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The synthesis of porphyrins from dipyrrolylmethanes

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Abstract. The methods for the synthesis of pyrroles, dipyrrolylmethanes and porphyrins derived from them are analysed, systematised and generalised. The bibliography includes 82 references.

I. Introduction

The methods for the synthesis of porphyrins are highly diverse and their choice is determined by the nature and mutual arrangement of substituents to be incorporated into the porphyrin molecule. Those suitable for the preparation of relatively simple porphyrins can be inapplicable for the synthesis of more complex compounds. Consideration of these methods is appropriate to begin with a brief survey of different types of porphyrins (compounds **1** – **4**).

The first type of porphyrins includes those which comprise identical substituents in the β-positions of the pyrrole rings and symmetrical *meso*-substituted porphyrins (compounds **1**). These compounds are usually prepared by one-step condensation of four identical pyrrole molecules into porphyrin.

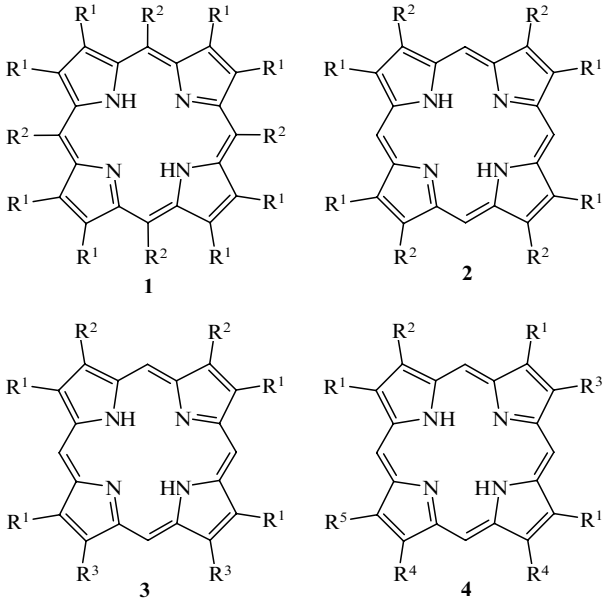
The second type of porphyrins (porphyrins **2**) have a more complex structure which retains certain features of symmetry. These compounds are synthesised *via* intermediate dipyrrolylmethanes, -methenes and pyrroketones; since these molecules contain two different substituents, four isomeric products can be formed.

The third group of porphyrins includes porphyrins **3** with three different substituents and symmetrical dipyrrolic fragments. In some cases, dipyrroles can be used as precursors of porphyrins **3**.

The fourth type of porphyrins (porphyrins **4**) comprise more than three different substituents. Their synthesis is preceded by the formation of linear tetrapyrrole molecules which are closed to form the corresponding cyclic structures in the final stage. Thus, *a*- and *b*-oxobilanes, *b*-bilenes and *a*,*c*-biladienes are typically used as intermediate compounds.

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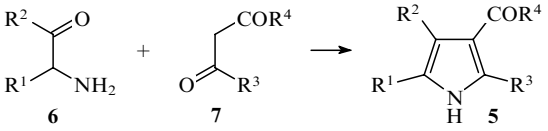
To date, numerous novel procedures for the synthesis of porphyrins have been developed. However, all of them include the formation of methine bridges from methyl or bromomethyl groups in the α-position of pyrrole, dipyrrolylmethane or -methene. The choice of a synthetic procedure is largely determined by the desired symmetry of the porphyrin molecule. The syntheses based on the use of symmetrical dipyrrolylmethanes the cyclisation of which yields porphyrins with a high degree of symmetry (C_{2v}) are of particular interest in this respect. The obvious advantages of this method are the simplicity of preparation of starting dipyrrolylmethanes and sufficiently high yields (50% – 60%) of porphyrins. Bisdipyrrolylmethanes were used in the synthesis of sterically hindered, dimeric and polymeric porphyrins.

II. Synthesis of pyrroles

Pyrroles are the key compounds in the synthetic chemistry of porphyrins. These compounds are readily available and yield porphyrins upon condensation. This circumstance determined the wide application of pyrroles in the synthesis of *meso*-alkyl- and *meso*-arylporphyrins including a whole array of sterically hindered porphyrins.

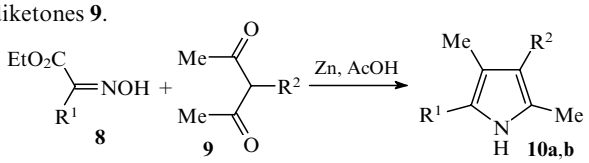
Unsubstituted pyrrole is usually prepared by pyrolysis of ammonium mucate.[1] Substituted porphyrins can be synthesised in two ways, *viz*., by chemical modification of the macrocycle and by condensation of pyrroles with a predetermined set of substituents. The latter approach is more advantageous, since it provides greater scope for synthesis.

A vast variety of pyrroles have been described in the literature. The derivatives **5** containing electron-withdrawing groups are synthesised, as a rule, by the Knorr method,[2] *viz*., by condensation of aminoketones **6** with β-dicarbonyl compounds **7**.



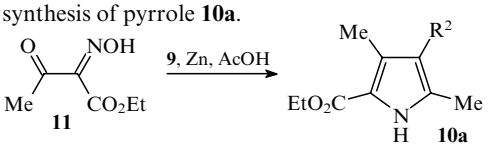
The aminoketones **6** are usually prepared by the reduction of the oximes which, in turn, are formed upon nitrosation of ketones or β-dicarbonyl compounds with sodium nitrite in glacial acetic acid.[2] Zinc in acetic acid is typically used as the reducing agent. Although the yields in this synthesis do not exceed 40%–60%, this procedure has found wide application owing to simplicity and availability of the starting compounds.

Kleinspehn [3] performed the synthesis of α-ethoxycarbonyl- (**10a**) or α-cyanopyrroles **10b** by condensation of oximes **8** with β-diketones **9**.

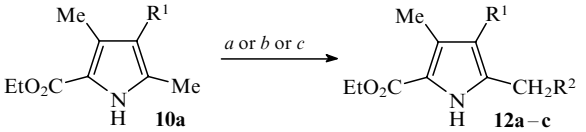


R^1 = CO_2Et (**a**), CN (**b**).

Later, it was shown [4] that α-hydroxyimino β-keto esters, *e.g*., compound **11**, can also enter into the reaction of reductive condensation with alkyl-β-diketones. This method was used in the synthesis of pyrrole **10a**.



