyl esters (LXIV, R=Me, R'=$\phi CH_2$, R"=H,Me,Ph) were either prepared in good yield from the corresponding ethyl esters or from benzyl 3,4-dimethyl-pyrrole-2-carboxylate by the reaction illustrated in Fig. 6. The ms-substituted acids (LXIV, R=Me, R'=H, R"=H,Me,Ph) were prepared either by hydrogenolysis of the benzyl esters or saponification of the ethyl esters. The former process proved to be more convenient.

The next step, viz. the decarboxylation of the diacids to the corresponding $\alpha$, $\alpha'$-unsubstituted dipyrromethanes (LXII, R=Me, R'=Me or Ph) proved a stumbling-block. Attempts resulted either in unchanged starting material or in decomposition products. Dipyrromethanes without stabilizing substituents are notoriously unstable, and the results obtained were not surprising. 3,3'-Diethyl-4,4'-dimethyldipyrromethane is the only known pyrromethane containing only alkyl substituents, and it has only been prepared in low and uncertain yields.[118] The preparation and stability of $\alpha$, $\alpha'$-unsubstituted dipyrromethanes with acetic and propionic acid residues in the $\beta$-positions by Arsenault, Bullock and McDonald[98] may mean that the

acetic acid groups confer greater stability on dipyrromethanes than alkyl groups. On further consideration of the compounds we were trying to prepare, we would not expect the introduction of an electron-donating substituent into the ms-position to stabilize the methane to heat, acid or alkali. Colacicchi[119] has found that even those ms-substituted dipyrromethanes which have stabilising groups are decomposed on distillation under reduced pressure and Treibs and Kolm[120] have shown that ms-groups are removed from such compounds in the presence of formaldehyde and acetic acid.

Four methods were used for the attempted decarboxylations. When iodine was used as the decarboxylating agent, the desired product was probably formed initially since the carboxyl peaks disappeared from the infrared spectrum; but it seems likely that the reagent oxidized the methane bridge, for a new carbonyl peak was evident. The thermal decarboxylation procedures of Chu and Chu[121] using ethanolamine, and of McDonald[98] using sodium hydroxide, were both unsuccessful. The procedure which showed the most promise was brominative decarboxylation. When bromine in acetic acid was added to an acetic acid solution of ms-phenyl-5,5'-dicarboxy-3,3',4,4'-tetramethyldipyrromethane, decarboxylation, bromination and

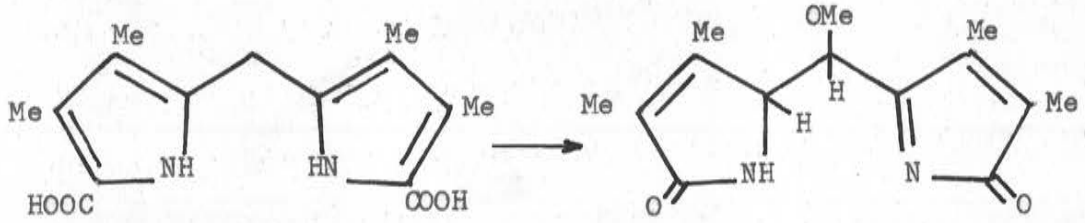
oxidation occurred to give ms-phenyl-5,5'-dibromo-3,3',4,4'-tetramethyldipyrromethene hydrobromide (LXXIII). The




LXXIII

relative proportions of bromine to diacid were found to be critical. By using a carefully standardized solution of bromine in acetic acid, it was found that the best yields were obtained when 4 mols. of bromine were used to one of diacid. Ratios of 3:1 (theoretical) and of 6:1 both resulted in decreased yields. The reasons for this specificity are not known for certain, but it is presumed that further reaction occurs when too much bromine is used. Various attempts to reduce the dibromo compound (LXXIII) with sodium amalgam were unsuccessful although the orange colour of the methene disappeared. Methanol was used as a solvent and it is interesting to note that bromination of the ms-unsubstituted diacid (LXXIV) with bromine in

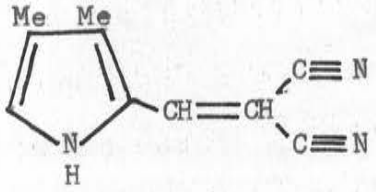
methanol gives the propentdyopent (LXXV),[122] (Fig. 9). It is possible that a similar reaction is occurring here. The other possible explanation for the new peak evident in the infra-red spectrum is that, during the work-up, oxidative cleavage of the methane bridge has occurred.




LXXIV LXXV

Fig. 9.

In an attempt to side-step the troublesome $\alpha$ ,$\alpha$'-unsubstituted dipyrromethanes, 2-($\beta$,$\beta$-dicyanovinyl)-3,4-dimethylpyrrole (LXXVI) and benzaldehyde were treated analogously to the dipyrromethane ester preparations; but, instead of the required ms-substituted dipyrromethane, the starting pyrrole was recovered unchanged.




LXXVI

Evidently the electron-withdrawing effect of the dicyanovinyl group causes sufficient deactivation of the

other $\alpha$-position to prevent nucleophilic attack on the carbonyl group of the aldehyde. This is supported by other studies in this department on this compound.[102] A more detailed mechanism for the dipyrromethane formation is given in Fig. 10.

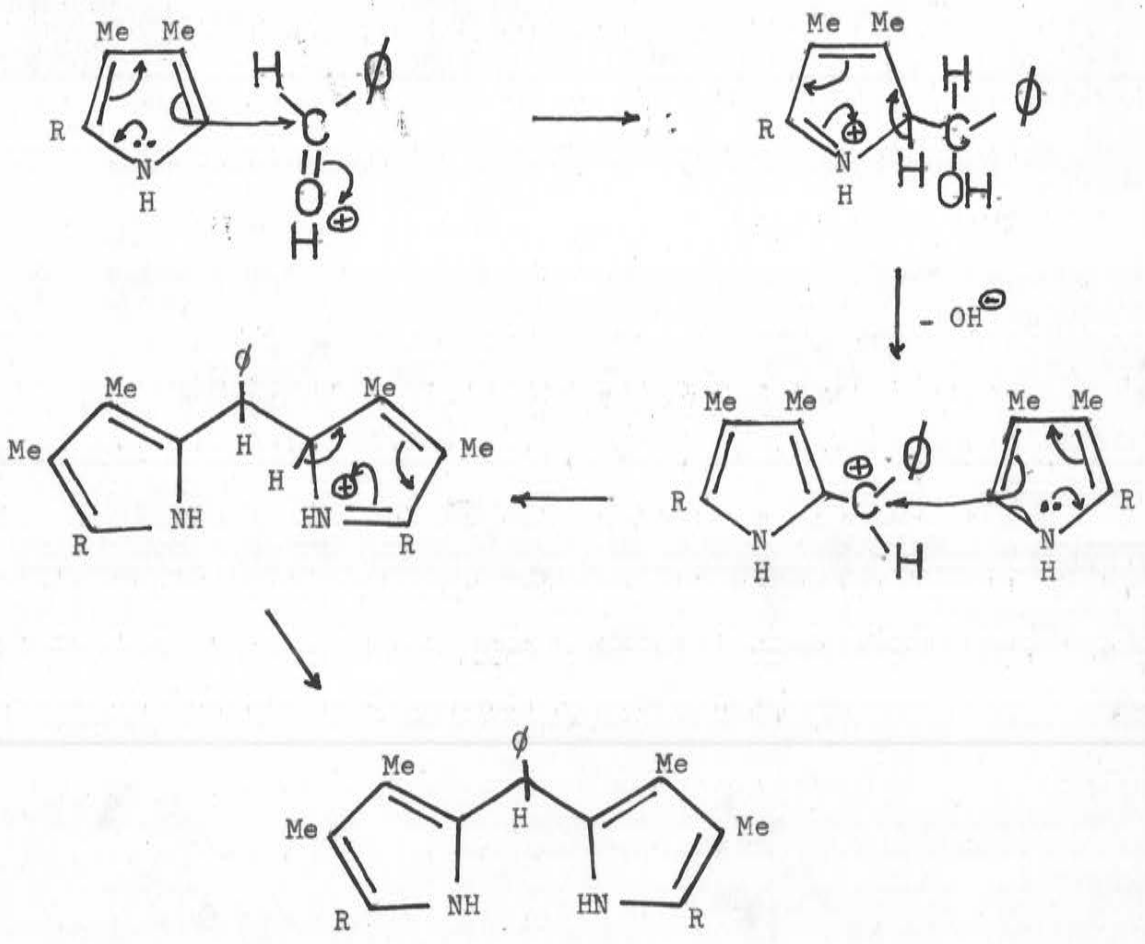
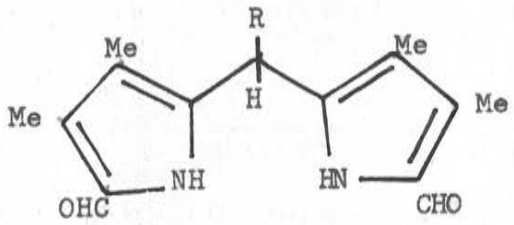



Fig. 10.

The recent discovery by Johnson *et al.*[123] that diacyldipyrromethanes could be prepared directly from the corresponding diacids by the Vilsmeier-Haak procedure opened the way to the desired *ms*-substituted diformyldipyrromethanes (LXXVII, R=H,Me,Ph), side-stepping the

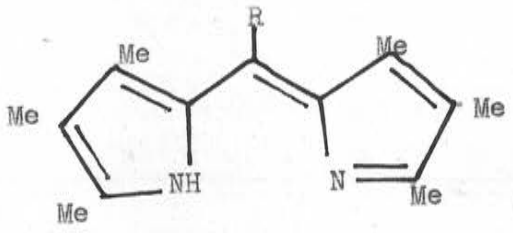



LXXVII

unstable $\alpha$, $\alpha'$-unsubstituted dipyrromethanes. Attempts at this procedure early in the course of the work had failed because insufficiently strong base was used to break down the intermediate complex formed. Like Johnson, we were unable to purify the *ms*-unsubstituted diformyldipyrromethane for analysis, and the *ms*-phenyl compound was likewise difficult to purify. However, the *ms*-methyl compound was successfully purified and analysed.

Before the dialdehydes were prepared, and because the synthetic scheme using these compounds seemed to be floundering, it was decided to use the *ms*-substituted dibromodipyrromethene (LXXIII) in one of Fischer's classical porphyrin syntheses from dipyrrylmethene units. Accordingly, the *ms*-substituted hexamethydipyrromethenes

(LXXVIII, R=H,Me,Ph) were prepared from 2,3,4-trimethyl-

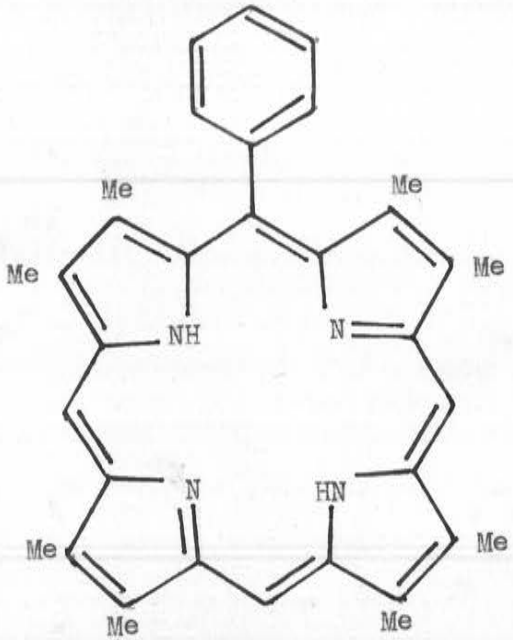



LXXVIII

pyrrole-5-carboxylic acid.

## 3.4 Cyclisation experiments

The first cyclization attempt was a Fischer condensation of the methene (LXXIII) with hexamethyldipyrromethene in a succinic acid melt.




LXXIX

It was hoped to obtain ms-phenyloctamethylporphyrin (LXXIX) by this method, and a small yield was estimated. A comparison of the visible spectra of the product and some related compounds is shown in Table IV.

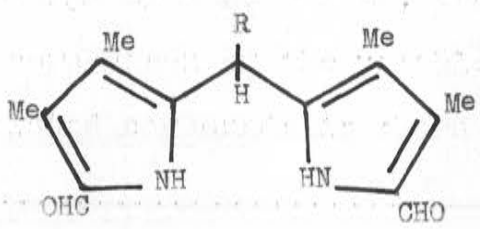
| Porphyrin | Solvent | λ max.(in mμ) | | | | | |
|---|---|---|---|---|---|---|---|
| octamethyl[102] | chloroform | 399 | 500 | 532 | 565 | 594 | 621 |
| ms-methyl-octamethyl[41] | benzene | 410 | 506 | 539 | 578 | | 630 |
| ms-phenyl octamethyl | chloroform | 404 | 504 | 536 | 571 | | 624 |

TABLE IV

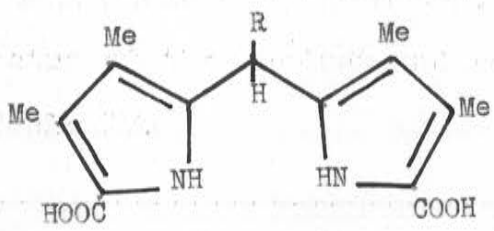
From the table, it is apparent that the porphyrin product is not octamethylporphin (which could arise by elimination of the ms-phenyl group.) However, the reaction would need to be carried out on a larger scale before it could be assumed that no elimination had occurred. The introduction of the phenyl group causes an overall bathochromic shift, but not as great a shift as a methyl group. This could be explained by the non-planarity of the phenyl group with the porphyrin ring causing less steric distortion than the symmetrical methyl group.

After the preparation of the ms-substituted diformyldipyrromethanes (LXXX) from the diacids (LXXXI), it was decided to revert to the original reaction path.

It was presumed that since the latter compound must have




LXXX




LXXXI

decarboxylated to give the former, they would decarboxylate under the similar acidic conditions necessary for the cyclisation, thereby eliminating the isolation of the troublesome $a$, $a'$-unsubstituted dipyrromethanes. The first experiments were carried out with the ms-unsubstituted compounds (LXXX and LXXXI, R=H). With hydriodic acid as catalyst, the cyclization gave only low yields, irrespective of whether air or copper acetate was used as the oxidising agent. The reaction involved is complicated, involving at least four steps, although they do not necessarily occur in the following order:

(a) decarboxylation of the diacid;

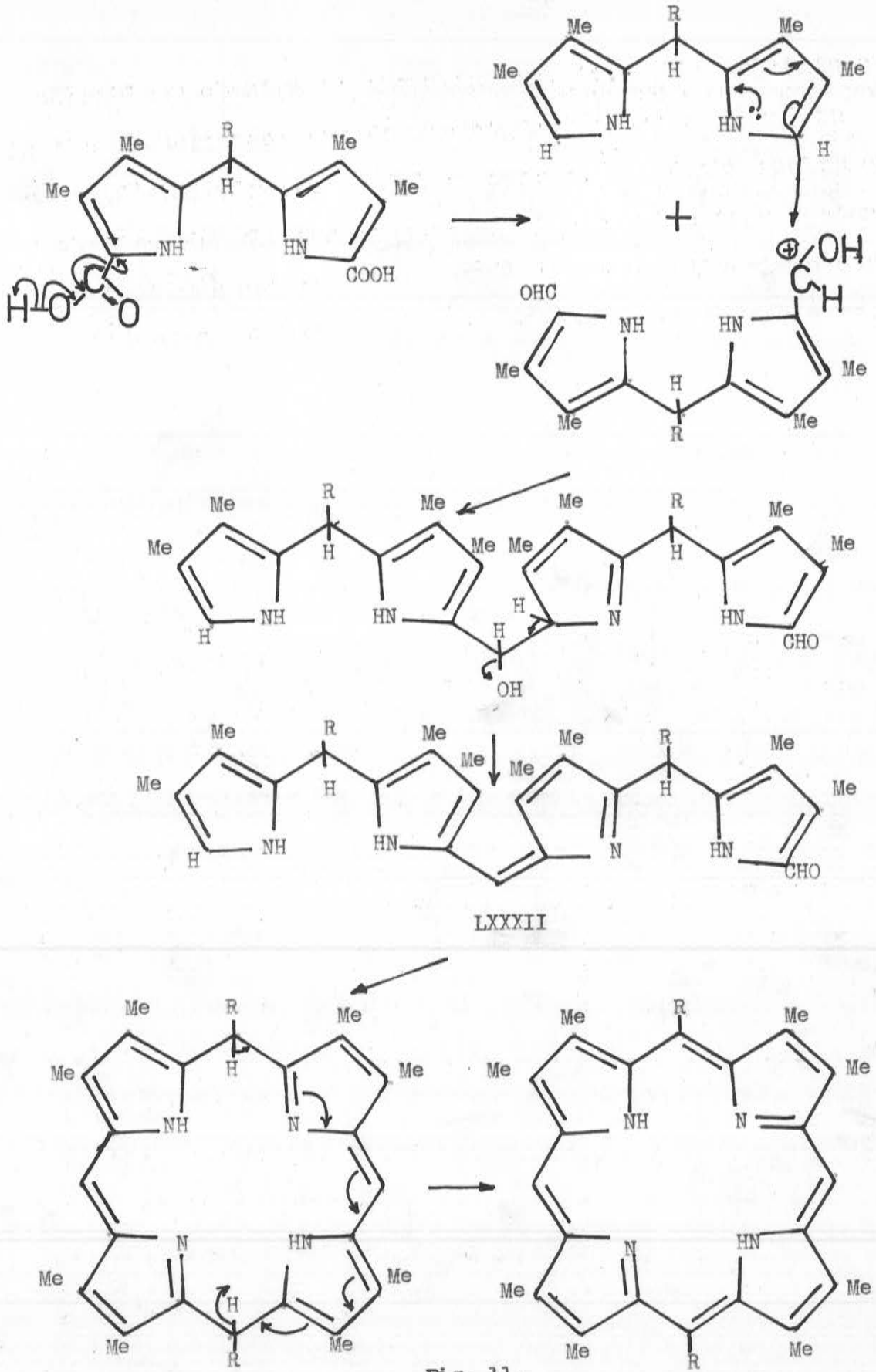
(b) condensation of the methanes to form the bilenes (LXXXII);

(c) cyclisation of the bilene to the dihydroporphyrins (LXXXIII); and

(d) oxidation to the corresponding porphyrin.