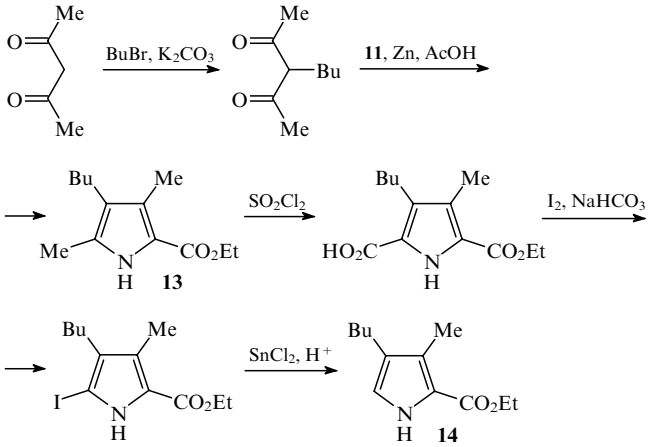
Pyrroles containing a halogenomethyl or an acetoxymethyl group in one of the α-positions are most commonly used in the synthesis of dipyrrolylmethanes. Different approaches to the synthesis of these compounds were compared by Semeikin *et al*.[5] α-Chloromethylpyrroles **12a** are prepared by treatment of pyrroles **10a** with sulfuryl chloride or *tert*-butyl hypochlorite on cooling.[5] The yields of reaction products strongly depend on the temperature of the reaction mixture. Diethyl ether, dichloromethane or glacial acetic acid are used as the solvents. Bromination of α-methylpyrroles **10a** with molecular bromine in diethyl ether or acetic acid results in strong resinification which significantly reduces the yields of pyrroles **12b**.



(*a*) SO_2Cl_2 [**12a**, R^2 = Cl (85%)]; (*b*) Br_2 [**12b**, R^2 = Br (73%)]; (*c*) $Pb(OAc)_4$ [**12c**, R^2 = OAc (95%)].

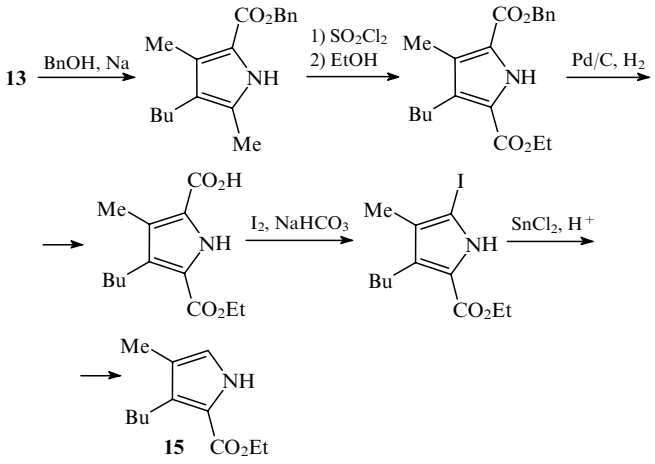
Acetoxymethylpyrroles **12c** can be prepared by the reaction of the halogenomethyl derivatives **12a**,**b** with sodium acetate in acetic acid; however, direct oxidation of α-methylpyrroles **10a** with lead tetraacetate is more efficient.[5] Acetoxymethyl derivatives are less readily hydrolysed and oxidised in air than compounds **12a**,**b**, which makes them especially attractive for further syntheses.

The methods for the synthesis of isomeric butylpyrrole derivatives in high yields have been proposed.[6–10] The reaction of acetylacetone with butyl bromide in DMF or acetone in the presence of anhydrous potassium carbonate yields 3-butylpentane-2,4-dione; its condensation with ethyl hydroxyiminoacetoacetate **11** in the presence of acetic acid and zinc dust gives 4-butyl-2-ethoxycarbonyl-3,5-dimethylpyrrole (**13**).



As a rule, α-monosubstituted pyrroles are the target products in such syntheses. The oxidation of the α-methyl group of pyrrole **13** with sulfuryl chloride in diethyl ether results in 4-butyl-5-carboxy-2-ethoxycarbonyl-3-methylpyrrole. Its decarboxylation is carried out in two steps, *viz*., by substitution of iodine for the carboxy group by treatment with iodine and sodium hydrogen carbonate in aqueous ethanol and subsequent reduction of the α-iodopyrrole formed with tin dichloride. These reactions result in 4-butyl-2-ethoxycarbonyl-3-methylpyrrole (**14**) in sufficiently high yield.[6–10]

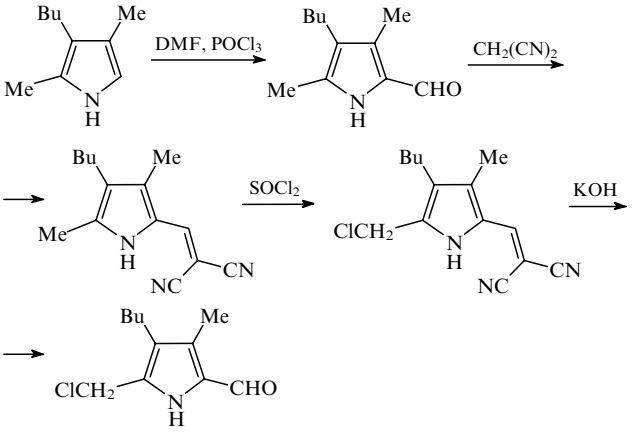
A reaction sequence was proposed [6–10] which leads to 3-butyl-2-ethoxycarbonyl-4-methylpyrrole (**15**), a key compound in the synthesis of many di- and tetrapyrroles,† from the readily available α-ethoxycarbonylpyrrole **13**. To this end, compound **13** was transesterified with benzyl alcohol; the resulting ester was oxidised with sulfuryl chloride at the α-methyl group and esterified with ethanol. The diester formed was subjected to hydrogenolysis on a palladium catalyst. The resulting 3-butyl-5-carboxy-2-ethoxycarbonyl-4-methylpyrrole was decarboxylated *via* the iodo derivative using a standard procedure:



The pyrroles **14** and **15** can be used for further transformations both directly and in the form of formyl derivatives which can be

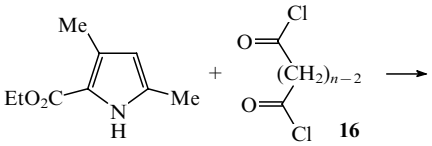
† It is of note that only α-unsubstituted pyrroles containing a small methyl group in the vicinal β-position have previously been used in the synthesis of dipyrrolylmethanes.[11–20] However, later it was found that the steric factor has no effect on the condensation reaction.[7,21–23]

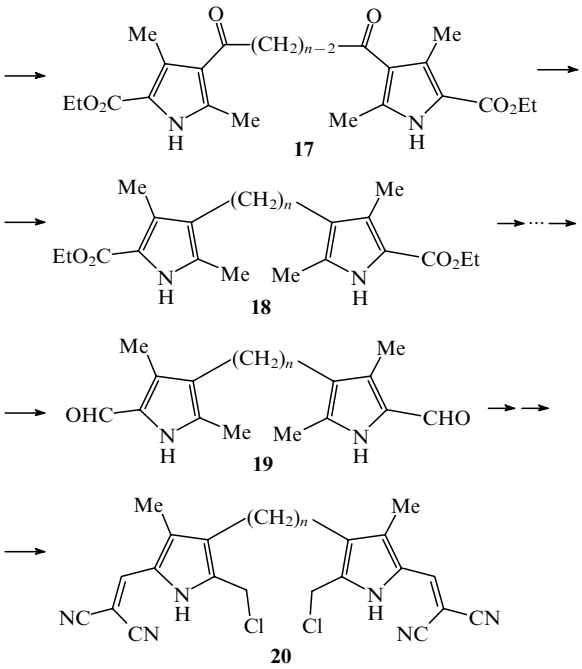
easily obtained by the reaction of these pyrroles with dimethylformamide in the presence of phosphorus oxychloride or benzoyl chloride. In many reactions, *e.g.*, in chlorination with thionyl chloride, the aldehyde group is protected.[7,24] To this end, formylpyrroles are treated with dicyanomethane; deprotection is carried out by alkaline treatment. This procedure was used in the synthesis of 4-butyl-5-chloromethyl-3-methylpyrrole 2-carbaldehyde from 3-butyl-2,4-dimethylpyrrole.



Dipyrrole structures in which pyrrole rings are linked through β-positions can be prepared from more readily available β-unsubstituted pyrroles.[25–27] These structures and the possibilities of their chemical modification present special interest, since they permit the design of novel types of porphyrin molecules.

The acylation of 3,5-dimethyl-2-ethoxycarbonylpyrrole with the dicarboxylic acid chloride **16** and subsequent reduction of the carbonyl groups of the diketone **17** formed with diborane result in compound **18**. The bispyrrole **18** is further converted into the benzyl ester, which is further subjected to hydrogenolysis followed by decarboxylation and formylation, eventually resulting in the aldehyde **19**.[25] The formyl groups of the dialdehyde are protected with dicyanomethane as described above, which is followed by chlorination with sulfuryl chloride. This method was used in the synthesis of the dipyrrole derivatives **20**.[25]



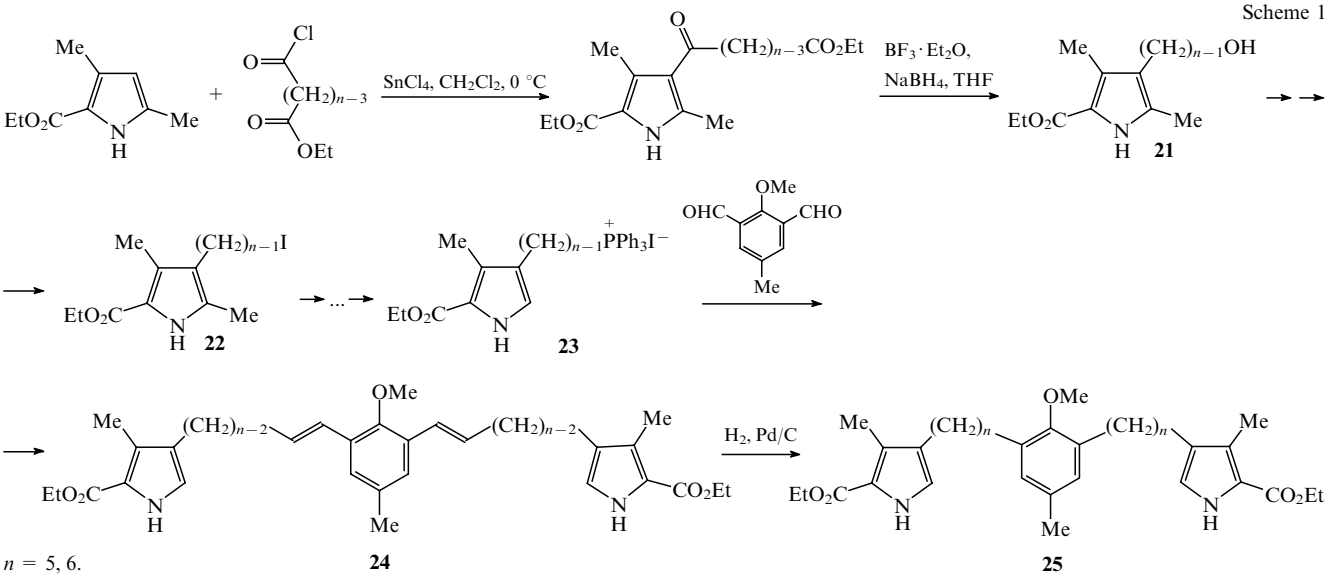


n = 9–11.

Later, Morgan and Dolphin [27] synthesised β-linked dipyrrolic derivatives containing an aryl fragment in their bridges. The acylation of 3,5-dimethyl-2-ethoxycarbonylpyrrole and subsequent reduction of the carbonyl group result in the hydroxy derivative **21**, which is converted into the iodo derivative **22** on substitution of iodine for the hydroxy group *via* the corresponding mesylate. The methyl group in compound **22** is eliminated from position 5 using the standard procedure, *i.e.*, *via* 5-iodopyrrole. Subsequent reaction with triphenylphosphine in boiling toluene affords the phosphonium salt **23**. Its condensation with 2,6-diformyl-4-methylanisole in dioxane in the presence of potassium carbonate results in the diene **24**. The final step in this synthesis is the catalytic hydrogenation of compound **24** leading to the target dipyrrole derivative **25** (Scheme 1).

Syntheses based on β-unsubstituted pyrroles are multistage processes, which is the common drawback, chemical conversions involve alternately α- and β-positions of the ring, which significantly complicates the synthesis. In our opinion, the use of relatively available α-unsubstituted pyrroles is more advantageous.