A possible mechanism is shown in Fig. 11. The substituents in the $\beta$-positions are different from those employed in McDonald's highly-successful syntheses,[98] and the inclusion of the decarboxylation step is another complicating factor, so that it was not surprising that the carefully-elaborated conditions of McDonald were not as successful in our case.

In the analogous preparation of decamethylporphin (LXXXIV, R=Me) from the diacid (LXXXI, R=Me) and the dialdehyde (LXXX, R=Me), similar low yields were estimated. However, in this experiment a possible intermediate, or by-product, was obtained in good yield as a red solid with a green reflex, and a high melting point. Its visible spectrum indicates a pyrromethene linkage and presumably at least one condensation step has taken place. However, it is not possible to distinguish between the bilene (LXXXII), dihydroporphyrin (LXXXIII) or polypyrrene (LXXXV) structures which are possible, on the basis of the visible spectrum. Various attempts at oxidising the compound to a porphyrin were made, but only traces were obtained so that the dihydroporphyrin structures seem unlikely. Purification of the unknown compound was not accomplished, and this makes deductions from the infrared spectrum risky. Clarification of the structure of this compound would undoubtedly help to improve the yields of porphyrin by this method.



LXXXII

LXXXIII

LXXXIV

Fig. 11.

Johnson[123] had reported a 29% yield of tetraethyl 1,4,5,8-tetramethylporphin-2,3,6,7-tetracarboxylate (LXXXVI) from the dialdehyde (LXXXVII) and the diacid (LXXXVIII) by heating methanolic solutions of the methanes under reflux with 12N hydrochloric acid (Fig. 12). Although the yields

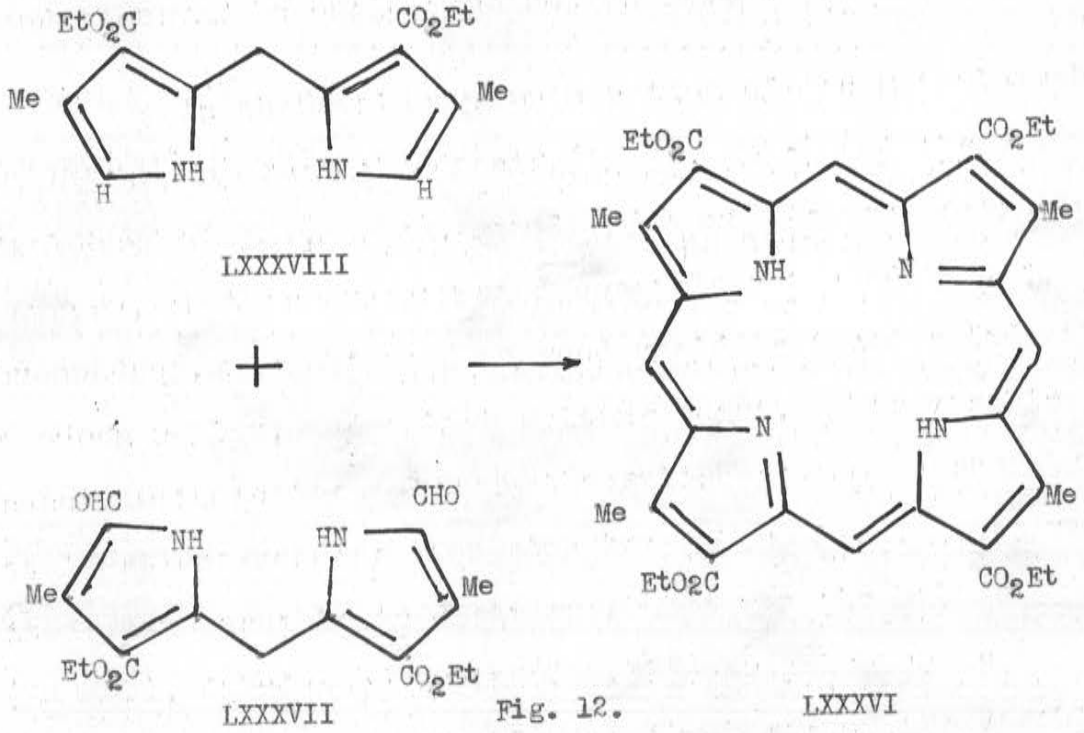



Fig. 12.

were lower than those obtained in McDonald's studies, it seemed advantageous to carry out the decarboxylation in the same vessel as the condensation. Because McDonald had emphasized the critical nature of the mineral acid, we decided to make a comparison between hydriodic, hydrobromic, hydrochloric and perchloric acids under these reaction conditions. Thus, the ms-methyl diacid (LXXXI, R=Me) and dialdehyde (LXXX, R=Me) were heated under reflux in methanol with the various acids and the yields were

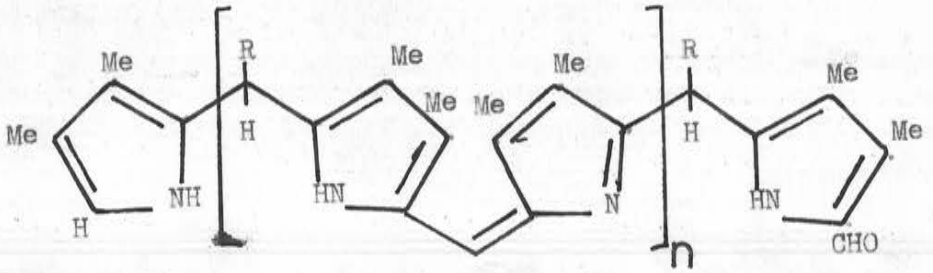
estimated spectroscopically. Under Johnson conditions, perchloric acid was found to be the most efficient cyclising agent, hydriodic was almost as efficient and hydrobromic and hydrochloric acids not nearly as good. This contrasts with McDonald's results, for he found that hydriodic acid was by far the most efficient. The extra step involved in our reactions probably accounts for the different results.

Because of the success of aqueous copper formate in increasing the yield of octamethylporphyrin from the diacid (LXXXI, R=H) and formic acid,[102] it was decided to attempt the preparation of the decamethylporphin under the same conditions. On the basis of Treibs' work,[120] it was expected that the ms-methyldipyrromethane (LXXXI, R=Me) would cleave in formic acid, and possibly give rise to two porphyrins. When the experiment was carried out, it was found that the yield was appreciably lower than for the ms-unsubstituted compound and there appeared to be two Soret bands evident in the visible spectrum. The overall lower yield of porphyrin can possibly be explained on the basis of the steric interaction of the ms-methyl group with the methyl groups in the $\beta$-positions. Cleavage at the ms-position was also detected in an attempted cyclisation of the diacid (LXXXI, R=Me) and the dialdehyde

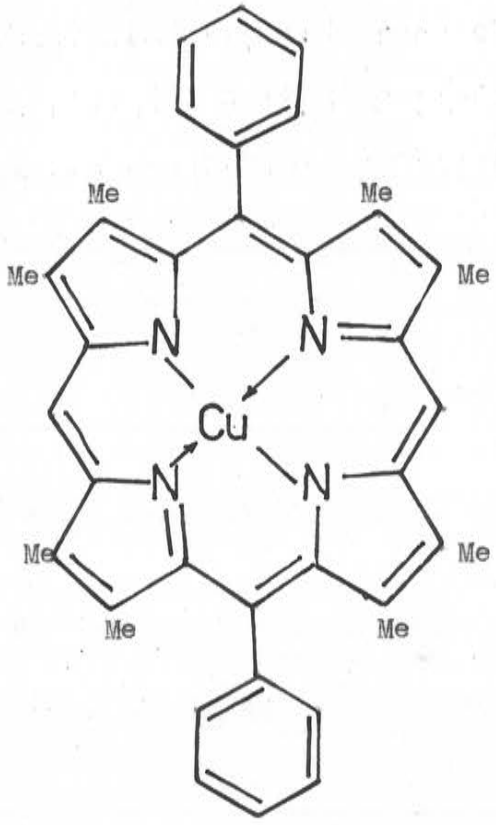
(LXXX, R=Me) in formic acid.

From these experiments, it was concluded that the best method tried for the preparation of ms-disubstituted porphyrins was to cyclize the dipyrromethanes with perchloric acid in methanol, and to carry out the final oxidation with aqueous copper formate. Working on a slightly larger scale than above, octamethylporphin and copper decamethylporphin were isolated in 21% and 10% yields respectively. The yield of the latter represents an appreciable increase on Kenner's yield[41] and the preparation has the advantage that it does not give such a complicated mixture of products. Copper ms-diphenyloctamethylporphin (LXXXIX) was prepared in a similar manner in 6% yield from the methanes (LXXX, R=Ph) and (LXXXI, R=Ph).

Although more work needs to be done, it appears we have found a more satisfactory method for preparing ms-disubstituted porphyrins than is described in the literature and the possibility of synthesizing other ms-substituted porphyrins remains open.




LXXXV



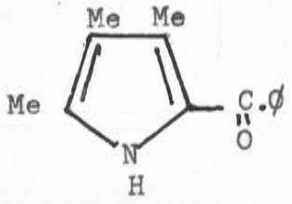

LXXXIX

# CHAPTER 4

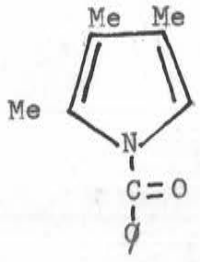
# BENZOYLPYRROLES

## 4.1 Introduction

From the reaction of 2,3,4-trimethylpyrrole and benzoyl chloride in acetic acid (see above), a compound of unknown structure was isolated as well as the expected ms-phenyldipyrromethene. The evidence provided by its elementary analysis and infrared spectrum suggested that it was 2-benzoyl-3,4,5-trimethylpyrrole (XC).




XC

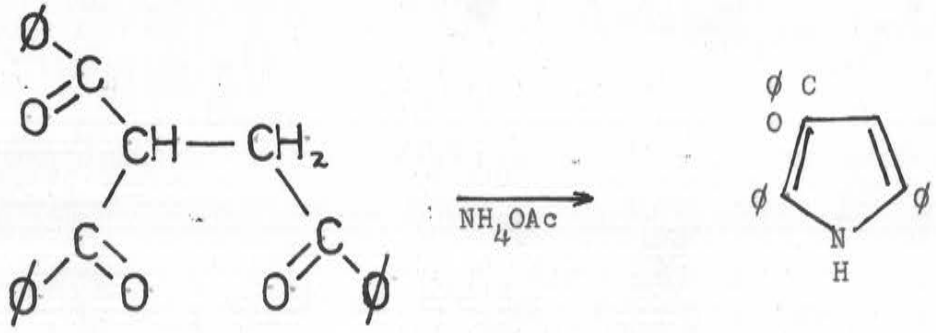



XCI

However, the melting point of our compound corresponded with that of a compound, prepared by Treibs and Derra-Scherer,[124] but to which they had assigned the 1-benzoyl structure (XCI). They had prepared their benzoylpyrrole by reacting 2,3,4-trimethylpyrrole with benzoyl chloride in excess sodium hydroxide solution under Schotten-Baumann

conditions. The discrepancy between our results and theirs prompted an investigation of the synthesis and infrared spectra of a series of 1- and 2-substituted benzoylpyrroles.

Appropriate modifications of many common acylation procedures have been used for the synthesis of a wide variety of benzoylpyrroles. Sometimes, however, direct ring formation is more convenient particularly if an unambiguous synthesis is required. For example, Sprio[125] has recently modified the well-known Paal-Knorr synthesis to produce 3-benzoyl-2,5-diphenylpyrrole (XCII) from the 1:4-diketone (XCIII) and ammonium acetate.




XCIII XCII

His syntheses[126,127] of 1-hydroxypyrroles from the oximes of α-haloketones, illustrated in Fig. 13, are also of interest. This is a modification of the Hantzch synthesis. The 1-hydroxypyrroles are readily converted to the 1-unsubstituted pyrroles. Dimroth and Pintschovius[128] have synthesized a benzoyl derivative (XCIV, R=COØ, R'=CN) in their recent ring synthesis of pyrrole derivatives from

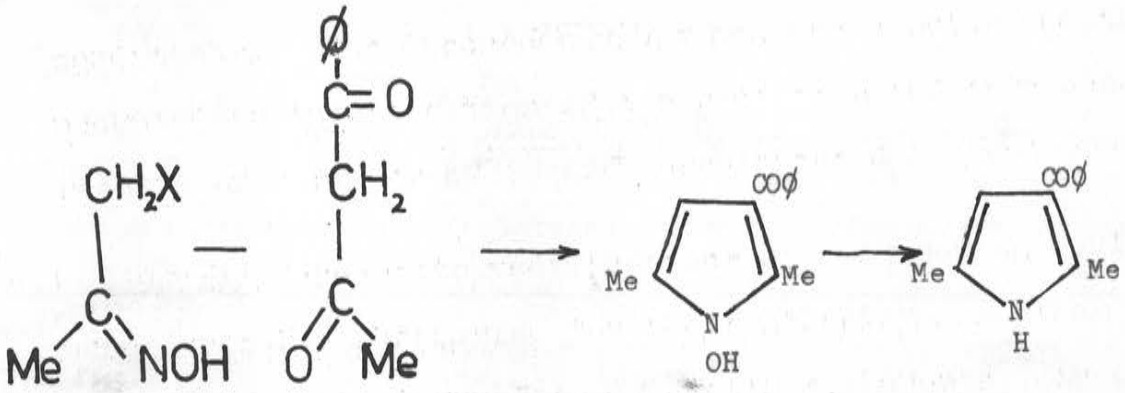


Fig. 13.

benzil (Fig. 14).

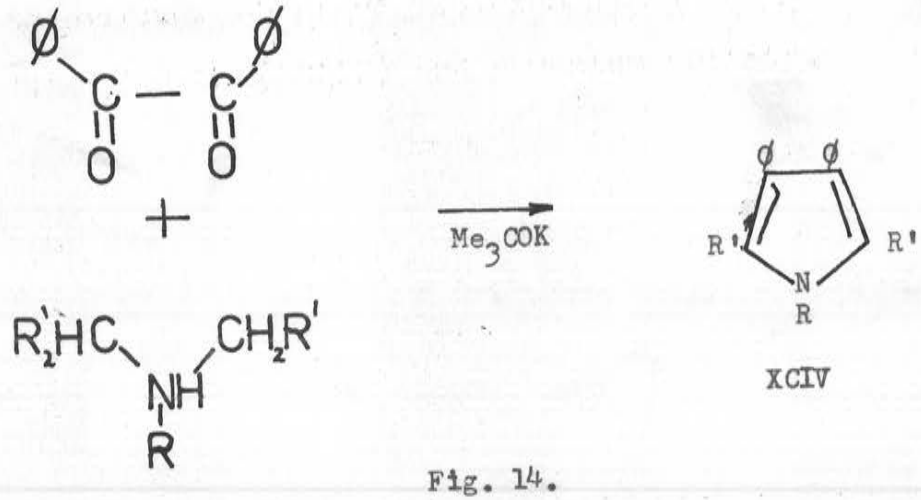


Fig. 14.

The above examples are confined to t hose of more recent application for benzoylpyrrole syntheses, and a number of other modified ring syntheses are possible.

When the pyrrole ring has already been formed, acylation procedures can be used. Grignard derivatives of pyrroles, over whose structure there has been considerable controversy in the literature, have been the source of 1-,

2- and 3- benzoylpyrroles. By the action of benzoyl chloride on 2,4,5-triphenylpyrrole, Giambrone and Sprio[129] obtained the 1-benzoyl derivative, the structure of which was confirmed by oxidative degradation to dibenzoylmethane. However, the melting point listed seems rather high and the compound reported could profitably be investigated by modern physical methods. Normally, the N-substituted compounds are believed to be intermediates in the formation of the C-substituted compounds.[130] Despite the fact that alkylation of pyrrylmagnesium halides gives mixtures of the 2- and 3-isomers, Skell and Bean[131] have shown that acylation gives only the 2-isomers. When both $\alpha$-positions are blocked, acylation involves the $\beta$-position.[132-134] Thus, the Grignard method of synthesizing pyrroles cannot be used for unequivocal structural assignments, without further confirmatory evidence.

The Friedel-Crafts, Houben-Hoesch and Vilsmeier-Haak acylation procedures cannot give 1-substituted derivatives because they are carried out in acid media. They normally give 2-acylpyrroles in good yields but will substitute in the $\beta$-positions if the $\alpha$-positions are blocked. The activation of the 2-position in the Friedel-Crafts reaction is illustrated by the following mechanism (Fig. 15). A complicating feature of the use of the Friedel-Crafts reaction was observed by Rips and Buu-Hoï.[135] They noticed,

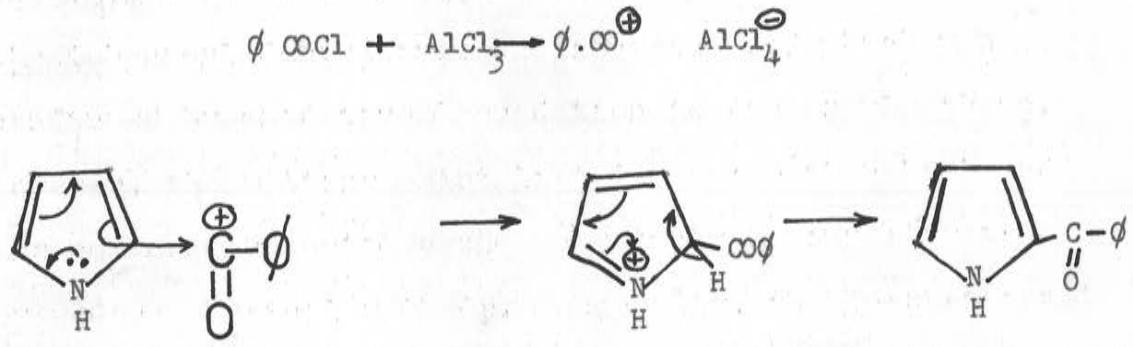


Fig. 15.

in the benzoylation of 1,2,5-substituted pyrroles, that dibenzoylation can occur because the pyrrole nucleus is so reactive. Thus, benzoylation of 1-phenyl-2,5-dimethylpyrrole in benzene with benzoyl chloride, using stannic chloride as catalyst, gave the 3-benzoyl and 3,4-dibenzoyl isomers. The Houben-Hoesch procedure[136] is illustrated in Fig. 16.