Scheme 1

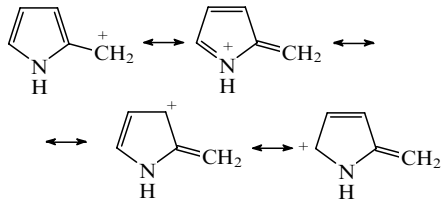


n = 5, 6.

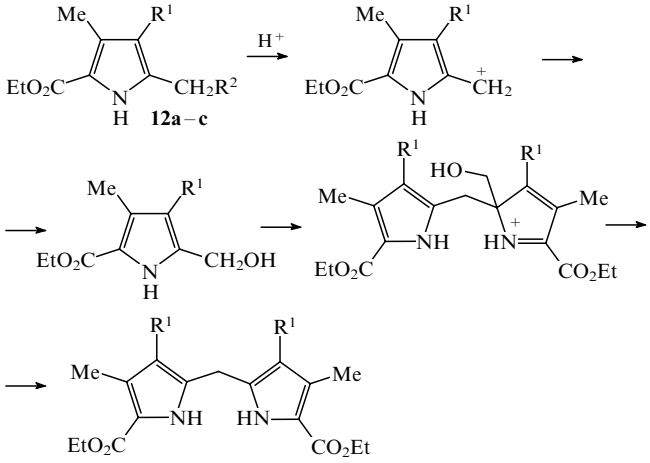
III. Synthesis of dipyrrolylmethanes

Porphyrins can also be synthesised from dipyrrolylmethanes and -methenes. However, both of them possess exceedingly high reactivity. This disadvantage can be overcome through the introduction of electron-withdrawing substituents. Synthesis of dipyrrolylmethenes containing such substituents is problematic. On the other hand, there exist simple and efficient procedures for the synthesis of stabilised dipyrrolylmethanes; their advantages in the synthesis of structurally complex porphyrins leave no doubt.[28,29]

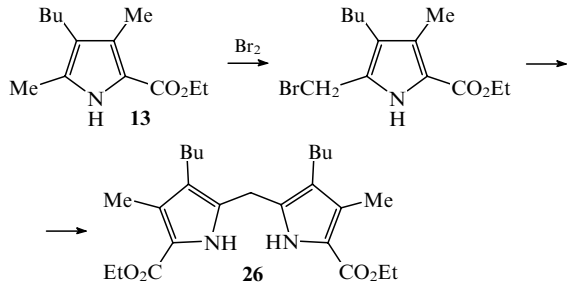
It has been established that the condensation of pyrroles **12a–c** occurs *via* pyrrolylmethyl carbocations stabilised due to the delocalisation of the positive charge.[2] Such cations are relatively stable both in inert solvents and in alcohols, carboxylic acids and even in water.



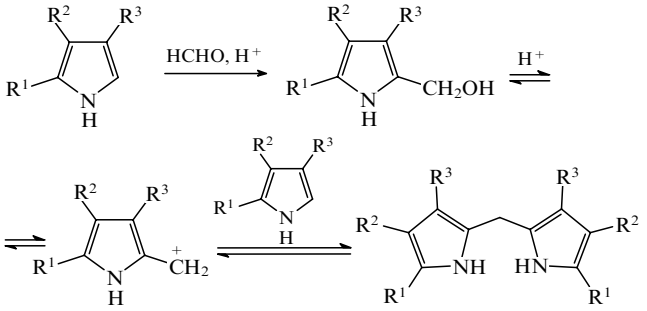
On boiling in ethanol in the presence of hydrobromic acid, pyrroles **12a–c** are converted into dipyrrolylmethanes in high yields.[2,5,7,30,31] If such pyrroles contain alkyl substituents in the β-positions, dipyrrole compounds are obtained in up to 90% yields.



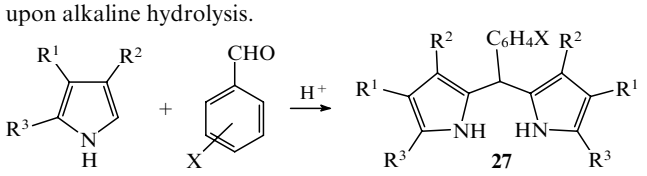
An efficient procedure for the synthesis of dipyrrolylmethanes containing butyl groups in positions 3 and 3′ has been proposed.[7–10,24,29,32] Bromination of the α-methyl group of the pyrrole **13** with subsequent condensation of 5-bromomethyl-4-butyl-2-ethoxycarbonyl-3-methylpyrrole in ethanol in the presence of an acid results in the 5,5′-diethoxycarbonyl derivative **26**; its alkaline hydrolysis affords bis(3-butyl-5-carboxy-4-methylpyrrol-2-yl)methane. As in the case of synthesis of bis(5-carboxy-3,4-dimethylpyrrol-2-yl)methane, lead tetraacetate proved to be the best oxidant for the starting pyrrole.[5]



Symmetrical dipyrrolylmethanes can also be prepared by the condensation of α-monosubstituted pyrroles with aldehydes. It is self-evident that the β-positions of the pyrrole ring must be substituted with at least one electron-withdrawing substituent, which thus stabilises the product.[33] This reaction occurs under the same conditions as the self-condensation of the pyrroles **12a–c**.



The reaction of 2-benzyloxycarbonyl-3,4-dimethylpyrrole with benzaldehyde in ethanol in the presence of hydrochloric acid results in *meso*-phenyldipyrrolylmethane **27a**. Under conditions of acid catalysis, 3-butyl-2-ethoxycarbonyl-4-methylpyrrole (**15**) reacts with benzaldehyde to give dipyrrolylmethane **27b**.[8] It was shown[7,23] that the reaction of 4-butyl-2-ethoxycarbonyl-3-methylpyrrole (**14**) with benzaldehyde and its derivatives (XC_6H_4CHO, X = OMe, NO_2, NMe_2) in the ethanol–hydrochloric acid system results in *meso*-aryl-substituted dipyrrolylmethanes **27c–i** in good yields. Similar to compounds **27a**,**b**, these products (except for compound **27i** which undergoes resinification) are converted into the corresponding dicarboxy derivatives upon alkaline hydrolysis.