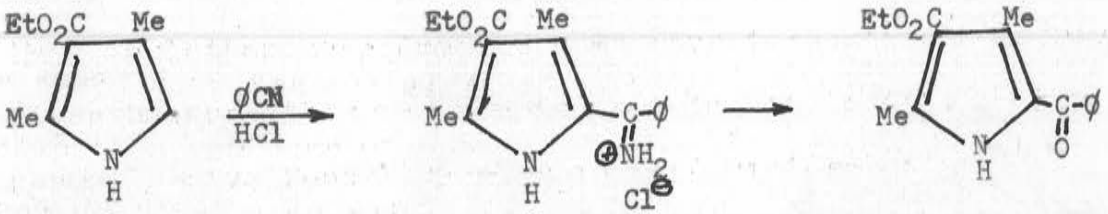


Fig. 16.

XCVI XCV

Its mechanism must be basically similar to that of the Friedel-Crafts reaction. Kleinspehn[137] has modified the well-known Vilsmeier-Haak procedure to produce benzoyl pyrroles. Pyrrole (XCV) was produced by the reaction of the pyrrole (XCVI) with N-benzoylmorpholine and phosphorus oxy-chloride, possibly according to the following mechanism (Fig. 17).

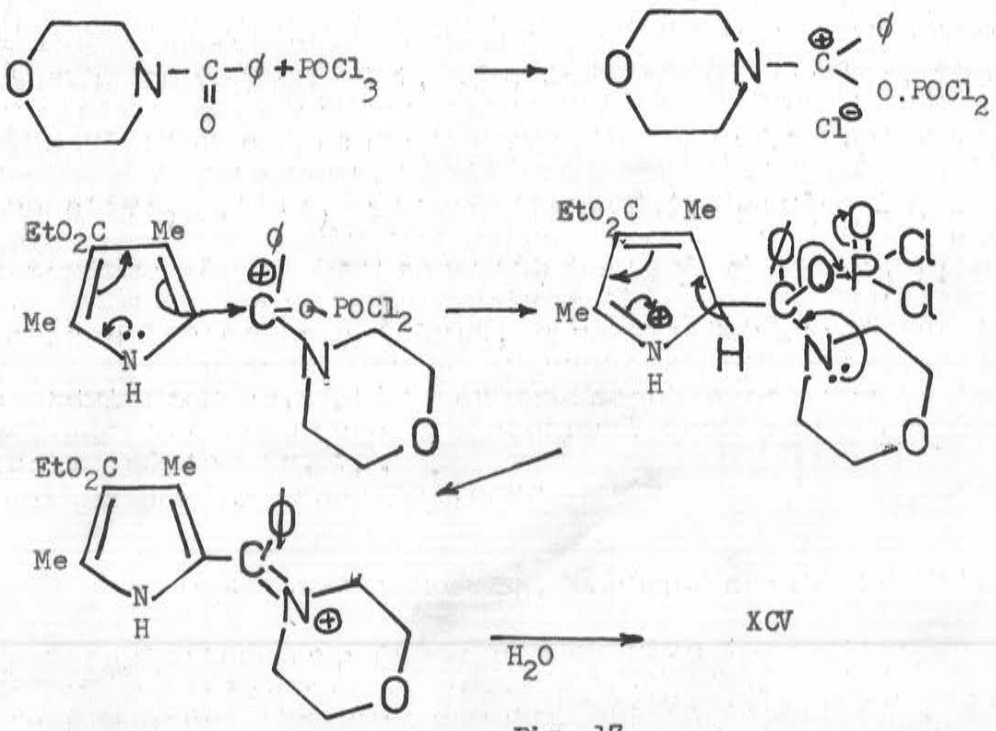



Fig. 17.

A convenient synthesis of 1-benzoylpyrroles was developed by Rainey and Adkins[138] when they treated potassio derivatives of pyrroles with benzoyl chloride. The initial mechanism is probably ionic since the 1-isomer can always be obtained but the question of the presence of the

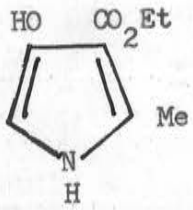
higher boiling 2-isomer in the reaction product before working up is open. In view of the relatively low yields which are obtained, and the fact that mixtures of 1- and 2-isomers have been obtained in the closely-related alkylation reactions with alkali metal salts of pyrrole,[139] it seems probable that the 2-isomers are present; but this has not been investigated. Another fact to be considered in this problem is that 1-acyl pyrroles are known to rearrange thermally to the 2-isomers.[140]

Two other procedures have been used to synthesize benzoylpyrroles. Some Japanese workers[141] have recently adapted the well-known pyrrole synthesis from furans to give pyrryl ketones. They obtained 2-benzoylpyrrole in 10-15% yield from the corresponding furan derivative by heating with ammonia.

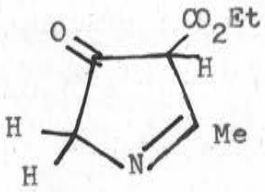
Heating pyrroles with benzoic acid anhydride to 200-240° gave 2-benzoyl derivatives whereas N-acyl derivatives were reported from aliphatic acid anhydrides under the same conditions.[130]

The literature on the Schotten-Baumann benzoylation of pyrroles is rather confusing. In 1924, Muller[142] reported that benzoylation of 2-hydroxy-4-ethoxycarbonyl-5-methylpyrrole gave a monobenzoyl derivative under

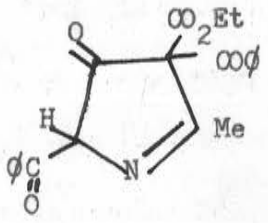
Schotten-Baumann conditions but 2-methyl-4-hydroxy-3-ethoxycarbonylpyrrole (XCVII) gave a dibenzoyl compound. He assumed that for both cases the hydroxy group reacted to give an ester and discussed whether the other benzoyl group was in the 1- or 2-position in the second pyrrole. He favoured the 2-position but did not prove its structure. Recent spectroscopic studies[143] have shown that 3-hydroxypyrroles are 4-oxo-2-pyrrolines and thus (XCVII) would have structure (XCVIII).



XCVII



XCVIII



XCIX

This structure suggests another possible structure (XCIX) for the dibenzoyl derivative, but the true nature of the compound should be capable of elucidation by modern physical methods. Working with pyrroles whose structures were known unequivocally, Treibs[144] reported that Schotten-Baumann benzoylation gave 1-substituted derivatives. He assumed this to be a general rule[124,130,144] and text-books[145,146] and reviews,[147] even as recently as 1963, have quoted this. However, Plieninger, Bauer and Katritzky[148] recently claimed that 2-ethoxy-3,4-dimethyl-

pyrrole benzoylated in the 5-position under Schotten-Baumann conditions. They gave no evidence to explain their difference in assignment from Treibs' rule despite the fact that the pyrrole used is activated in a similar manner to the compounds employed by Treibs. Theoretically, Schotten-Baumann benzoylation would be expected to give 2-substituted derivatives as it is difficult to imagine the hydrogen attached to the pyrrolic nitrogen being removed in aqueous alkali. When an electron-withdrawing substituent is placed in the 2-position, this would activate the pyrrole nitrogen to electrophilic attack, as Fig. 18 illustrates.

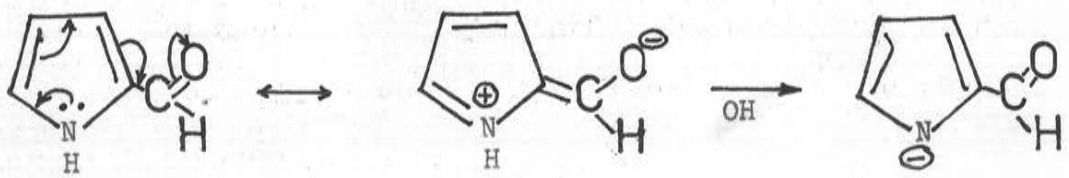



Fig. 18.

Thus, it was not surprising that the same benzoylpyrrole was prepared by Schotten-Baumann benzoylation of pyrrole-2-aldehyde and by reaction of its sodium salt with benzoyl chloride.[149]

No systematic infrared study of benzoylpyrroles has previously been undertaken, but it was expected that the 1-benzoylpyrroles would exhibit no N-H stretching

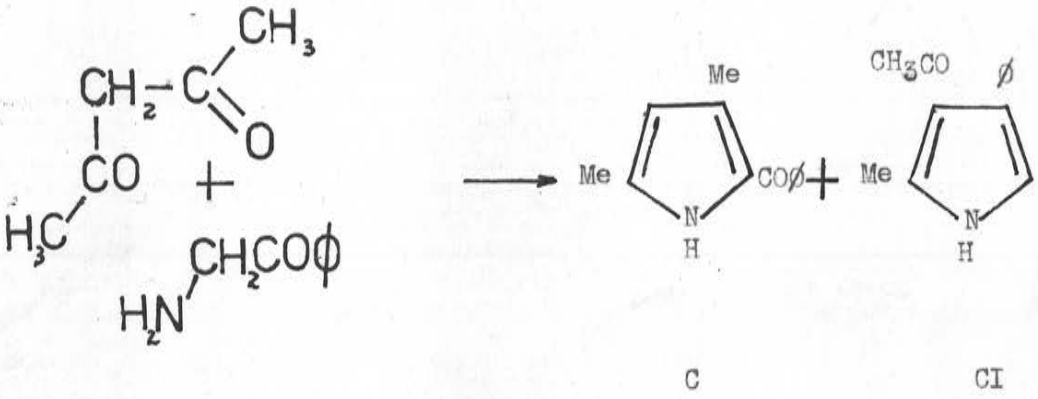
frequency and would have an amide-type carbonyl stretching frequency. Their 2-substituted counterparts should have an N-H stretching frequency and a carbonyl stretching frequency in a region similar to those of dipyrroketone and Michler's ketone (di-[p-dimethylaminophenyl]ketone), which occur at 1597 and 1598 cm.$^{-1}$ respectively.[150] The above results summarize past work on benzoylpyrroles and provide background material for our investigations of the problem of whether or not our benzoylpyrrole was a 1- or a 2-isomer.

## 4.2 The isomer problem

Initially, we repeated the work of Treibs and Derra-Scherer.[124] They had reduced 2,4-dimethyl-3-ethoxycarbonylpyrrole with lithium aluminium hydride to give 2,3,4-trimethylpyrrole whose benzoyl derivative was then prepared by Schotten-Baumann benzoylation. Our product from the repetition of this reaction was identical in melting point with the one they had obtained. It was identical in infrared spectrum, melting point and mixed melting point with the compound we had obtained in the ms-phenyldipyrromethene preparation. As determined by these same three criteria, the products obtained by Schotten-Baumann benzoylation of 2,3,4-trimethylpyrrole (prepared

by an alternative method from 2,3,4-trimethyl-5-ethoxycarbonylpyrrole) and Houben-Hoesch procedure were also identical with those above. Since the latter procedure can only reasonably be expected to give a 2-benzoyl derivative, we concluded that our unknown compound did, in fact, have the structure we originally assigned to it. This assignment was supported by the infrared evidence ($\nu_{NH}$ = 3450, $\nu_{C=O}$ = 1593 cm.$^{-1}$). Attempts to form this compound by Vilsmeier-Haak benzoylation of 2,3,4-trimethylpyrrole using dimethylbenzamide, which had been successfully employed in the azulene series,[151] were surprisingly unsuccessful. Authentic 1-benzoyl-2,3,4-trimethylpyrrole (XCI, $\nu_{C=O}$ = 1685 cm.$^{-1}$), a liquid, was synthesized from the potassium salt of 2,3,4-trimethylpyrrole and benzoyl chloride. It seemed conclusive that Treibs' assignment was incorrect, and led us further to doubt that Schotten-Baumann benzoylation always gives 1-benzoylpyrroles.

It was therefore decided to investigate Treibs' original paper[130] on 1-benzoylpyrroles. It was ironical to discover that this refuted a claim that 2-benzoyl-3,5-dimethylpyrrole (C) had been prepared as a by-product in the Knorr synthesis of 2-methyl-3-acetyl-4-phenylpyrrole (CI) from phenacylamine and acetylacetone (Fig. 19).[152]




C CI

Fig. 19.

The basis of Treibs' reputation was that Almstrom's compound had the same melting point as "1-benzoyl-2,5-dimethylpyrrole", which had been prepared by Schotten-Baumann benzoylation of 2,4-dimethylpyrrole. The difficulty of explaining how a 1-benzoyl derivative could be formed was avoided by assuming that Almstrom's compound was a mixture. The basis for the assignment of the Schotten-Baumann product was that the compound obtained by Houben-Hoesch synthesis from 2,4-dimethylpyrrole and benzonitrile had a higher melting point and, furthermore, admixture of these products gave a sharp depression of melting point. Confirmatory evidence for the assignment came from the fact that the '1-benzoyl derivative' gave no reaction with hydroxylamine while the '2-benzoyl derivative' reacted readily to form an oxime. Bromo compounds (not characterized) of different melting point were obtained from the

two compounds but somewhat surprisingly, the 'N-benzoylpyrrole' was recovered unchanged on heating in a sealed tube.

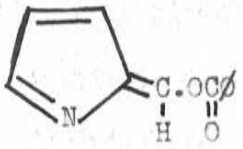
In contrast to Treibs' results, the products we obtained on repetition of the Houben-Hoesch and Schotten-Baumann benzoylation reactions with 2,4-dimethylpyrrole were identical in melting point, mixed melting point and infrared spectra. The melting point obtained was identical with the literature melting point for authentic 2-benzoyl-3,5-dimethylpyrrole, prepared by saponification and decarboxylation of 2,4-dimethyl-3-ethoxycarbonyl-5-benzoylpyrrole.[137] The infrared evidence supported the 2-benzoyl structure ( $\nu_{NH}$ = 3447, $\nu_{C=O}$ = 1598 cm.$^{-1}$). Authentic 1-benzoyl-2,4-dimethylpyrrole ( $\nu_{C=O}$ = 1687 cm.$^{-1}$), a liquid, was synthesized by the Rainey-Adkins procedure. From these reactions, it seems certain that Schotten-Baumann benzoylation of alkyl pyrroles gives the theoretically expected 2-benzoyl derivatives, and not the 1-isomer as reported hitherto.

This was further borne out by preparing the well-known 1- and 2-benzoyl derivatives of pyrrole itself. 2-Benzoylpyrrole ( $\nu_{NH}$ = 3454 cm.$^{-1}$, $\nu_{C=O}$ = 1612 cm.$^{-1}$) was prepared by the Schotten-Baumann procedure and 1-benzoylpyrrole ( $\nu_{C=O}$ = 1691 cm.$^{-1}$) by the Rainey-Adkins procedure.

The scope of the readily-executed Schotten-Baumann reaction for the preparation of 2-benzoylalkylpyrroles seems, however, to be limited. Treibs[130] has reported that N-methylpyrrole and 2,4-diphenylpyrrole do not react, and we have made unsuccessful attempts to prepare derivatives of 2-methylpyrrole and 3,4-dimethylpyrrole. 2,4-Dimethyl-3-ethylpyrrole gives a monobenzoyl derivative,[130] 2,3,4,5-tetramethylpyrrole gives a dibenzoyl derivative[153] and 2,5-dimethylpyrrole has not been tried.

Treibs' claim to have prepared 1-benzoylpyrrole-2-aldehyde[149] by the Schotten-Baumann procedure on pyrrole-2-aldehyde has been substantiated. Reaction of the sodium salt of the aldehyde with benzoyl chloride gave the desired compound, the infrared spectrum* of which ($\nu_{C=O}$ = 1690, 1790 cm.$^{-1}$) supported its proposed structure. However, Schotten-Baumann benzoylation of 2-ethoxycarbonylpyrrole gave only unchanged starting material. It is interesting to note that two products are obtained on benzoylation of pyrrole-2-aldehyde in sodium hydroxide (less than the required amount). Apart from the N-benzoylpyrrole, another product, for whose structure Treibs has postulated the benzoic acid ester of the hydroxymethylene form of the aldehyde (CII). Treibs gives us no supporting evidence

* Infracord.



CII

and ignores the dimeric nature of the product, which was elucidated by earlier workers.[154,155]

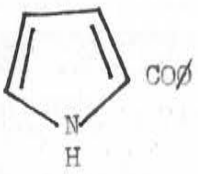
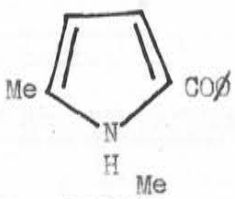
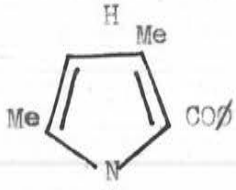
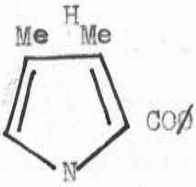
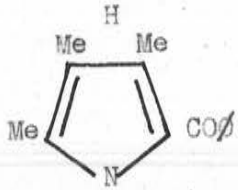
## 4.3 Infrared Studies

Table V shows the NH and C=O stretching modes of a number of 2-benzoylpyrroles which constitutes a section of a larger investigation being carried out in this department.[156] It includes two compounds which were not mentioned in the previous section, viz. 5-methyl-2-benzoylpyrrole and 3,4-dimethyl-2-benzoylpyrrole. Both these compounds were prepared by reaction of the Grignard derivative of the appropriate alkylpyrrole with benzoyl chloride, since the Schotten-Baumann procedure was found to be ineffective. The Grignard reaction was used in preference to the alternative Houben-Hoesch and Friedel-Crafts procedures because it is milder.