Compound **27**	R^1	R^2	R^3	X
a	Me	Me	CO_2Bz	H
b	Bu	Me	CO_2Et	H
c	Me	Bu	CO_2Et	H
d	Me	Bu	CO_2Et	4-OMe
e	Me	Bu	CO_2Et	3-OMe
f	Me	Bu	CO_2Et	2-OMe
g	Me	Bu	CO_2Et	4-NO_2
h	Me	Bu	CO_2Et	3-NO_2
i	Me	Bu	CO_2Et	3-NMe_2

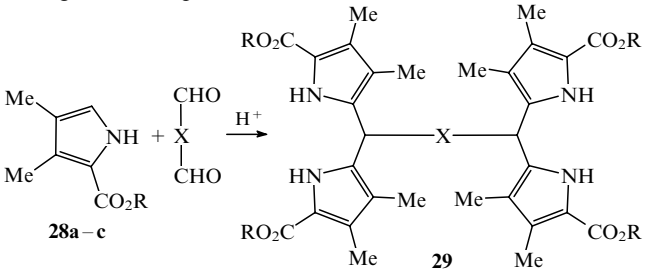
The structures of a series of *meso*-substituted dipyrrolylmethanes were calculated by the molecular mechanics methods (the force field MM^+).[34–36] The strain energies of isomeric compounds of the type **27** are listed in Table 1.

Table 1. The strain energies of isomeric dipyrrolylmethanes **27** (E_{MM} /kJ mol^{-1}) and their constituents, *viz*., bond strain energies (E_{bnd}), bond angle energies (E_{ang}), torsion angle energies (E_{dih}) and Van der Waals energies (E_{vdw}).

R^1	R^2	R^3	Y[a]	E_{MM}	E_{bnd}	E_{ang}	E_{dih}	E_{vdw}
H	H	H	H	97	3.66	86.1	−12.0	−7.0
Me	Bu	CO_2Et	H	139	2.28	133.5	−12.8	16.8
Me	Bu	CO_2H	H	111	1.49	93.4	−6.0	2.3
Bu	Me	CO_2Et	Ph	106	3.20	100.3	−31.7	20.2
Me	Bu	CO_2Et	Ph	104	2.83	92.3	−28.1	10.2
Me	Et	CO_2Et	Ph	105	2.56	87.5	−24.2	10.1
Bu	Me	CO_2H	Ph	86	0.73	67.8	−17.7	8.0
Me	Bu	CO_2H	Ph	83	1.49	75.6	−21.4	4.3
Me	Et	CO_2H	Ph	87	1.78	72.4	−16.2	4.1

[a] Y is *meso*-substituent.

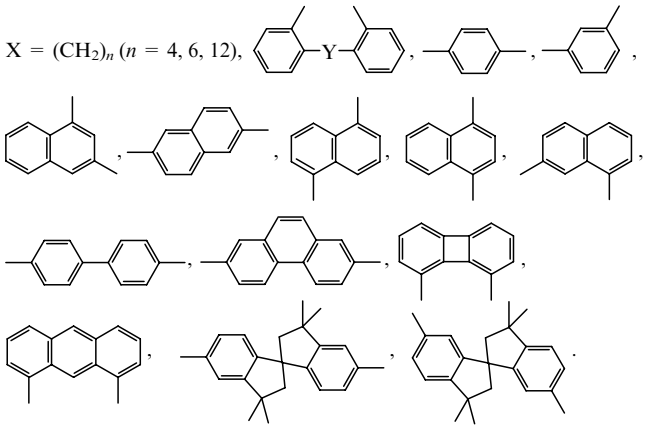
The above-described procedure is widely employed in the synthesis of bisdipyrrolylmethanes.[13–16,18,22] The reaction of pyrroles **28a–c** with dialdehydes in acid media gives high yields of compounds **29** the dipyrrolic fragments of which are linked through the *meso*-positions.



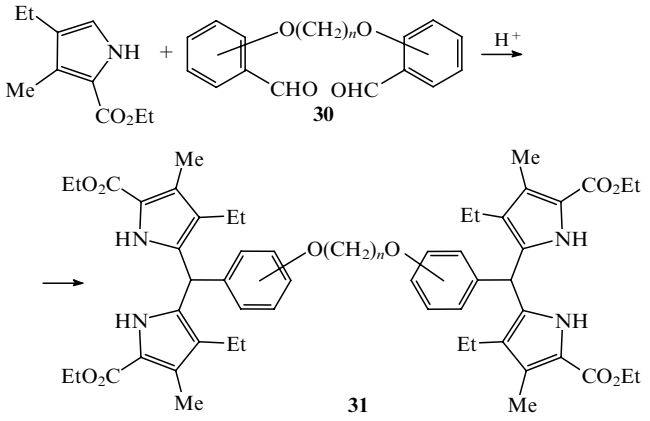
28a–c **29**

R = H (**a**), Et (**b**), Bn (**c**);

X = $(CH_2)_n$ (n = 4, 6, 12),



3-Methyl-2-ethoxycarbonyl-4-ethylpyrroles are easily condensed in acid media with dialdehydes **30** the phenyl fragments of which are linked by ether bridges [$O(CH_2)_nO$] of different lengths (n = 2–4).[23] The resulting esters **31** are easily hydrolysed to the corresponding acids in alkaline media.



30 **31**

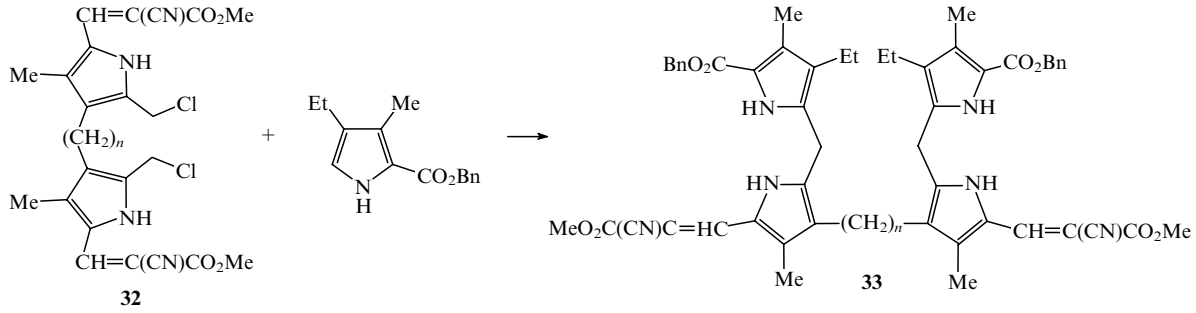
n = 2–4.