The determination of the NH stretching mode of the pyrroles was made in very dilute solution to eliminate intermolecular hydrogen bonding. No evidence was found

## TABLE V

## STRETCHING MODES OF 2-BENZOYLPYRROLES

| | $\nu_{NH}$ ($cm^{-1}$) | | $\nu_{CO}$ ($cm^{-1}$) | |
|---|---|---|---|---|
| | Obs. | Calc. | Obs. | Calc. |
|  | 3496 | 3496 ✱ | - | - |
|  | 3454 | 3454 | 1612 | 1612 |
|  | 3452 ✱✱ | 3445 | 1605 | 1604 |
|  | 3447 | 3447 | 1598 | 1598 |
|  | 3459 | 3458 | 1601 | 1600 |
|  | 3450 | 3449 | 1593 | 1592 |

✱ See Ref. 158.

✱✱ Inorganic Dept.

for intramolecular hydrogen bonds between the NH and C=O groups in these compounds and this result agrees with results from a related study of the NH stretching modes of 2-acetylpyrroles.[156] By comparison of NH stretching modes of the benzoylpyrroles with those of the corresponding alkylpyrroles which had been previously reported by Abraham et al.,[157] we observed that the introduction of the electron-withdrawing benzoyl group caused a shift to lower frequency of 42 cm.$^{-1}$. The overall results were such that the NH stretching mode ($\nu_{NH}$) could be approximately calculated from the following equation.

$$\nu_{NH} = 3496 - 9\, n_{\alpha_1} + 2\, n_{\beta_1} - 42\, n_{\alpha_2}$$

where $n_{\alpha_1}$, $n_{\beta_1}$ and $n_{\alpha_2}$ represent the number of methyl groups in the $\alpha$-position, the number of methyl groups in the $\beta$-position and the number of benzoyl groups in the $\alpha$-position respectively. This equation has been calculated recently in this department,[156] and follows a pattern similar to the results observed for alkyl,[157] acetyl[158] and ethoxycarbonylpyrroles.[159]

The carbonyl stretching band shifts to lower frequency as the number of alkyl groups increases, with the methyl groups in the $\alpha$-positions exerting a greater effect than those in the $\beta$-positions. This effect can

be described quantitatively by the expression,

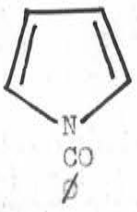
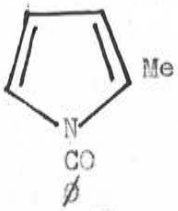
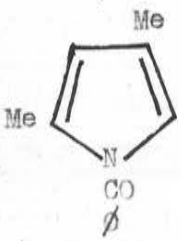
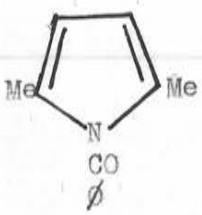
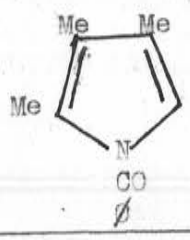
$$\nu_{CO} = 1612 - 8\,n_{\alpha} - 6\,n_{\beta}$$

where $\nu_{C=O}$ is the carbonyl stretching mode, and $n_{\alpha}$ and $n_{\beta}$ are the number of methyl groups in the $\alpha$- and $\beta$-positions respectively. These shifts are to be expected from the inductive and hyperconjugative effects of the methyl groups which tend to increase the single bond character of the carbonyl group.

The results of measuring the carbonyl stretching modes of various 1-benzoylpyrroles are listed in Table VI. Those pyrroles which have not been mentioned above were prepared by the Rainey-Adkins procedure of treating the potassium salts of the appropriate alkylpyrroles with benzoyl chloride. 2,5-Dimethyl-1-benzoylpyrrole, which previously had been described as an oil,[130] was obtained crystalline, and its identity was further confirmed by nuclear magnetic resonance spectroscopy. The carbonyl stretching mode of the N-benzoyl compounds was found to be at a higher frequency than the corresponding C-benzoyl compounds. This is to be expected from a comparison of the carbonyl stretching modes of benzanilide[160] and 4,4'-bis(dimethylamino)-benzophenone,[150] which occur at 1680 and 1598 cm.$^{-1}$ respectively. As observed with the CO stretching modes of the 2-benzoylpyrroles, the introduction

## TABLE VI

## CARBONYL STRETCHING MODES OF 1-BENZOYLPYRROLES

| PYRROLES. | $\nu_{CO}$ (in $cm^{-1}$) |
|---|---|
|  | 1691 |
|  | 1691 |
|  | 1687 |
|  | 1687 |
|  | 1685 |

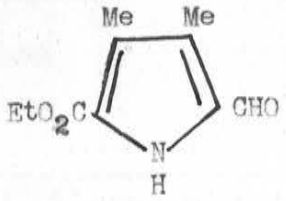
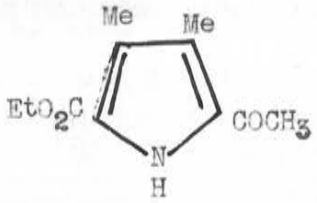
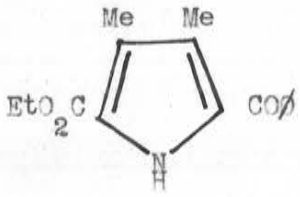
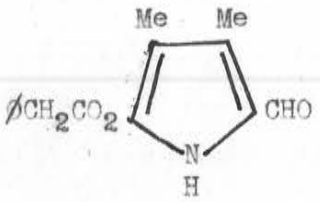
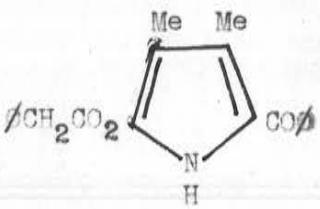
of alkyl groups caused a shift to lower frequency. In this case, however, the position of the methyl groups is not as important since methyl groups have approximately the same effect in both the $\alpha$- and $\beta$-positions. This could possibly mean a predominance of the inductive effect of the methyl groups.

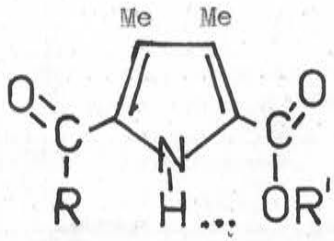
Since we had observed the effect on the NH stretching mode of introducing one electron-withdrawing group, it was decided to further our investigations by observing the effect of introducing two electron-withdrawing groups in the $\alpha$-positions of 3,4-dimethylpyrrole. Because they could also possibly be useful synthetic intermediates, the acylated derivatives of the ethoxycarbonyl and benzyloxycarbonylpyrroles were prepared. Although four of these compounds were readily prepared by standard procedures, the synthesis of benzyl 5-benzoyl-3,4-dimethylpyrrole-2-carbonylate was troublesome, possibly because of the lability of the benzyl group under acid conditions, and eventually the only successful synthesis was by transesterification of the corresponding ethyl ester.

Because of intramolecular hydrogen bonding, it might have been expected that more than one NH stretching mode might be observed, since the pyrroles could exist in the free NH form (CIII) and in the bonded NH ...$CO_2Et$ form (CIV).

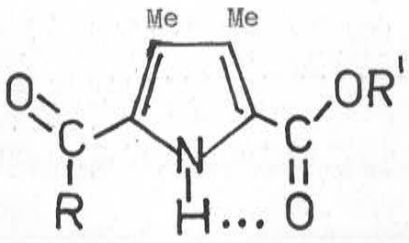
## TABLE VII

## STRETCHING MODES OF 3,4-DIMETHYLPYRROLES WITH TWO ELECTRON-WITHDRAWING SUBSTITUENTS

| | $\nu_{NH}$ ($cm^{-1}$) |
|---|---|
|  | 3436 , 3447 |
|  | 3442 |
|  | 3442 |
|  | 3435 , 3448 |
|  | 3441 |




CIII




CIV

The results obtained are listed in Table VII. The bonds obtained were very broad, and probably contained at least two separate bands, but because of their complexity in the NH region, no useful results were obtained. The expected fact that the introduction of another electron-withdrawing substituent would cause a further shift to lower frequency was, however, observed as can be seen by comparison of the values for 2-benzoyl-3,4-dimethylpyrrole ($\nu_{NH}$ = 3459 cm.$^{-1}$), ethyl 5-benzoyl-3,4-dimethylpyrrole-2-carboxylate ($\nu_{NH}$ = 3443 cm.$^{-1}$), and benzyl 5-benzoyl-3,4-dimethylpyrrole-2-carboxylate ($\nu_{NH}$ = 3441 cm.$^{-1}$).

# CHAPTER V

# EXPERIMENTAL

## 5.1 Introduction

### (1) Melting Points

Melting points were determined in capillaries using a Gallenkamp melting point apparatus and were corrected.

### (2) Infrared Spectra

The majority of the infrared spectra were measured on a Perkin-Elmer model 137 Infracord spectrometer. The NH frequencies of the benzoylpyrroles were determined using $10^{-4}$ M solutions in carbon tetrachloride in a 100 mm. cell on the Unicam SP700 recording spectrometer. The carbonyl frequencies of the benzoylpyrroles were determined using 0.189 M solutions in chloroform in a 0.106 mm. cell on the Perkin -Elmer model 21 spectrometer.

### (3) Ultraviolet and Visible Spectra

Qualitative electronic absorption spectra were measured on an Optica $CF_4$ spectrometer. Quantitative electronic absorption spectra were measured on the Unicam SP700 spectrometer.

### (4) Nuclear Magnetic Resonance Spectra

The nuclear magnetic resonance spectra were measured

on a Varian D.P.60 nuclear magnetic resonance spectrometer at 60 Mc/s. Tetramethylsilane was employed as an internal standard and the sideband technique used for calibration.

(5) Analyses

The microanalyses were performed by the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

(6) Chromatography

Several grades of alumina were used for chromatography. "Grade IV alumina" is B.D.H. "alumina for chromatography" to which has been added 10% by weight of water, distributed evenly by mechanical shaking for ½ hr., and "grade IV alumina, acid washed" is B.D.H. "alumina for chromatography" which has been washed with 1% hydrochloric acid, until the eluate was acidic, then washed with water until the eluate was neutral, dried in an oven at 160° for 12-18 hr., and finally deactivated by the addition of 10% by weight of water as described above.

Vapour phase chromatography was performed at 80° on a Griffin and George vapour phase chromatography apparatus, Mk. II, using a dinonyl phthalate column and nitrogen as the carrier gas.

(7) Solvents

All solvents were redistilled. $X_4$ is a light petroleum, b.p. 40-70°.

## 5.2 The Rothemund Reaction

### Materials -

Pyrrole, benzaldehyde, and o-chlorobenzaldehyde were commercial samples, redistilled prior to use. o-Methoxybenzaldehyde, b.p. 242° (lit.[161], 242-245°), mesitaldehyde, b.p. 124°/19 mm. (lit.[162a], 118-121°/16 mm.), and anhydrous zinc acetate were all prepared by literature methods. Zinc tetra-ms-(p-methoxyphenyl)porphin was a gift from Miss M. Mitchell.

### o-Tolualdehyde -

o-Tolualdehyde was prepared by modification of the procedure of Brown et al.[163] Anhydrous ethanol (13.8 g.) was added dropwise to a suspension of lithium aluminium hydride (3.8 g.) in anhydrous ether (300 ml.) at 0° with continuous stirring. o-Tolunitrile(11.7 g.) was then added to this solution while the temperature was maintained at 0°. The reaction mixture was stirred at 0° for a further hr., and then methanol (130 ml.) was cautiously added. After standing overnight, the product was steam-distilled. The distillate was extracted with chloroform and the chloroform extract evaporated. Distillation gave o-tolualdehyde (3 g., 25%) as a colourless liquid, b.p. 108°/28 mm. (lit.[162b], 200°/760 mm.). Its

2:4-dinitrophenylhydrazone was obtained as orange needles, m.p. 192-4° (lit.[162b], 194°).

ms-Tetra-p-methoxyphenylporphin -

A solution of zinc ms-tetra-(p-methoxyphenyl)porphin in benzene was washed with 12N hydrochloric acid, water, and ammonium hydroxide. The benzene solution was evaporated, and recrystallization of the product from benzene-methanol gave ms-tetra-p-methoxyphenylporphin as purple needles. Its visible spectrum in benzene showed λ max. 424, 488, 518, 556, 595, 652 mμ in agreement with the literature.[66] Its n.m.r. spectrum (in deuterochloroform) showed singlets at τ 1.13, 2.65 5.91, and a multiplet at τ 1.87 and (in trifluoroacetic acid) it showed singlets at τ 2.50, 2.68, 3.30, 4.30, a multiplet at τ 2.33, and a broad peak at τ 5.77.

Calculation of percentage chlorin impurity in porphyrins-

The following example illustrates the method used to calculate the percentage chlorin impurity:- The visible spectrum of the particular sample of ms-tetraphenylporphin in benzene had the following characteristics: ([Wavelength (in mμ), optical density] 485, 0.246; 515, 1.35; 547, 0.49; 590, 0.337; 6.50, 0.545). Pure ms-tetraphenylporphin[66] has the following absorption characteristics in benzene: ([Wavelength (in mμ), $\epsilon \times 10^{-3}$] 485, 3.4; 515, 18.7;

548, 8.1; 592, 5.3; 647, 3.4). and the pure chlorin[63] has: ([Wavelength (in mμ), $\epsilon \times 10^{-3}$] 518, 15.0; 543, 10.8; 600, 5.8; 654, 41.7). The optical d ensity of the band at 485 mμ in the reference sample is 0.246 and, therefore, since the pure porphyrin has equal $\epsilon \times 10^{-3}$ values at 485 and 647 mμ, the optical density corresponding to pure porphyrin in the band at 650 mμ is 0.246. By subtraction the optical d ensity due to chlorin is 0.299 and since an optical density of 0.246 corresponds to an $\epsilon \times 10^{-3}$ value of 3.4, the $\epsilon \times 10^{-3}$ value corresponding to chlorin is 4.15. Comparison of this value with the $\epsilon \times 10^{-3}$ for pure chlorin (41.7) shows that the sample contains approximately 10% of ms-tetraphenylchlorin.

ms-Tetraphenylporphin -

The following method was found to be slightly superior to that given in the literature.[66] A mixture of benzaldehyde (12 ml.), anhydrous pyridine (14 ml.), pyrrole (7 ml.) and anhydrous zinc acetate (7 g.) was heated in a stainless steel autoclave (capacity 100 ml.) at 185°, for 48 hr., according to the procedure of Ball, Dorough and Calvin.[60] The product was washed with acetone (to remove adhering tar) and the resulting crystals collected (2.76 g., 15.6%). Purification was effected by dissolving this product (0.5 g.) in redistilled trichloroethylene and

passing the solution through a bed of talc (3" x 2"). The eluate was evaporated and the resulting zinc ms-tetraphenylporphin (0.4 g.) had characteristic absorption bands (in benzene) at 430, 515, 550, and 590 mμ (lit.[110], 430, 515, 550 and 590 mμ). A benzene solution of the zinc complex was allowed to stand for 2 hr. with an equal volume of 9N hydrochloric acid. The benzene layer was separated, washed with water, 2N ammonium hydroxide, water, and dried. Evaporation gave ms-tetraphenylporphin (0.3 g., 83%) as purple needles. Its absorption spectrum (in benzene) showed maxima at 420, 485, 515, 550, 594, and 650 mμ, (lit.[66] 419, 485, 515, 548, 592 and 647 mμ). Its nuclear magnetic resonance spectrum (in deuterochloroform) showed singlets at τ 1.15, 2.67 and multiplets centred at τ 1.80 (1.72, 1.75, 1.82, 1.87) and τ 2.27 (2.23, 2.27, 2.32).

In another experiment, the crude zinc complex was decomposed with hydrochloric acid and the resulting free base purified. A solution of crude base (0.93 g., containing 2% ms-tetraphenylchlorin) in trichloroethylene (100 ml.) was shaken for ½ hr. with talc (3 g.), and then set aside for 2 days. After removal of the talc, the filtrate was evaporated and gave ms-tetraphenylporphin (0.8 g.), whose absorption spectrum indicated that it was now chlorin-free since the band at 650 mμ was now approximately equal in intensity to the one at 485 mμ.

ms-Tetramesitylporphin -

A mixture of mesitaldehyde (100 g.), pyrrole (43 g.), anhydrous zinc acetate (43 g.), and pyridine (86 ml.) was heated in a stainless steel autoclave (capacity 700 ml.) at 180° for 48 hr. The reaction vessel was cooled slowly and the resulting "tar" filtered. The residue was washed with acetone, to give purple needles (1.4 g., 1%), the visible spectrum of which showed bands at 424, 516, 550, 603, 624 mμ and indicated a zinc porphyrin containing 65% zinc chlorin. The crystals were dissolved in benzene, allowed to stand overnight and then the solution was run onto a column of alumina (Spence). The metal was removed by washing with 12N hydrochloric acid and the free base obtained by washing with ammonium hydroxide. The benzene solution was finally washed with water and evaporated. Recrystallization of the residue from benzene-methanol gave ms-tetramesitylporphin as purple needles (Found: C, 83.1; H, 7.9; N, 6.6. $C_{56}H_{54}N_4$ requires C, 85.9; H, 7.0; N, 7.2%). Its nuclear magnetic resonance spectrum (in deuterochloroform) showed singlets at τ 1.38, 2.21, 7.37, 8.15, 8.73. Its zinc complex crystallized as purple needles from the chromatographed solution above.

In another experiment, an orange solution with an intense green fluorescence was also obtained. Its

visible spectrum showed an intense peak at 490 mμ. Attempts to crystallize the product were unsuccessful.

ms-Tetra-(o-chlorophenyl)porphin -

A mixture of o-chlorobenzaldehyde (103 g.), anhydrous zinc acetate (49 g.), pyrrole (49 g.) and anhydrous pyridine (98 ml.) was heated in a stainless steel autoclave (capacity 700 ml.) at 175° for 48 hr. The resulting tar was dissolved in pyridine (1 l.) and aqueous methanol (4 l., 85%) was added. The solution was refrigerated overnight, the purple tarry residue filtered off, dissolved in chloroform, and the chloroform solution evaporated. The last traces of contaminating pyridine were removed by warming on a hot-plate and extraction with $X_4$. The purple solid (127 g.) was dissolved in chloroform and run onto a column of alumina (Spence). Elution with benzene gave three separate fractions.