Compounds with fundamentally different structures can be prepared on the basis of β-linked pyrroles. The condensation of bispyrroles **32** containing chloromethyl groups with 2-benzyloxycarbonyl-4-ethyl-3-methylpyrrole in acetic acid results in bisdipyrrolylmethanes **33** the dipyrrole fragments of which are linked by methylene bridges through the 3,3′-positions (n = 9–11) (Scheme 2).[25]

An alternative approach involves the condensation of 5,5′-unsubstituted bispyrrole **34** with the α-chloromethyl derivative **35** (Scheme 3).[27]

The reaction of compounds of the type **12a–c** with α-unsubstituted pyrroles gives nonsymmetrical dipyrrolylmethanes. It was proposed[37] to start from bromomethylpyrrole in a sodium acetate–glacial acetic acid buffer. It is the intermediate acetoxymethylpyrrole formed that enters into the reaction. Unfortu-

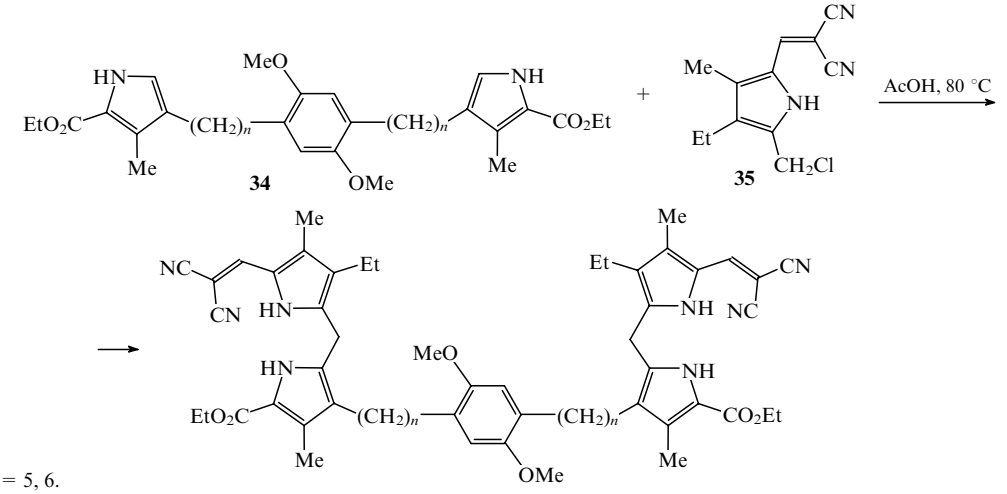
Scheme 2



32 **33**

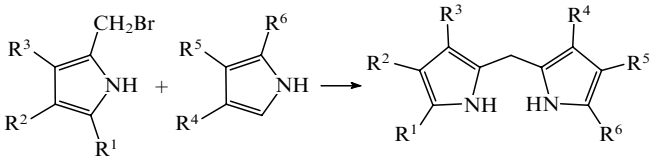
n = 9–11.

Scheme 3

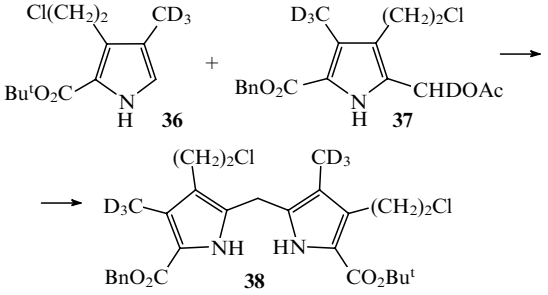


n = 5, 6.

nately, this reaction yields a large amount of the symmetrical dipyrrolylmethane as the side product.



The reaction of pyrroles **36** and **37** in the presence of *p*-toluenesulfonic acid in AcOH gives dipyrrolylmethane **38** in 85% yield.[38]

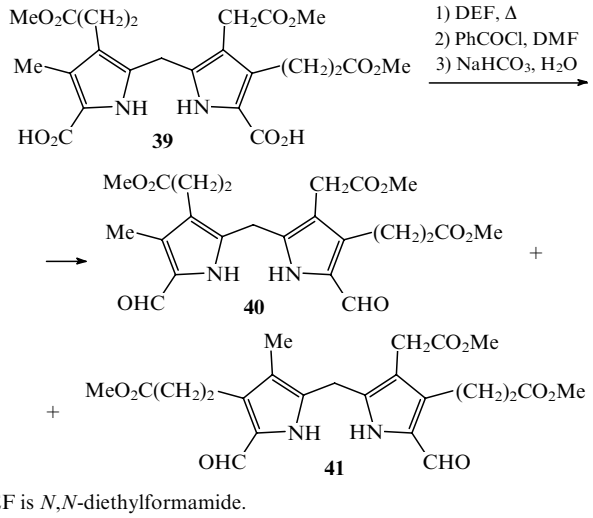


Other methods for the synthesis of dipyrrolylmethanes are less popular. If chemical modification of dipyrrolylmethanes is envisaged, allowance must be made for the fact that their stabilities and reactivities with respect to electrophilic reagents are similar to those of pyrroles. Dipyrrolylmethanes are stable if they contain at least one electron-accepting group in each of their pyrrole nuclei. Also the methylene unit in dipyrrolylmethanes is readily oxidised to form dipyrrolylmethenes or ketone.

Dipyrrolylmethane 5,5′-dicarboxylic acids are prepared by heating the corresponding 5,5′-diethyl esters with aqueous alkalis with subsequent precipitation of the reaction product with a mineral acid or by hydrogenation of 5,5′-dibenzyl esters on a palladium catalyst in THF at atmospheric pressure and at room temperature.[7, 32]

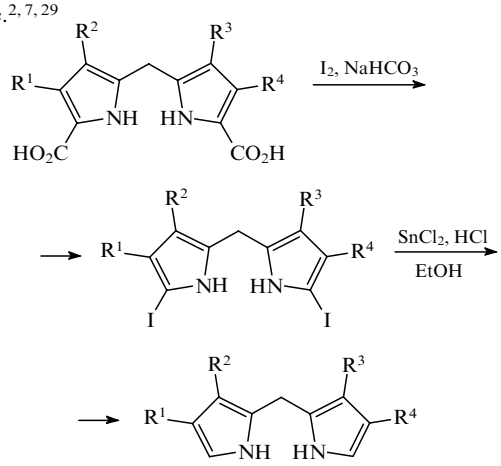
Heating of dry bis(5-carboxypyrrol-2-yl)methanes is accompanied by profound destruction; therefore, McDonald *et al.*[39] proposed to conduct the decarboxylation in sealed tubes in aqueous solutions of alkalis at 170–180 °C, which causes only partial destruction. In an alternative procedure,[40] the decarboxylation is carried out by boiling the dicarboxylic acids prepared from diethyl esters in DMF in an inert atmosphere.

N,N-Diethylformamide was used as a solvent for increasing the boiling temperature of the reaction mixture.[41] Unfortunately, the decarboxylation of dipyrrolylmethane **39** is accompanied by intramolecular rearrangements. Subsequent formylation gives a mixture of dialdehydes **40** and **41** in a total yield of 60%.

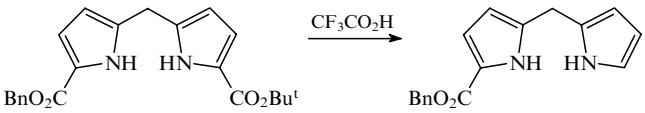


DEF is *N,N*-diethylformamide.

If dipyrrolylmethanes have different substituents in the β-positions of the pyrrole ring, a mixture of isomeric products can be formed. To avoid this, the decarboxylation is carried out in two steps. First, the carboxy groups are substituted by iodine and then the iodo derivatives are reduced, *e.g.*, with tin(II) chloride.[2, 7, 29]

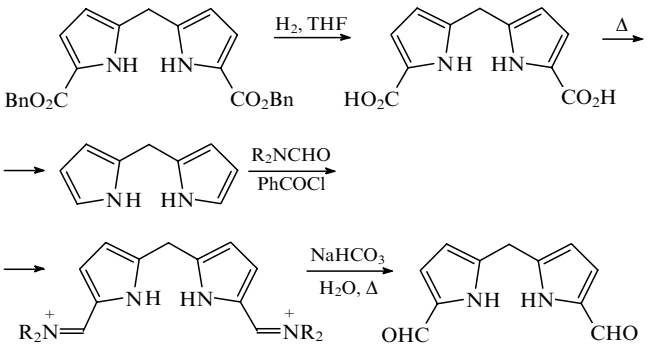


Dipyrrolylmethane dicarboxylic acids can be decarboxylated by trifluoroacetic acid (TFA). It was found[42] that 5,5′-unsubstituted dipyrrolylmethanes thus formed are stable in TFA at room temperature for a week. Trifluoroacetic acid was used, for example, for decarboxylation of 5-benzyloxycarbonylpyrrol-2-yl-5′-*tert*-butoxycarbonylpyrrol-2′-ylmethane.[42] However, TFA can induce intramolecular rearrangements in dipyrrolylmethanes.



Heating of carboxy derivatives in aqueous alkalis in the presence of hydrazine as a stabiliser seems to be the method of choice for decarboxylation of β-alkylated dipyrrolylmethanes.[8, 29] In this case, the yield of the target product reaches 85%.

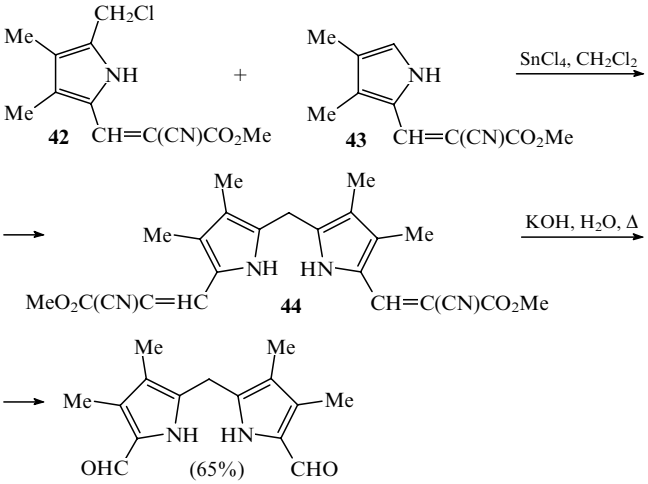
Bis(5-formylpyrrol-2-yl)methane was obtained from bis(5-benzyloxycarbonylpyrrol-2-yl)methane by the Wilsmeyer reaction. The use of phosphorus oxychloride or benzoyl chloride results in dialdehydes with practically equal yields (45% – 50%).[33]



An alternative procedure for the synthesis of dipyrrolylmethanedialdehydes was proposed by Mamardashvili *et al.*[24] who used triethyl orthoformate in TFA as the formylating reagent. 5,5′-Dicarboxy derivatives of dipyrrolylmethanes obtained by hydrogenolysis of dibenzyl esters are first dissolved 5–10 minutes after the completion of decarboxylation and triethyl orthoformate is added to the reaction mixture. This enters into the reaction with the 5,5′-unsubstituted dipyrrolylmethane formed. Apparently, a part of dipyrrolylmethane undergoes rearrangement.

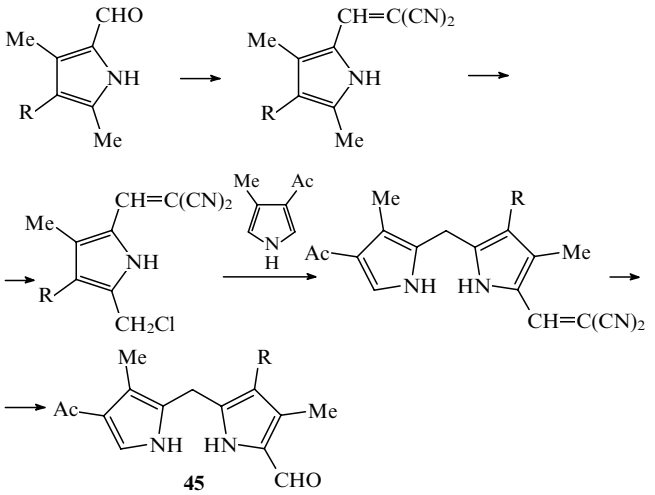
The synthesis of dipyrrolylmethanes from pyrroles containing electron-withdrawing groups, *e.g.*, cyano groups, is of particular interest. This method was developed by Dolphin *et al.*[43] for the

synthesis of bis(5-formyl-3,4-dimethylpyrrol-2-yl)methane. This reaction consists in the condensation of pyrroles **42** and **43** in dry dichloromethane in the presence of catalytic amounts of tin(IV) chloride resulting in dipyrrolylmethane **44**; its hydrolysis by heating on a water bath with a solution of KOH in aqueous ethanol gives a poorly soluble target dipyrrolylmethane. The yield of the final product can be significantly increased by performing deprotection in an inert atmosphere.