Fraction (1), eluted first from the column, was an orange solution, containing only a trace of red fluorescent porphyrin. Rechromatography on alumina (grade IV, acid-washed) with benzene/hexane (1:1) as eluant gave an orange solution with a strong green fluorescence. The contaminating porphyrin was eluted with benzene and the solution added to fraction (2). The orange solution on

evaporation gave an orange solid (0.154 g., 0.1%). Recrystallization from chloroform/methanol gave zinc ms-o-chlorophenyl-5,5'-di-o-chlorobenzyldipyrromethene as orange needles with a green reflex, m.p. 203-205° (Found: C, 64.5; H, 3.5; N, 5.0; Cl, 20.3; Zn (calculated from zinc oxide) 6.5. $C_{58}H_{40}N_4Cl_6Zn$ requires C, 65.1; H, 3.8; N, 5.2; Cl, 19.8; Zn, 6.1%. Its n.m.r. spectrum (deuterochloroform/carbon tetrachloride, 60/40) showed a complex series of multiplets from $\tau$ 2.73 to $\tau$ 4.00 and a doublet at $\tau$ 6.07 ( J = 6 c.p.s.). Its ultraviolet and visible spectrum in carbon tetrachloride showed $\lambda$ max. 303, 351, 481, 502 mμ (log $\epsilon$ 3.36, 3.14, 4.10, 4.62). Its infrared spectrum, measured as a 0.34 M solution in chloroform in a 0.106 mm. cell on the Perkin-Elmer model 21 spectrometer, is shown in Fig. 20. Its molecular weight determination (Rast) gave a dark solution and a result of 667 (calculated 1071).

Fraction (2) was a purple solution with a strong red fluorescence. After rechromatography on alumina, the crude zinc complex (17.2 g., 12%), containing 9% chlorin impurity, was obtained as purple needles. The needles were dissolved in benzene, allowed to stand overnight, and run onto a column of alumina (Spence). The purple fraction eluted was evaporated and the residue recrystallized from

benzene-methanol to give zinc ms-tetra(o-chlorophenyl)porphin as purple prisms. (Found: C, 65.6, 64.0, 68.1; H, 3.3, 3.0, 3.8; N, 7.4, 6.1, 6.8; Cl, 16.3, 16.9. $C_{44}H_{24}N_4Cl_4Zn$ requires C, 64.8; H, 3.0; N, 6.9; Cl, 17.4%). The free base (1.03 g., 75%), obtained from the zinc complex (1.49 g.) by treatment with 12N hydrochloric acid and ammonium hydroxide, crystallized from benzene-methanol to give ms-tetra-(o-chlorophenyl)porphin as purple needles (Found: C, 70.5; H, 3.8; N, 7.1; Cl, 19.2. $C_{44}H_{26}N_4Cl_4$ requires C, 70.2; H, 3.5; N, 7.5; Cl, 18.9%). Its n.m.r. spectrum (in deuterochloroform) showed a singlet at $\tau$ 1.31, multiplets at $\tau$ 1.87, 2.23, and a broad peak at $\tau$ 12.60 and (in trifluoroacetic acid) singlets at $\tau$ 3.40, 4.28, multiplets at $\tau$ 2.0, 2.47 and a broad peak at $\tau$ 12.10.

Fraction (3) gave black tars, from which no identifiable compounds were isolated.

In another experiment, the initial tarry reaction product was distilled, and the various fractions were examined by vapour phase chromatography. The chromatographs showed peaks with retention times corresponding to pyridine, but the shape of the bands and the fact that the mixtures gave positive Ehrlich tests suggested that they were pyridine-pyrrole mixtures. It has been shown that such mixtures cannot be separated satisfactorily.[164]

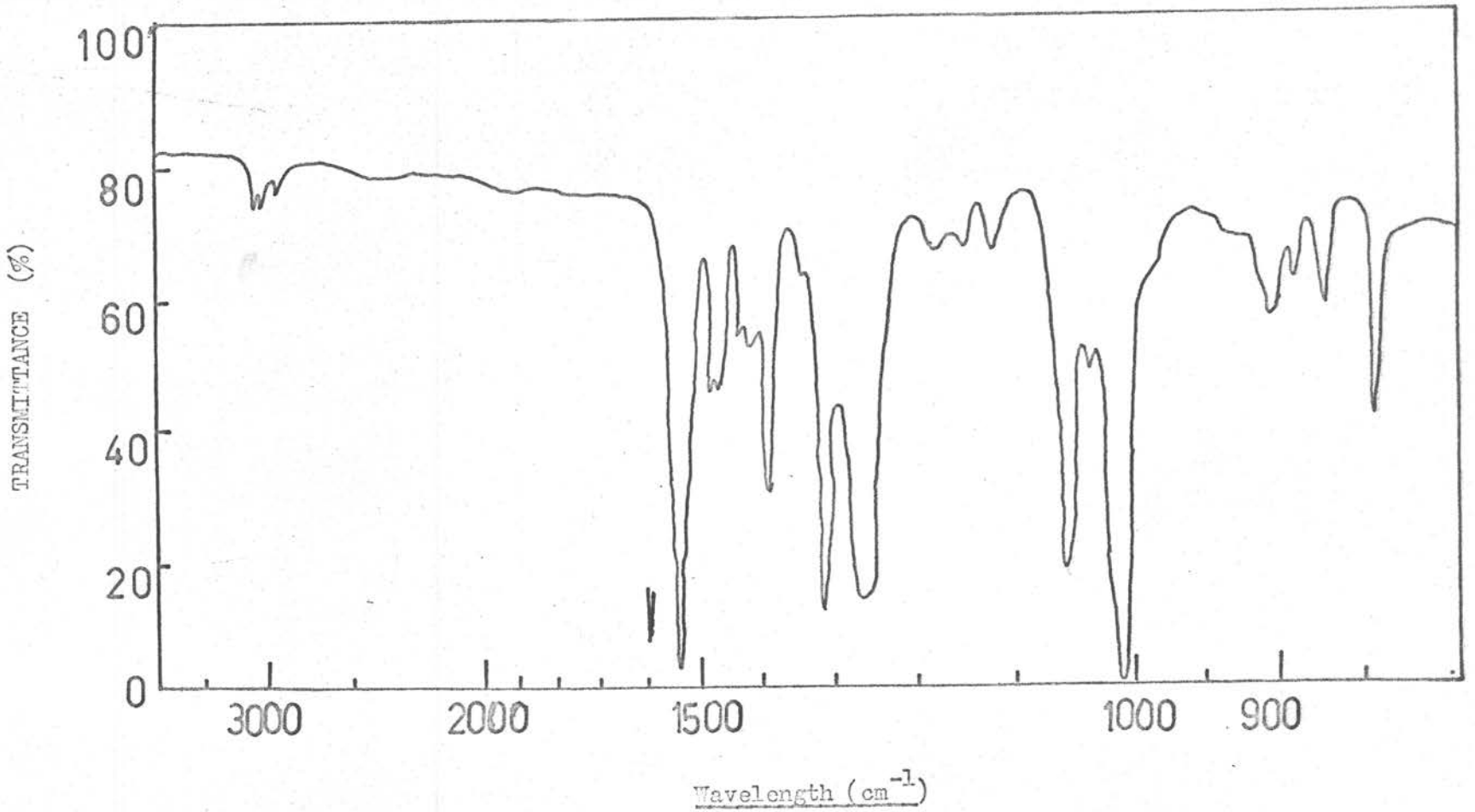

100
80
60
40
20
0
TRANSMITTANCE (%)
3000
2000
1500
1000
900
Wavelength (cm$^{-1}$)

Fig. 20

ms-Tetra(o-methoxyphenyl)porphin -

A mixture of o-methoxybenzaldehyde (100 g.), anhydrous zinc acetate (49 g.), pyrrole (49 g.), and anhydrous pyridine (98 ml.) was heated in a stainless steel autoclave (capacity 700 ml.) at 170° for 48 hr. The resulting tar was dissolved in pyridine (1 l.) and diluted with aqueous methanol (80%, 4.5 l.). The insoluble residue was extracted with chloroform and the chloroform solution was evaporated to dryness. The pyridine fraction was filtered, the residue dissolved in chloroform and the chloroform solution evaporated. The solids were combined, heated on a hot-plate (to remove the contaminating pyridine), dissolved in chloroform and the chloroform solution was run onto a bed of alumina (Spence). By eluting with hexane, an orange solution having a green fluorescence was obtained, but on evaporation it yielded only an orange gum. The ultraviolet and visible spectrum (in chloroform) showed $\lambda$ max. 475, 505 mμ. Further elution with benzene gave a purple solution with an intense red fluorescence. Evaporation gave the crude zinc complex (4.4 g., 2.6 %) as a purple solid, whose absorption spectrum showed bands at 424, 515, 554, 593 mμ and indicated 25% zinc chlorin. The zinc complex was dissolved in benzene, allowed to stand overnight and then run onto a column of alumina (Spence). The

benzene-eluted fraction was evaporated to give zinc ms-tetra(o-methoxyphenyl)porphin as purple prisms. (Found: C, 71.1; H, 4.9. $C_{48}H_{36}N_4O_4Zn$ requires C, 72.2; H, 4.6; N, 7.0%). The metal was removed with 12N hydrochloric acid and the free base obtained by washing the benzene solution with ammonium hydroxide. Recrystallization from benzene-methanol gave ms-tetra(o-methoxyphenyl)porphin as purple needles (Found: C, 77.7; H, 5.4. $C_{48}H_{38}N_4O_4$ requires C, 78.4; H, 5.2; N, 7.6%). Its n.m.r. spectrum (in deuterochloroform) showed singlets at τ 1.22, 2.58, 6.45, a doublet at τ 2.70 and multiplets centred at τ 2.0 (1.93, 1.97, 2.02, 2.05, 2.08, 2.13, 2.17) and τ 2.30 (2.25, 2.28, 2.38, 2.40).

Porphyrin Purification Attempts -

(a) Pyrolysis

ms-Tetraphenylporphin -

Crude ms-tetraphenylporphin (0.3 g., containing approximately 10% of the corresponding chlorin) was placed in a glass boat (2 x 20 cm.) half-way along a horizontal tube of Pyrex glass (4 x 110 cm.), the ends of which were plugged with glass wool. Nitrogen, which had been passed through an acidic solution of vanadyl sulphate containing zinc

amalgam, 35N sulphuric acid, and sodium hydroxide, flowed continuously through the system. The boat and its contents were heated by an asbestos-covered heating coil (4 x 20 cm.) to 450° for 30 min. A brown oil collected on the cooler part of the tube approximately 10-15 cm. from the heating coil while long purple needles (0.02 g.) sublimed to a distance of 5 cm. from the coil. The visible absorption spectrum of the sublimed crystals showed peaks at 515, 549, 589, 648 mμ and indicated no contaminating chlorin. The residue (0.2 g.) of purplish-black needles had a visible absorption spectrum with bands at 484, 515, 548, 593 mμ and now appeared to contain only 5% chlorin impurity.

ms-Tetramesitylporphin -

Crude ms-tetramesitylporphin (0.25 g.), containing 10% chlorin impurity, was pyrolysed at 430° under nitrogen for 1 hr. in the above apparatus. A trace of porphyrin sublimed but the majority of the porphyrin decomposed to give a black intractable residue (0.2 g.). The visible spectrum of the sublimed product showed λ max. 515, 546, 585, 633 mμ (rel. intensities 1.3, 1, 1.6, 2.5).

Zinc ms-tetra-o-chlorophenylporphin-

Crude zinc ms-tetra-o-chlorophenylporphin (1 g.) was heated in the above pyrolysis apparatus for 1 hr. at

450°. Decomposition occurred to give a black residue, insoluble in chloroform and a trace of a red compound sublimed. The visible spectrum of the latter compound showed λ max. 418, 446, 497 mμ (rel. intensity, 1, 1.7, 2.4).

Zinc ms-tetraphenylporphin -

Zinc ms-tetraphenylporphin (2.9 g.) containing 1.7% chlorin, was heated in the pyrolysis apparatus at 430° under nitrogen for 3 hr. A purplish-black residue (2.2 g.) remained while some purple crystals sublimed. The visible spectrum of both compounds was identical, showing the characteristic zinc peaks, disappearance of the zinc chlorin peak, and the appearance of a new peak at 468 mμ.

(b) Sublimation -

ms-Tetraphenylporphin (200 mg.), containing 10% chlorin impurity, was sublimed at 420-430° under 0.01 mm. pressure for ½ hr. The product (0.17 g.) contained only 8% chlorin impurity. ms-Tetramesitylporphin sublimed neatly but the chlorin impurity sublimed with it. ms-Tetra-o-chlorophenylporphin sublimed nicely at 250° at 0.05 mm. pressure but so did its contaminating chlorin. Zinc ms-tetra-o-chlorophenylporphin decomposed on attempted sublimation but zinc ms-tetraphenylporphin sublimed without decomposition.

(c) Oxidation -

A solution of ms-tetraphenylporphin (100 mg.), containing 3.3% chlorin, in dry benzene (50 ml.) was treated with a solution of chloranil (30 mg.) in benzene (30 ml.) and the mixture was allowed to stand at room temperature in the dark for 24 hr. The product only contained 3.0% chlorin but prolonged exposure did not cause any reduction in the concentration of chlorin. Zinc ms-tetramesitylporphin was treated in a similar manner and the concentration of its chlorin impurity was likewise virtually unchanged.

## 5.3 The Stepwise Synthesis

Materials -

2,3,4-Trimethyl-5-ethoxycarbonylpyrrole, m.p. 128° (lit.[165] 128°), the sodium acetate complex of diethyloximinomalonate, m.p. 86.5-88° (lit.[166] 87-88°), 2,3,4-trimethylpyrrole, m.p. 39° (lit.[167] 39°), the hydroxymethyleneketone of desoxybenzoin, m.p. 110° (lit.[168] 110°), desoxybenzoin, m.p. 54-57° (lit.[169] 56-58°), potassium 3,4,5-trimethylpyrrole-2-carboxylate[27] and 5,5'-diformyl-3,3',4,4'-tetramethyldipyrromethane[123] were all prepared by literature methods. t-Butyl 2,3,4-trimethylpyrrole-5-carboxylate was a gift from Miss M. Mitchell and 2-($\beta$, $\beta$-dicyanovinyl)-3,4-dimethylpyrrole was a gift from Mr. R.L.N. Harris.

Methods -

Spectroscopic estimations of porphyrin yields were based on comparisons of the intensities of the Soret peaks with the known extinction coefficients or with values estimated from similar compounds.

2-Ethoxycarbonyl-3,4-dimethylpyrrole-5-carboxylic acid -

Ethyl 2,3,4-trimethylpyrrole-5-carboxylate (30 g.) was reacted with sulphuryl chloride (46.8 g.) according to the method of Fischer and Hierneis.[116] 2-Ethoxycarbonyl-3,4-dimethylpyrrole-5-carboxylic acid (3 g., 17%) was obtained as colourless needles, m.p. 243° (lit.[116], 243°) and 2-ethoxycarbonyl-3,4-dimethyl-5-formylpyrrole (2.1 g., 13%) was obtained as a brown powder m.p. 100-104° (lit.[116], 108°). The infrared spectrum of the latter compound, determined as a Nujol mull, showed carbonyl frequencies at 1650 and 1680 cm.$^{-1}$.

Ethyl 3,4-dimethylpyrrole-2-carboxylate -

(a) Modification of Kleinspehn's[117] method (without isolating diethyloximinomalonate)

A solution of redistilled diethylmalonate (120 g.) in glacial acetic acid (135 g.) was stirred vigorously at 0-5° while a solution of sodium nitrite (142.5 g.) in water

(250 ml.) was added dropwise during 3 hr. The mixture was stirred for a further 20 hr. and allowed to separate into two layers. The lower aqueous layer was discarded and the upper layer, containing the required diethyloximinomalonate, used. To this layer (100 ml.) were added the sodium salt (70 g.) of 3-formylbutan-2-one[170] and a solution of glacial acetic acid (250 ml.) in water 100 ml.). The mixture was then warmed slowly to 95° during which it became homogenous. Between the limits of 95° and 110°, zinc dust (110 g.) was added over a period of 70 min. The mixture was then heated at 100-105° with continuous stirring for a further 1 hr. and then poured into ice-water. The mixture was left in the refrigerator overnight, filtered, and the residue dissolved in hot ethanol. The contaminating zinc dust was removed by filtration, and the mother liquor poured into ice-water. The crude product (19 g., 23%) was thus obtained as a colourless solid, m.p. 68-84° which rapidly turned pink on exposure to air. Subsequent recrystallization, once with absolute ethanol and twice with 2,2,4-trimethylpentane, gave ethyl 3,4-dimethylpyrrole-2-carboxylate as colourless needles, m.p. 93-95° (lit.[117] 94-95°).

(b) <u>Modification of Kleinspehn's method</u> (<u>via</u> sodium acetate complex of diethyloximinomalonate.)

Glacial acetic acid (116 ml.) was mixed with the

sodium salt (28 g.) of 3-formylbutan-2-one[170] in a 250 ml. 3-necked flask fitted with a thermometer and stirrer. The mixture was slowly heated to 85°, and the sodium acetate complex (49.6 g.) of diethyloximinomalonate together with a solution of glacial acetic acid (48 ml.) in water (20 ml.) were added. Between the limits of 95° and 105°, zinc dust (44 g.) was introduced in small portions. The reaction mixture was then heated and stirred for a further 30 min. Ethyl 3,4-dimethylpyrrole-2-carboxylate (7.1 g., 21%) was then isolated and purified as in (a).

2-t-Butoxycarbonyl-3,4-dimethylpyrrole-5-carboxylic acid -

t-Butyl 2,3,4-trimethylpyrrole-5-carboxylate (20 g.) was dissolved in anhydrous ether (1 l.) at room temperature. Sulphuryl chloride (26 g.) was added cautiously. The flask was closed with a calcium chloride tube and allowed to stand overnight. Removal of the ether gave a thick residue which was extracted with alcohol/water (1:1). The filtered solution was then shaken four times with ether and the ethereal extract washed with water, 1% sodium hydroxide solution (twice) and water. The dried solution was evaporated to dryness and the residue extracted with warm water containing a drop of alcohol.

The mixture was kept in the refrigerator overnight and the product then collected, taken up in ethanol, and the solution poured into ice-water. Brown needles (0.007 g., m.p. 85-95°) were obtained. The infrared spectrum had absorption peaks at 3300 cm.$^{-1}$ and 1650 cm.$^{-1}$ with a shoulder at 1680 cm.$^{-1}$. By analogy with the preparation of 2-ethoxycarbonyl-3,4-dimethylpyrrole-5-carboxylic acid, this substance was probably t-butyl 3,4-dimethyl-5-formylpyrrole-2-carboxylate.

To the above sodium hydroxide extract which had been cooled to -10°, 6N hydrochloric acid was added dropwise with stirring until neutrality (Congo red paper) was achieved. The temperature was kept below 5°. After brief standing the product was collected, washed free of mineral acid, dried in a vacuum desiccator over potassium hydroxide and stored in the dark. 2-t-Butoxycarbonyl-3,4-dimethylpyrrole-5-carboxylic acid (1.5 g., 7%) crystallized from aqueous ethanol and formed colourless needles, m.p. 212°. (Found: C, 60.7; H, 7.3; N, 6.1. $C_{12}H_{17}O_4N$ requires C, 60.2; H, 7.2; N, 5.9).

Attempted preparation of Ethyl 3,4-diphenylpyrrole-2-carboxylate -

A mixture of the hydroxymethyleneketone of desoxybenzoin (4 g.) and glacial acetic acid (10 ml.) was

heated to 85°, and the sodium acetate complex (6.6 g.) of diethyloximinomalonate together with glacial acetic acid (3 ml.) in water (2 ml.) were added. Between the limits of 95-105°, zinc dust (3 g.) was added in small portions. The reaction mixture was then heated and stirred for a further 15 min. On pouring into water (170 ml.), a yellow oil separated. The oil was extracted with chloroform, and the chloroform solution was dried and evaporated. The product was distilled to give a pale yellow solid, b.p. 112°/1 mm. Recrystallization from petroleum ether gave desoxybenzoin as yellow plates m.p. 55-57° (lit.[169] 56-58°). The infrared spectrum of the compound, determined as a Nujol mull, was identical with that of an authentic sample.

Diethyl ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylate -

Recrystallized ethyl 3,4-dimethylpyrrole-2-carboxylate (5.2 g., 0.03 ml.) was dissolved in absolute ethanol (10 ml.), and acetaldehyde (4.0 ml., 0.07 mol.) was added at room temperature. 12N Hydrochloric acid (0.2 ml.) was then added and the mixture heated under reflux for 30 min., using an efficient condenser. A drop of the reaction mixture was removed and rubbed with a stirring rod to induce crystallization. The small crystals obtained were used as seeds in the reaction mixture, which was refrigera-

ted overnight. Diethyl ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylate (4.6 g., 85%) crystallized from ethanol as colourless needles, m.p. 153-155°. (Found: C, 66.6; H, 7.9; N, 7.8. $C_{20}H_{28}N_2O_4$ requires C, 66.6; H, 7.8; N, 7.8%).

Diethyl ms-phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate -

A mixture of ethyl 3,4-dimethylpyrrole-2-carboxylate (1 g.), benzaldehyde (1 ml.), absolute ethanol (2 ml.) and 11N hydrochloric acid (0.1 ml.) was heated under reflux on a water bath. A white solid separated almost immediately. After cooling, the solution was filtered and the solid obtained was extracted with hot water to remove contaminating benzoic acid. After two recrystallizations from ethanol, diethyl ms-phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate (1.2 g., 95%) formed colourless prisms m.p. 199-201° (Found: C, 71.3; H, 7.1; N, 6.5. $C_{25}H_{30}N_2O_4$ requires C, 71.1; H, 7.2; N, 6.6).

Benzyl 3,4-dimethylpyrrole-2-carboxylate -

A mixture of ethyl 3,4-dimethylpyrrole-2-carboxylate (13.4 g.), redistilled benzyl alcohol (40 ml.), and sodium (0.2 g.) was heated on a boiling water-bath under reduced pressure (16 mm.), for 4 hr. The excess benzyl

alcohol was removed by distillation under reduced pressure (0.1 mm.), and a brown glass remained. The ethereal extract (500 ml.) of this residue was washed with water, dried over anhydrous magnesium sulphate, and evaporated to dryness. On washing with hexane, the crude product (14.6 g., 79%) was obtained as brownish-white needles. Recrystallization from hexane gave benzyl 3,4-dimethylpyrrole-2-carboxylate as colourless needles, m.p. 73-74° (Found: C, 73.4; H, 6.7; N, 6.2. $C_{14}H_{15}NO_2$ requires C, 73.3; H, 6.6; N, 6.1%). In another experiment, distillation was used to purify the benzyl ester, which had b.p., 152°/0.05 mm.

Dibenzyl ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylate -

(a) Diethyl ms-3,3'-4,4'-pentamethyldipyrromethane-5,5'-dicarboxylate (2 g., 0.006 mol.) was dissolved in redistilled benzyl alcohol (20 ml., 0.19 mol.) on a boiling water-bath. Sodium (0.13 g., 0.006 mol.) was added, and the mixture heated at 100° under reduced pressure (16 mm.) for 4 hr. The excess benzyl alcohol was removed by distillation under reduced pressure, and a brown glossy residue was obtained. The ether extract (200 ml.) of this gum was washed with water, dried over anhydrous magnesium sulphate and evaporated to dryness. On washing with hexane, dibenzyl

ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylate (1.5 g., 56%) was obtained as a pale pink powder, m.p. 156-157°, (mixed m.p. with diethyl ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylate, 139-141°). Recrystallization from ethanol gave colourless needles, m.p. 158.5-160° (Found: C, 74.6; H, 6.7; N, 6.1. $C_{30}H_{32}N_2O_4$ requires C, 74.4; H, 6.7; N, 5.8%).

(b) The above dibenzyl ester was also prepared from benzyl 3,4-dimethylpyrrole-2-carboxylate (2.5 g.) by a method analogous to that employed in the preparation of the diethyl ester. It was not necessary to seed the reaction mixture, as it crystallized on cooling. The dibenzyl ester (2.65 g., 100%) was obtained as colourless needles, m.p. 152-160°. One recrystallization from ethanol gave colourless needles, m.p. 157-160°.

Dibenzyl ms-phenyl-3,3'-4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate -

A mixture of benzyl 3,4-dimethylpyrrole-2-carboxylate (0.25 g., 0.001 mol.), redistilled benzaldehyde (0.058 g., 0.0005 mol.), absolute ethanol (3 ml.) and 11N hydrochloric acid (0.1 ml.) was heated under reflux on a water-bath for 30 min. Seed crystals were obtained by removal of a drop of the reaction mixture and scratching.

These were added to the reaction mixture which was then refrigerated overnight. Dibenzyl ms-phenyl 3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate (0.29 g., 97%) was obtained as a pink powder, m.p. 145-148°. On recrystallising four times from ethanol and twice from methanol, colourless prisms m.p. 148-150° were obtained. (Found: C, 77.0; N, 6.3; N, 5.4. $C_{35}H_{34}N_2O_4$ requires C, 76.9; H, 6.3; N, 5.1).

Dibenzyl 3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate -

A mixture of benzyl 3,4-dimethylpyrrole-2-carboxylate (0.4 g.), paraformaldehyde (0.4 g.), absolute ethanol (5 ml.) and 11N hydrochloric acid (0.1 ml.) was heated under reflux on a water-bath for 30 min. The product was isolated as in the previous example. Dibenzyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate (0.36 g., 88%) crystallized from ethanol as colourless needles, m.p. 182-184° (lit.[41], 179°) (Found: C, 74.3; H, 6.4; N, 6.2. Calc. for $C_{29}H_{30}N_2O_4$: C, 74.0; H, 6.4; N, 6.0). Its n.m.r. spectrum (carbon tetrachloride) showed singlets at τ 8.05, 7.82 (methyl), 6.33 (ms-methylene), 4.88 (benzyl $CH_2$), 2.87 (aromatic), and -0.10 (NH) in agreement with the structure assigned.

ms-Phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylic acid -

(a) 10% Sodium hydroxide (16 ml.) was added slowly over 1 hr. to a suspension of diethyl ms-phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate (5 g.) in ethanol (400 ml.), which was then heated under reflux for 6 hr. On cooling, the sodium salt (4.0 g.) precipitated as pale pink prisms. The acid was obtained by bubbling in sulphur dioxide to an aqueous solution of the sodium salt. ms-Phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylic acid crystallized from deaerated acetone-hexane as pale pink prisms, m.p. 175° (decomp.)

(b) Dibenzyl ms-phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate (8.2 g.) in methanol (400 g.) was hydrogenated over 5% palladium charcoal (0.8 g.). The solution was filtered, the residue extracted with 10% sodium hydroxide and the acid precipitated with glacial acetic acid. The diacid (5.5 g., 100%) was obtained as pale pink amorphous solid.

ms-3,3',4,4'-Pentamethyldipyrromethane-5,5'-dicarboxylic acid -

(a) A solution of sodium hydroxide (3 g.) in water (30 ml.) was added dropwise during 6 hr. to a solution of diethyl ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-

dicarboxylate (9 g.) in ethanol (200 ml.)(95%), which was being heated under reflux. The heating was continued for 1 hr. after the addition was complete. During the saponification, a colourless precipitate slowly formed. The mixture was cooled to 0° and the residue, obtained by filtration, was dried in a vacuum desiccator over sodium hydroxide. More product was obtained by treatment of the mother liquor with ether. Disodium ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylate tetrahydrate crystallized from water/ethanol (1:5) as colourless plates, which had no definite m.p. (Found: C, 45.5; H, 6.1; N, 6.6. $C_{16}H_{26}N_2O_8Nc_2$ requires C, 45.7; H, 6.3; N, 6.7). Attempts to obtain a satisfactory analysis for the anhydrous compound were unsuccessful.

The disodium salt tetrahydrate (1 g.) was dissolved in water (20 ml.) and sulphur dioxide was bubbled into the solution until no more solid precipitated. The resulting yellow solid (0.8 g., 97%) was washed with water and dried under vacuum over sodium hydroxide. The acid, m.p. 151-153° turned pink on exposure to light and air. Attempts to isolate the acid by precipitation with mineral acids resulted in lower yields and cruder products, even at 0°, but glacial acetic acid gave reasonable yields of comparatively pure ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylic acid.

(b) Dibenzyl ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylate (2.05 g.) in methanol (400 ml., redistilled from potassium hydroxide) was hydrogenated over 5% palladium charcoal (0.3 g.) at room temperature and pressure for 12 hr. The catalyst was removed, and the filtrate evaporated to dryness under reduced pressure. The pale pink diacid (1.26 g., 98%) identical in m.p. and infrared spectrum with the product from (a), was not purified further before use.

3,3',4,4'-Tetramethyldipyrromethane-5,5'-dicarboxylic acid -

The acid, m.p. 196° (lit.[41], 196-198°) was prepared from its dibenzyl ester by hydrogenation in ethyl acetate, as described by Kenner et al.[41] Methanol (redistilled from potassium hydroxide) was found also to be an effective solvent.

Attempted preparation of 5,5'-diiodo-ms-3,3',4,4'-pentamethyldipyrromethane -

ms-3,3',4,4'-Pentamethyldipyrromethane-5,5'-dicarboxylic acid (0.07 g.) was dissolved in 5% potassium bicarbonate solution (10 ml.) and to this solution, iodine (0.067 g.) in potassium iodide solution was added dropwise. Nitrogen was passed into the mixture throughout. The iodine colour quickly disappeared and a black precipitate was obtained. The mixture was extracted with ether (80 ml.)

and the dried ethereal solution ($MgSO_4$) was evaporated. The infrared spectrum of the product indicated a new carbonyl peak at 1740 $cm.^{-1}$ as well as the original carbonyl peak, which occurred at 1660 $cm.^{-1}$.

Attempted preparation of ms-3,3',4,4'-pentamethyldipyrromethane -

(a) A mixture of ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylic acid (0.05 g.) and ethanolamine (1 ml.) was heated under nitrogen at 120° for 1 hr. The reaction mixture was poured into deaerated water, into which nitrogen was bubbling, and extracted with ether. The dry ether was removed by bubbling in nitrogen. The infrared spectrum of the product showed a strong carbonyl peak at 1660 $cm.^{-1}$.

(b) A mixture of disodium ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylate tetrahydrate (0.2 g.), water (5 ml.), 10% sodium hydroxide solution (2.5 ml.) and hydrazine (0.1 ml.) was heated at 150° in a sealed Teflon tube for $4\frac{1}{2}$ hr. The contents of the tube were poured into deaerated water and the mixture was extracted with benzene. The dried benzene ($K_2CO_3$) was evaporated to give an oil, the infrared spectrum of which showed a carbonyl band at 1660 $cm.^{-1}$.

(c) The product from attempted iodinative decarboxylation of ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylic acid in ethanol (95%) was hydrogenated over 10% palladium charcoal for 15 hr., in the presence of magnesium oxide. The catalyst was removed, and evaporation of the solvent under reduced pressure under nitrogen yielded a black tar.

Standardization of a solution of bromine in acetic acid -

The concentration of bromine was determined by titration of the iodine liberated, on addition of potassium iodide, against sodium thiosulphate solution prepared from the anhydrous analytical reagent, using starch solution as indicator.

ms-Phenyl-5,5'-dibromo-3,3',4,4'-tetramethyldipyrromethene -

Dibenzyl ms-phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate (1 g., 0.0018 mol.) in Analar acetic acid (60 ml.) was hydrogenated over 5% palladium charcoal for 8 hr. The catalyst was removed, and a standardized solution (10.8 ml.) of bromine (0.0068 mol.) in acetic acid was added. The solution was warmed for a few minutes and, after standing for 30 min., poured into water. The chloroform extract was washed with ammonium

hydroxide (0.880) and water. Evaporation of the solvent gave an orange powder, which was dissolved in benzene-hexane, and the solution was run onto a short column of alumina (grade IV, acid-washed). Elution with hexane (containing a trace of benzene) gave an orange solution, which gave the free base (0.254 g., 31%) on evaporation of the solvent. ms-Phenyl-5,5'-dibromo-3,3',4,4'-tetramethyldipyrromethene recrystallized twice from pyridine-water and once from hexane as red needles with a green reflex, which decomposed at 200° but did not melt below 250° (Found: C, 53.0; H, 4.1; N, 6.3; Br, 37.0. $C_{19}H_{18}N_2Br_2$ requires C, 52.6; H, 4.2; N, 6.5; Br, 36.8%). In another experiment with the same ratio of bromine to diacid, but on half the scale, the methene (0.174 g.) was obtained in 44% yield; but, when the ratios of bromine to methane were 3:1 and 6:1, the yields were drastically reduced. The hydrobromide was readily prepared by treatment of an ethanolic solution of the dipyrromethene with hydrobromic acid.

Attempted preparation of ms-phenyl-3,3',4,4'-tetramethyldipyrromethane -

(a) To a stirred solution of disodium ms-phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylate (1.35 g.) and potassium bicarbonate (1.5 g.) in water (60 ml.) was added slowly iodine (0.7 g.) in potassium iodide solution (25 ml.).

The iodine colour disappeared quickly and a precipitate formed. The dried product (1.16 g.) was a brown amorphous powder, with no definite m.p. It was unstable in solution, particularly to heat. Attempted recrystallization from aqueous ethanol under reduced pressure gave a pale pink powder, whose infrared spectrum showed a broad carbonyl peak at 1650 $cm.^{-1}$ The crude product in ethanol was hydrogenated over 5% palladium charcoal in the presence of magnesium oxide. Removal of the catalyst and solvent gave a green powder. A benzene solution of this product was run onto short columns of alumina (grade I and grade IV). Elution with benzene gave a number of bands, but evaporation of the solvent from the various products yielded oils, all the infrared spectra of which had bands at 3400-3500 and 1660-1680 $cm.^{-1}$.

(b) A mixture of meso-phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylic acid (1.3 g.) and ethanolamine (5 ml.) was heated under reflux for 1 hr. The cooled mixture was poured into water (400 ml.) and extracted thrice with benzene. The dried, concentrated benzene solution ($Mg\ SO_4$) was run onto a column of alumina (grade I). Elution with benzene/chloroform (1:1) gave a number of fractions, which on evaporation yielded oils. The infrared spectra of these fractions, determined in chloroform solution

in a 0.2 mm. cell, showed no bands in the region 3,300-3,500 cm.$^{-1}$ and strong bands at 1700 cm.$^{-1}$. Further elution with chloroform gave samples whose infrared spectra were identical with authentic starting material.

(c) A suspension of ms-phenyl-5,5'-dibromo-3,3',4,4'-tetramethyldipyrromethene (100 mg.) in methanol (100 ml., 95%) was stirred magnetically with 2% sodium amalgam (fresh amount each hour) for 5 hr. The orange colour gradually disappeared. The mixture was poured into water and extracted with chloroform. The solvent was removed at 0° to give an oily solid, which gave a positive Ehrlich's test. The infrared spectrum of the product, determined as a Nujol mull, showed strong bands at 3400 (approx.) and 1680 cm.$^{-1}$.

Attempted preparation of ms-Phenyl-5,5'-bis( $\beta,\beta$-dicyanovinyl)-3,3',4,4'-tetramethyldipyrromethane-

A mixture of 2-( $\beta,\beta$-dicyanovinyl)-3,4-dimethylpyrrole (0.05 g.), benzaldehyde (0.02 g.), ethanol (25 ml.) and 10N hydrochloric acid (0.02 g.) was heated under reflux for 2 hr. The product, obtained on filtration had m.p. 225°, which was identical with the starting material. Admixture of the two caused no depression of m.p.

3,4,5-Trimethylpyrrole-2-carboxylic acid -

Acidification of a cold aqueous solution of the potassium salt of 3,4,5-trimethylpyrrole-2-carboxylic acid with 6N hydrochloric acid gave the acid as a white precipitate. The residue was washed with water and dried *in vacuo* over potassium hydroxide. The pyrrole acid was obtained as a pale pink powder, which was not purified further.

Zinc complex of ms-3,3',4,4',5,5'-heptamethyldipyrromethene -

A mixture of 3,4,5-trimethylpyrrole-2-carboxylic acid (2.2 g.), glacial acetic acid (2 ml.) and redistilled acetyl chloride (2 ml.) was heated in a water-bath until hydrogen chloride evolution ceased (1 hr.). The red solution was cooled, diluted with water (100 ml.) and neutralized with 2N ammonium hydroxide. To a solution of the resulting yellow solid in ethanol (25 ml.) was added a saturated solution of zinc acetate in ethanol (10 ml.) and one drop of 0.880 ammonia. The mixture was then warmed for 5 min. On cooling, the zinc complex of the pyrromethene (0.5 g., 25%) separated as orange needles with a green metallic sheen. After crystallization from chloroform-methanol, the zinc complex sintered at 260°, but did not melt below 300°. (lit.[89], 288° after sintering at 260°). (Found: N, 10.2. Calc. for $C_{32}H_{42}N_4Zn$: N, 10.2). The

ultraviolet spectrum of the complex agreed with the published spectrum.[89]

ms-Phenyl-3,3',4,4',5,5'-hexamethyldipyrromethene -

A mixture of potassium 3,4,5-trimethylpyrrole-2-carboxylate (5 g.), glacial acetic acid (10 ml.) and benzoyl chloride (5 ml.) was heated under reflux for 90 min. after the initial vigorous evolution of hydrogen chloride. The dark red solution was poured into water. The benzene extract of this mixture was washed with ammonium hydroxide, then water, and evaporated to dryness. The product was dissolved in benzene-hexane (1:1) and run onto a column of alumina (acid-washed, grade IV). On elution with benzene, a solution of 2-benzoyl-3,4,5-trimethylpyrrole was first obtained (See following chapter). Further elution with benzene gave a yellow solution which had the property of staining red. On evaporating this to dryness, crude ms-phenyl-3,3',4,4',5,5'-hexamethyldipyrromethene (1.75 g., 44%) was obtained as a green solid and on recrystallization from hexane, it formed dark-green plates, m.p. 193-195° (Found: C, 82.7; H, 8.1; N, 9.6. $C_{21}H_{24}N_2$ requires C, 82.9; H, 8.0; N, 9.2%).

5,5'-Diformyl-ms-3,3',4,4'-pentamethyldipyrromethane -

Freshly prepared ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylic acid (0.76 g.) was suspended in

ethylene chloride (20 ml.), and N,N-dimethylformamide (0.6 ml.), and phosphorus oxychloride (0.6 ml.) were added. The mixture was warmed gently on a steam-bath until reaction commenced, and then allowed to stand for 9 hr. The solvent was removed under reduced pressure, and the residue treated with hot water until the filtrate was colourless. Addition of sodium hydroxide (10%) to the aqueous filtrate precipitated the crude aldehyde (0.391 g., 58%), which was dissolved in acetone and passed through a short column of charcoal/Celite (1:1). The colourless solution obtained was evaporated to give the product. 5,5'-Diformyl-ms-3,3',4,4'-pentamethyldipyrromethane crystallized from acetone-hexane as colourless needles, which decomposed at approx. 260°. (Found: C, 70.3; H, 7.4; N, 10.4. $C_{16}H_{20}N_2O_2$ requires C, 70.6; H, 7.4; N, 10.3%).

5,5'-Diformyl-ms-phenyl-3,3',4,4'-tetramethyldipyrromethane -

Dry, freshly-prepared ms-phenyl-3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylic acid (2.5 g.) was suspended in ethylene chloride (60 ml.) and N,N-dimethylformamide (1.3 ml.) and phosphorus oxychloride ( 1.3 ml.) were added. The mixture was warmed gently until reaction commenced and then kept at room temperature for 12 hr. The solvent was removed under reduced pressure to give a green gum, which was extracted with hot water

until the washings were colourless. The crude aldehyde (0.36 g., 16%) was precipitated with aqueous sodium hydroxide, but could not be obtained crystalline.

*a*-Phenyl-1,2,3,4,5,6,7,8-octamethylporphin -

A mixture of *mg*-phenyl-5,5'-dibromo-3,3',4,4'-tetramethyldipyrromethene hydrobromide (0.106 g.), 3,3',4,4',5,5'-hexamethyldipyrromethene hydrobromide (0.046 g.) and succinic acid (3 g.) was ground in a mortar. The mixture was dried at 20° under high vacuum for 5 hr., and heated at 190° (oil-bath) for 20 min. On cooling, the reaction mixture was extracted with chloroform, and then with nitrobenzene. No trace of porphyrin was detected in the chloroform extract. The nitrobenzene extract was diluted with chloroform, and run onto a column of alumina (Spence). Elution with chloroform gave a solution, which exhibited a strong red fluorescence, but its visible spectrum showed a strong band at 488 mμ and a smaller peak at 404 mμ. (Assuming the latter to be the Soret peak and, assuming its extinction coefficient was 15,000, it was calculated that 4 mg. (4%) of porphyrin was present.) The solvent was evaporated and the residue extracted with ethanol. The visible spectrum of the residue in chloroform had an intense peak at 404 mμ and bands at 504, 536, 571, and 624 mμ in decreasing order of intensity (aetio spectrum).

1,2,3,4,5,6,7,8-Octamethylporphin -

(a) 3,3',4,4'-Tetramethyldipyrromethane-5,5'-dicarboxylic acid (0.029 g.) and 5,5'-diformyl-3,3',4,4'-tetramethyldipyrromethane (0.026 g.) were dissolved separately in warm acetic acid (10 ml. each), cooled, and then combined. To the mixture, a solution of hydriodic acid (0.3 ml.) in acetic acid (10 ml.) was added. The volume of acetic acid was made up to 50 ml., the mixture was allowed to stand for 15 min., and then divided into two parts. To one portion, cupric acetate (50 mg.) in acetic acid was added and the mixture was allowed to stand overnight. The filtrate was poured into water and extracted with chloroform, while the residue was extracted (Soxhlet) with chloroform. The chloroform extracts were combined and shown spectroscopically to contain copper octamethylporphin (0.7 g., 3%), $\lambda$ max. 402, 528, 566 mμ (lit.[91], 399, 527, 563 mμ).

To the other portion, sodium acetate (1 g.) in acetic acid (10 ml.) was added and the mixture was aerated for 48 hr. After evaporation of the solvent, the residue was extracted (Soxhlet) with chloroform and shown spectroscopically to contain octamethylporphin (0.9 mg., 4%), $\lambda$ max. 400, 499, 533, 566, 592, 621 mμ (lit.[102], 399, 500

532, 565, 594, 621 mμ).

(b) A mixture of 5,5'-diformyl-3,3',4,4'-tetramethyldipyrromethane (0.194 g.), 3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylic acid (0.128 g.), methanol (50 ml.) and perchloric acid (30 ml.) was heated under reflux for 4 hr. and then allowed to stand overnight. Filtration gave a black solid (93 mg.). Visible absorption (in chloroform): λ max. 396, 416 and 447 mμ. To the filtrate was added copper formate (700 mg.) in water and the mixture was kept at 40° for 24 hr. Filtration gave a purple powder (130 mg.), shown spectroscopically to contain 41% copper octamethylporphin ( λ max. (in chloroform) 401, 524, 562 mμ). The filtrate was evaporated to dryness, and the residue was washed with ammonium hydroxide, water, conc. sulphuric acid, water, ammonium hydroxide, and water. The chloroform extract (Soxhlet) was shown spectroscopically to contain octamethylporphin (20 mg.) (λ max. 401, 502, 534, 567, 594, 622). The overall yield of porphyrin was 21%.

(c) Copper octamethylporphin was also prepared in 50% yield by the action of aqueous copper formate on 3,3',4,4'-tetramethyldipyrromethane-5,5'-dicarboxylic acid in formic acid, according to the method of Badger *et al.*[102]

α , γ-1,2,3,4,5,6,7,8-Decamethylporphin -

(a) ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylic acid (115 mg.) and 5,5'-diformyl-ms-3,3',4,4'-pentamethyldipyrromethane (110 mg.) were separately dissolved in warm acetic acid, cooled and mixed. A solution (10 ml.) of hydriodic acid (0.6 ml.) in acetic acid and the volume of acetic acid was increased to 50 ml. Nitrogen was bubbled in for 15 min. The solution turned deep red, and a green solid (152 mg.), m.p. 300°, precipitated. The compound was decomposed on alumina (Spence) and attempts at recrystallization resulted in gums. The infrared spectrum (in Nujol) is shown in Fig. 21. The visible spectrum (in chloroform) showed two very broad overlapping peaks at 454 and 501 mμ. A new peak at 410 mμ appeared on aeration of a chloroform-o-dichlorobenzene solution of the compound (10 mg.). Assuming this to be a Soret band, however, the yield of porphyrin was estimated as 0.4 mg. only. The addition of iodine in chloroform to a chloroform solution of the green compound caused no noticeable effect on the visible spectrum; but when an acetic acid/chloroform solution of the compound was treated with aqueous copper formate solution, new bands appeared at 414 and 504 mμ.

In another experimant using the diacid (23 mg.) and the dialdehyde (20 mg.), the reaction mixture was allowed to

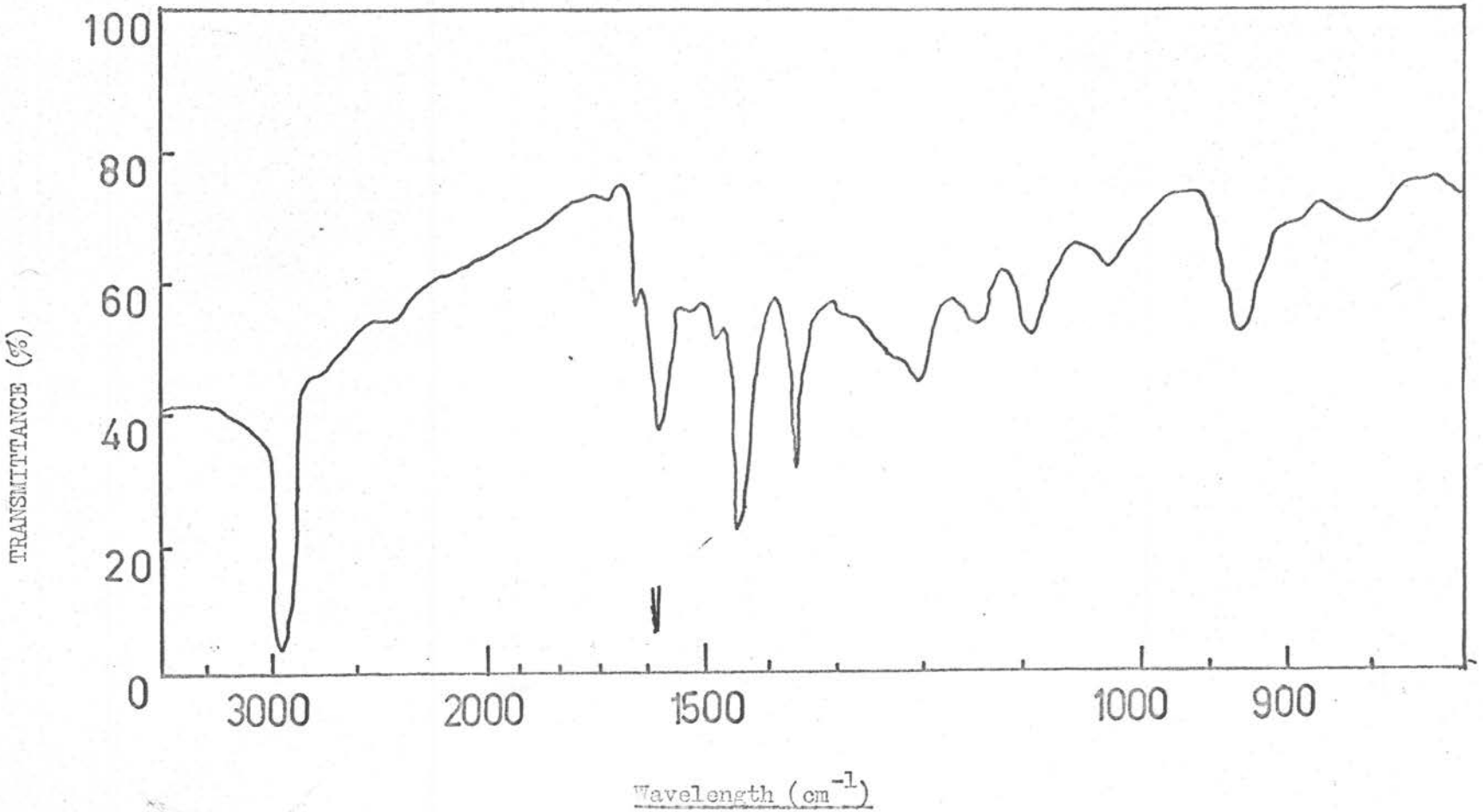

100
80
60
40
20
0
TRANSMITTANCE (%)
3000
2000
1500
1000
900
Wavelength (cm-1)

Fig. 21

stand for 1 hr. after the addition of the hydriodic acid. Then anhydrous sodium acetate (1 g.) in acetic acid (15 ml.) was added, and the solution was aerated for 72 hr., light being excluded. The combined chloroform extracts of the residue (Soxhlet) and filtrate were run onto a short column of alumina (Spence), and eluted with chloroform. The red fluorescent solution was shown spectroscopically to contain decamethylporphin (1.3 mg., 4%). A purer sample was obtained by chromatography on alumina (Spence) in chloroform. $\lambda$ max. 410, 511, 541, 580, 631 mμ (lit.[41] (in benzene) 416, 512, 547, 584, 632 mμ.)

When copper acetate was used as the oxidizing agent, a 4% yield of copper decamethylporphin was estimated on the basis of the band at 414 mμ.

(b) A mixture of dialdehyde (20 mg.), diacid (23 mg.), methanol (50 ml.) and 12N hydrochloric acid (1 ml.) was heated under reflux for 4 hr. On cooling, the solution was aerated for 72 hr. Spectroscopic estimation (in chloroform) indicated a 7% yield of porphyrin. In parallel experiments with hydriodic acid, hydrobromic acid and perchloric acid (0.3 ml. each), yields of 20, 16 and 34% respectively were estimated. The sample from the perchloric acid fraction was purified on alumina and its chloroform solution showed bands at 413, 513, 542, 582 and 632 mμ.

In another experiment, a mixture of dialdehyde (300 mg.), diacid (335 mg.), methanol (500 ml.) and perchloric acid (4.5 ml.) were heated under reflux for 4 hr. and allowed to stand overnight. Copper formate (1.5 g.) in water (50 ml.) was added and the mixture was kept at 40° for 24 hr. Filtration gave a purple-black solid (159 mg.), which was shown spectroscopically to be 35% pure. The overall yield of porphyrin copper complex was 10%. The crude solid was purified by extraction with ethanol and chloroform (Soxhlet). Copper α,γ -1,2,3,4,5,6,7,8-decamethylporphin crystallized from chloroform as purple needles (Found: C, 68.9; H, 6.2; N, 11.6. $C_{30}H_{32}N_4Cu$ requires C, 70.3; H, 6.3; N, 10.9%) λmax. (in chloroform) 414, 545, 573 mμ.

(c) ms-3,3',4,4'-pentamethyldipyrromethane-5,5'-dicarboxylic acid (50 mg.) was suspended in formic acid (90%, 5 ml.) at 40° overnight. A solution (2 ml.) of copper formate (100 mg.) in water was added and the mixture was kept at 40° for 5 hr. The yield of porphyrin copper complex was estimated spectroscopically to be 14%, but the product was probably a mixture as it had two Soret peaks at 402 and 416 mμ.

(d) A mixture of the dialdehyde (20 mg.), the diacid (40 mg.), and formic acid (20 ml.) was kept at 40° overnight. Copper formate (120 mg.) in water (2 ml.) was added and the

mixture kept at 40° for 5 hr. The porphyrin yield was estimated as 5.2 mg. but again two Soret peaks at 402 and 416 mμ were observed.

Copper α,γ-Diphenyl-1,2,3,4,5,6,7,8-octamethylporphin -

A mixture of 5,5'-diformyl-ms-phenyl-3,3',4,4'-tetramethyldipyrromethane (226 mg.), ms-phenyl-3,3',4,4'-tetramethyl-5,5'-dicarboxylic acid (248 mg.), methanol (500 ml.) and perchloric acid (3 ml.) were heated under reflux for 6 hr. Copper formate (1.2 g.) in water (40 ml.) was added and the mixture kept at 40° for 24 hr. Filtration gave a reddish purple powder (25 mg., 6%). Recrystallization from chloroform-methanol (Soxhlet) gave copper α,γ-diphenyl-1,2,3,4,5,6,7,8-octamethylporphin as purple needles (Found: C, ; H, ; N, . $C_{40}H_{36}N_4Cu$ requires C, 75.5; H, 5.7; N, 8.8%). λ max. (chloroform) 405, 535, 571 mμ.

5.4 Benzoylpyrroles -

Materials -

2,4-Dimethylpyrrole, b.p. 53°/0.1 mm. (lit.[171], 72°/25 mm.), 3,4-dimethylpyrrole, b.p. 70-73°/16 mm. (lit.[172],

65-70°/12 mm.), dimethylbenzamide, m.p. 43° (lit.[173], 43°), and 1-benzoylpyrrole-2-aldehyde, m.p. 89° (lit.[149], 90°) were all prepared by literature methods. 2-Carbethoxypyrrole, 2-methylpyrrole, and 2,5-dimethylpyrrole were gifts from Dr. R.A. Jones, pyrrole-2-aldehyde was a gift from Mr. J.A. Lindner, and benzyl 5-benzoyl-3,4-dimethylpyrrole-2-carboxylate was supplied by Dr. A.D. Ward.

Ethyl 2,4-Dimethylpyrrole-3-carboxylate -

2,4-Dimethylpyrrole-3-ethoxycarbonylpyrrole-5-carboxylic acid was prepared from 2,4-diethoxycarbonyl-3,5-dimethylpyrrole according to the procedure of Filippovich et al.[174] The pyrrole acid was decarboxylated using ethanolamine, and ethyl 2,4-dimethylpyrrole-3-carboxylate was obtained as light, biscuit-coloured needles m.p. 73-74° (lit.[175], 75-76°).

2-Benzoyl-3,4,5-trimethylpyrrole -

(a) The first fraction obtained when the crude reaction product from the preparation of ms-phenyl-3,3',4,4',5,5'-hexamethyldipyrromethene (See previous chapter) was chromatographed on alumina in benzene, was a yellow solution which did not stain red. Removal of the solvent gave the crude pyrrole (2.05 g., 37%) as an orange solid; and

recrystallization from hexane gave pale yellow needles, m.p. 136-137°, of 2-benzoyl-3,4,5-trimethylpyrrole (Found: C, 79.2; H, 7.0; N, 6.5. $C_{14}H_{15}NO$ requires C, 78.8; H, 7.1; N, 6.5%).

(b) The benzoylpyrrole was also obtained by shaking 2,3,4-trimethylpyrrole with excess benzoyl chloride in 10% sodium hydroxide solution. Sublimation of the crude product at 95-105° for 3 hr. at 0.5 mm., followed by recrystallization from hexane gave yellow needles, m.p. 136-137°. The mixed m.p. with the sample prepared as in (a) was 134.5-136°. The infrared spectra of the two samples determined for chloroform solutions in 0.2 mm. cells were identical.

(c) The lithium aluminium hydride reduction of 2,4-dimethyl-3-carbethoxypyrrole recorded by Treibs[124] was repeated and the product obtained shaken with excess benzoyl chloride in 10% sodium hydroxide solution. The 2-benzoyl-3,4,5-trimethylpyrrole was obtained as yellow needles, m.p. 135-137° (lit.[124], 1-benzoyl-2,3,4-trimethylpyrrole, m.p. 136°), which showed no depression of melting point on mixing with the sample from (a). The infrared spectra were also identical.

(d) 2,3,4-Trimethylpyrrole (2.16 g.) was dissolved in anhydrous ether (30 ml.) and benzonitrile (3.6 g.) added.

The solution was saturated at 0° with dry hydrogen chloride, and allowed to stand overnight, care being taken to exclude moisture. The ether was removed under reduced pressure and the residue refluxed for 6 hr. with water. It was set aside for 2 days, and the green plates collected. Recrystallization from hexane gave 2-benzoyl-3,4,5-trimethylpyrrole as yellow needles, m.p. 135-137°. The mixed m.p. with the sample from (a) was 134-135°. The infrared spectra of the two compounds were identical.

1-Benzoyl-2,3,4-trimethylpyrrole -

A mixture of potassium (1.95 g.), 2,3,4-trimethylpyrrole (4.05 g.) and benzoyl chloride (6.5 ml.) in toluene was treated according to the procedure of Rainey and Adkins.[138] The reflux time was 5 hr. and the heating time 3 hr. After removal of the toluene, the ethereal extract of the product was washed with ammonium hydroxide, water and then dried. The ether was evaporated and the product distilled to give 1-benzoyl-2,3,4-trimethylpyrrole (3.6 g., 45%) as a colourless oil, b.p. 110-114°/0.02 mm. The benzoylpyrrole was redistilled four times for analysis (Found: C, 78.6; H, 6.9; N, 6.7. $C_{14}H_{15}NO$ requires C, 78.8; H, 7.1; N, 6.5%).

2-Benzoyl-3,5-dimethylpyrrole -

(a) 2,4-Dimethylpyrrole was shaken with excess benzoyl chloride in 10% sodium hydroxide solution. The product obtained was recrystallized from hexane to give 2-benzoyl-3,5-dimethylpyrrole as colourless needles or prisms (depending on the rate of cooling) m.p. 118.5-119° (lit.[130], 1-benzoyl-2,4-dimethylpyrrole, m.p. 119°).

(b) The Houben-Hoesch procedure employed by Treibs[130] for the preparation of 2-benzoyl-3,5-dimethylpyrrole was repeated, but the product obtained on recrystallization from hexane had m.p. 117-118° (lit.[130], 136°). The yield obtained was 28%. A mixed melting point with the previous sample showed no depression. The infrared spectra of the two samples, determined as Nujol mulls, were identical.

1-Benzoyl-2,4-dimethylpyrrole -

A mixture of potassium (2.6 g.), 2,4-dimethylpyrrole (5.2 g.), and benzoyl chloride (10.4 ml.) in toluene was treated according to the procedure of Rainey and Adkins.[138] The reflux time was 5 hr., and the heating time 2 hr. After evaporation of the toluene, the residue was treated with ammonium hydroxide, and then extracted with hexane. The hexane solution was dried over anhydrous magnesium sulphate and the solvent evaporated. The product was distilled to give 1-benzoyl-2,4-dimethylpyrrole (4.2 g., 39%) as a

colourless oil, b.p. 126-128°/0.5 mm. (Found: C, 77.9; H, 6.6; N, 6.8. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%).

2-Benzoylpyrrole -

When the Schotten-Baumann benzoylation procedure was carried out on pyrrole under normal conditions, the reaction proceeded with extreme vigour and the procedure was therefore modified as follows. Benzoyl chloride (20 ml.) was added dropwise to an ice-cold mixture of pyrrole (8.25 g.) and 10% sodium hydroxide solution (25 ml.) over a period of 10 min. The solution was stirred magnetically for 3 hr. The chloroform extract of this solution was washed with 10% sodium hydroxide, water, and then dried. After removal of the solvent, the residue was distilled under reduced pressure. A white solid (5.27 g.) m.p. 100-120° was obtained. The sodium hydroxide extract of this was extracted with ether, but the ethereal extract, after washing with water, and drying, gave an oily solid. This was dissolved in hexane and run onto a column of alumina (grade IV, acid-washed). Elution with hexane gave a trace of a sweet-smelling oil, which was not identified, while further elution with chloroform gave a black oil, which crystallized on cooling in the refrigerator to give black needles (0.2 g.), m.p. 71-77°. Recrystallization from hexane gave

2-benzoylpyrrole as pale yellow needles, m.p. 78-79° (lit.[176a], 79°).

1-Benzoylpyrrole -

A mixture of potassium (7.8 g.), pyrrole (10 g.) and benzoyl chloride (26 ml.) in toluene was allowed to react according to the procedure of Rainey and Adkins.[138] The reflux time was 5 hr. and the heating time 3 hr. After evaporation of the toluene, the product was distilled to give 1-benzoylpyrrole (18.0 g., 70%) as a colourless oil, b.p. 94-96°/0.2 mm. (lit.[177], 276°/715 mm.).

Attempted preparation of Ethyl 1-Benzoylpyrrole-2-carboxylate -

A mixture of 2-carbethoxypyrrole (1.03 g.), 10% sodium hydroxide solution (20 ml.) and benzoyl chloride (2 ml.) was shaken for ½ hr. The solution was then extracted with chloroform, the chloroform solution washed with water and dried. After removal of the solvent, the product was distilled to give 2-carbethoxypyrrole as a colourless oil, b.p. 70°/0.1 mm. (lit.[176b], 80-90°/1 mm.). The infrared spectrum of the pyrrole was identical with that of an authentic specimen.

2-Benzoyl-3,4-dimethylpyrrole -

The Grignard derivative of 3,4-dimethylpyrrole[172]

(3.7 g.) in ether (100 ml.) was prepared from magnesium (1 g.) and ethyl bromide (4.8 g.). This solution was treated during 20 min. with benzoyl chloride (5.5 g.) in dry ether (10 ml.). When the vigorous reaction had subsided, the mixture was heated under reflux for 12 hr. After cooling at 0°, a saturated solution of ammonium chloride (50 ml.) was added cautiously, and the ethereal layer separated. The aqueous layer was extracted several times with chloroform and the chloroform and ether extracts were combined. The dried (anhydrous magnesium sulphate) extracts were warmed to remove the solvents and the residual oil was then heated at 100° under 15 mm. pressure for 5 hr. to remove unchanged benzoyl chloride and 3,4-dimethylpyrrole. The product (2.2 g., 23%) was distilled to give a viscous oil, b.p. 155°/0.05 mm., which subsequently crystallized. 2-Benzoyl-3,4-dimethylpyrrole was obtained as colourless needles, m.p. 76-77°, on recrystallization from hexane. (Found: C, 78.7; H, 6.6; N, 6.9. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%). Attempts to prepare the substance by the Schotten-Baumann benzoylation procedure on 3,4-dimethylpyrrole led to a mixture of oils.

2-Benzoyl-5-methylpyrrole -

The Grignard derivative of 2-methylpyrrole (0.7 g.) in ether (100 ml.) was prepared from magnesium (0.22 g.) and ethyl bromide (1.06 g.). This solution was treated

during 10 min., with benzoyl chloride (1.2 g.) in dry ether (10 ml.). The mixture was heated under reflux for 18 hr. A saturated solution of ammonium chloride was added to the cooled (0°) solution and the ethereal layer separated. The aqueous solution was extracted several times with ether and the ethereal extracts were combined. The dried (anhydrous magnesium sulphate) extracts were warmed to remove ether and the residual solid was then heated at 100°/15 mm. for 5 hr. to remove unchanged benzoyl chloride. The product was extracted with alcohol and poured into water. 2-Benzoyl-5-methylpyrrole (0.56 g., 35%) was obtained as golden prisms, m.p. 142° on recrystallization from hexane. (Found: C, 77.7; H, 6.1; N, 7.4. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%).

1-Benzoyl-2-methylpyrrole -

A mixture of potassium (1.2 g.),2-methylpyrrole (2 g.) and benzoyl chloride (4.7 ml.) in toluene was allowed to react according to the procedure of Rainey and Adkins. The reflux time was 5 hr. and the heating time 3 hr. After removal of the toluene, the residue was treated with ammonium hydroxide (0.880) and extracted with hexane. The hexane was dried and evaporated. The product was distilled to give 1-benzoyl-2-methylpyrrole (0.3 g., 7%) as a pale yellow oil b.p. 160-162°/23 mm. (Found: C, 77.1;

H, 6.0; N, 7.1. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%).

1-Benzoyl-2,5-dimethylpyrrole -

A mixture of potassium (2.5 g.), 2,5-dimethylpyrrole (5 g.) and benzoyl chloride (10 ml.) in toluene was allowed to react according to the procedure of Rainey and Adkins.[138] The reflux time was 5 hr. and the heating time 2 hr. After removal of the toluene, the residue was treated with ammonia (0.880), and extracted with hexane. The hexane solution was dried over anhydrous magnesium sulphate and the solvent evaporated. The product was distilled to give 1-benzoyl-2,5-dimethylpyrrole (4.3 g., 40%) as a pale yellow oil, b.p. 106°/0.3 mm. This subsequently crystallized, and the benzoylpyrrole was recrystallized from hexane to give pale yellow prisms, m.p. 38°. (Found: C, 78.3; H, 6.9; N, 7.0. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%). Treibs[130] reports this compound as an oil. The nuclear magnetic resonance spectrum[178] of this compound supports the structure stated.

Ethyl 5-Formyl-3,4-dimethylpyrrole-2-carboxylate -

Phosphorus oxychloride (5.75 g.) was gradually added down a condenser to an ice-cold mixture of ethyl 3,4-dimethylpyrrole-2-carboxylate (5 g.) and N,N-dimethyl-

formamide (2.75 g.). When the addition was complete, a calcium chloride tube was attached, and after the vigorous reaction had subsided, the reaction mixture was heated under reflux on a steam-bath for 2 hr. The hot solution was poured into ice-water, and the mixture quickly neutralized with a saturated sodium acetate solution. The mixture was cooled in the refrigerator overnight, and the product was then collected as brown needles (6.0 g., 100%) m.p. 106-108°. Recrystallization from aqueous ethanol gave ethyl 5-formyl-3,4-dimethylpyrrole-2-carboxylate as colourless needles m.p. 107.5-108° (lit.[116], 108°).

Ethyl 5-Acetyl-3,4-dimethylpyrrole-2-carboxylate -

(a) A mixture of ethyl 3,4-dimethylpyrrole-2-carboxylate (2.2 g.), glacial acetic acid (2 ml.) and redistilled acetyl chloride (2 ml.) was heated under reflux for 30 min. The mixture was allowed to cool, and then poured into water. The black oil which separated was extracted with chloroform, and the chloroform solution dried and evaporated to dryness. The brown crystals (1 g., 36%) obtained were recrystallized once from 2,2,4-trimethylpentane and then had m.p. 103-105°. Three subsequent recrystallizations from the same solvent gave ethyl 5-acetyl-3,4-dimethylpyrrole-2-carboxylate as colourless needles, m.p.

105.5-106° (lit.[179], 106°).

(b) Ethyl 3,4-dimethylpyrrole-2-carboxylate (1 g.) was dissolved in carbon disulphide and acetyl chloride (2.5 g.) and anhydrous aluminium chloride (2.5 g.) added. The reaction mixture was heated under reflux on a water-bath for 7 hr. The solvent was removed and the residue, after treatment with water, was recrystallized from aqueous ethanol. Ethyl 5-acetyl-3,4-dimethylpyrrole-2-carboxylate (0.84 g., 67%) was obtained as brown needles, which on recrystallization from benzene/2,2,4-trimethylpentane had m.p. 106°.

(c) Phosphorus oxychloride (1.15 g.) was gradually added to a cold mixture of ethyl 3,4-dimethylpyrrole-2-carboxylate (1 g.) and N,N-dimethylacetamide (0.66 g.) through a condenser. After the initial reaction, the mixture was heated on a steam-bath for 2 hr., poured into ice-water, and neutralized with a saturated solution of sodium acetate. It was allowed to stand in the refrigerator; ethyl 5-acetyl-3,4-dimethylpyrrole-2-carboxylate (0.84 g., 67%) was then obtained as brown needles, which on recrystallization from 2,2,4-trimethylpentane had m.p. 106°.

Ethyl 5-Benzoyl-3,4-dimethylpyrrole-2-carboxylate -

Ethyl 3,4-dimethylpyrrole-2-carboxylate (1 g.) was dissolved in carbon disulphide and benzoyl chloride (1 g.)

and anhydrous zinc chloride (2 g.) added. The reaction mixture was heated under reflux on a water-bath for 6 hr. and then allowed to stand at room temperature overnight. The solvent was removed and the residue, after treatment with water, was recrystallized from aqueous ethanol. The crude product (0.92 g., 57%) was recrystallized five times from hexane to give ethyl 5-benzoyl-3,4-dimethylpyrrole-2-carboxylate as colourless needles m.p. 120°. (Found: C, 70.5; H, 6.3; N, 5.2. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%).

Benzyl 5-Formyl-3,4-dimethylpyrrole-2-carboxylate -

Alkali-catalysed transesterification of ethyl 5-formyl-3,4-dimethylpyrrole-2-carboxylate (1 g.) was carried out as for the preparation of benzyl 3,4-dimethylpyrrole-2-carboxylate. Benzyl 5-formyl-3,4-dimethylpyrrole-2-carboxylate (0.53 g., 40%) was obtained as brown prisms, m.p. 110-115°; but recrystallization from hexane gave the pure substance as colourless prisms, m.p. 118-119°. (Found: C, 70.0; H, 6.2; N, 5.3. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.4%).

Benzyl 5-Benzoyl-3,4-dimethylpyrrole-2-carboxylate -

(a) Attempted Schotten-Baumann benzoylation of benzyl 3,4-dimethylpyrrole-2-carboxylate resulted in unchanged

starting material, identified by comparison of m.p. and infrared spectrum with an authentic sample.

(b) Phosphorus oxychloride (0.85 g.) was gradually added to a cold mixture of benzyl 3,4-dimethylpyrrole-2-carboxylate (1 g.) and dimethylbenzamide (0.82 g.). The reaction mixture was heated on a steam-bath for 2 hr., poured into ice-water, and then neutralized with saturated sodium acetate solution. It was set aside for some time in the refrigerator, but a black intractable tar was obtained.

(c) A mixture of benzyl 3,4-dimethylpyrrole-2-carboxylate (1.01 g.), glacial acetic acid (10 ml.) and benzoyl chloride (0.7 ml.) was heated under reflux for ½ hr., and then allowed to stand for 2 days. The mixture was extracted with chloroform, the chloroform extract dried, and then evaporated to dryness. Chromatography on alumina was not successful as a purification technique as the infrared spectrum of the product obtained, after this procedure had been carried out, indicated that it was probably a mixture of starting material and 5-benzoyl-3,4-dimethylpyrrole-2-carboxylic acid. There was insufficient material to enable a separation to be effected and this method was not investigated further.

(d) Benzyl 3,4-dimethylpyrrole-2-carboxylate (1 g.)

was dissolved in dry carbon disulphide, and benzoyl chloride (3.25 g.) and anhydrous aluminium chloride (3.3 g.) added. There was a vigorous initial reaction. The mixture was refluxed on a water-bath for 6 hr., the carbon disulphide was evaporated, and the reaction mixture treated with water. A tarry product which resisted all attempts at purification was obtained.

(e) The sample of benzyl 3,4-dimethylpyrrole-2-carboxylate supplied by Dr. Ward (prepared by transesterification of the corresponding ethyl ester) was recrystallized five times from hexane for analysis. It was obtained as colourless, hairy needles, m.p. 102°. (Found: C, 76.0; H, 5.8; N, 4.1. $C_{21}H_{19}NO_3$ requires C, 75.7; H, 5.7; N, 4.2%).

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