The synthesis of 5-formyl-5′-unsubstituted dipyrrolylmethanes deserves special attention. The first compound of this series, *viz*., 3,3′-diethyl-5-formyl-4,4′-dimethyldipyrrol-2-ylmethane, was obtained by Dolphin *et al*.[44] using decarboxylation of 5-carboxy-5′-ethoxycarbonyl-3,3′-diethyl-4,4′-dimethyldipyrrol-2-ylmethane with subsequent Wilsmeyer formylation of the resulting product (Scheme 4).

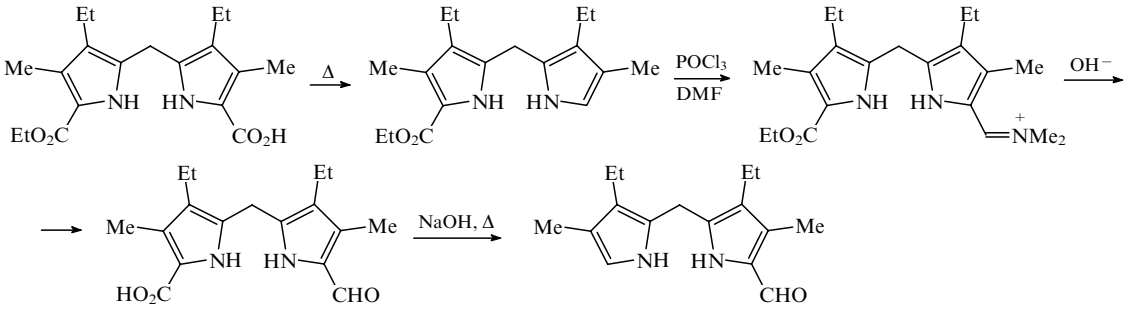
In the synthesis of the monoaldehyde **45**, the formyl group of the original pyrrole was protected by reaction with malononitrile.[45]



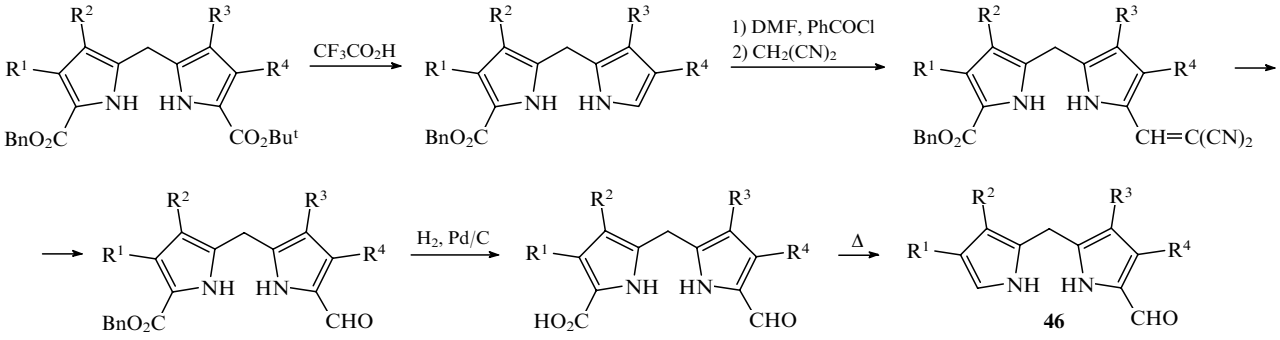
R = $(CH_2)_2CO_2Me$.

The monoformyldipyrrolylmethanes of the type **46** commonly employed in the synthesis of linear tetrapyrrolic compounds [42] can be prepared from esters of the corresponding dicarboxylic acids using various approaches (Schemes 5 and 6).

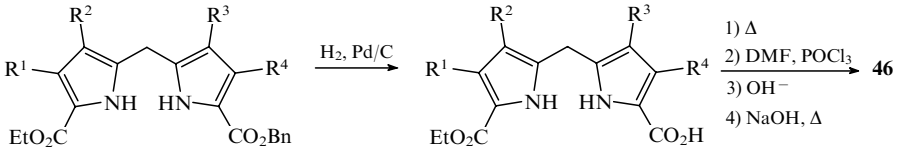
Scheme 4



Scheme 5

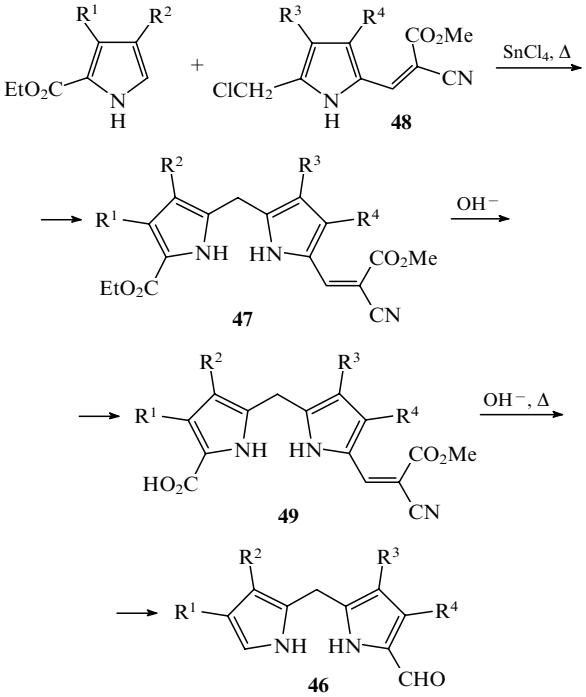


Scheme 6



One of these approaches consists in thermal decarboxylation of intermediate 5-formyl-5′-carboxydipyrrolylmethanes; however, if the carboxypyrrolyl fragment contains electron-withdrawing groups, the reaction is carried out *via* iodo derivatives. The presence of even one electron-withdrawing aldehyde group increases the resistance of the methylene group of dipyrrolylmethane to oxidants and prevents intramolecular rearrangements, fragmentation and resinification. The monoformyldipyrrolylmethane **46** formed can be stored for a long period of time in a dry state in the absence of oxygen.[42]

Unsymmetrical dipyrrolylmethanes **47** are formed in high yields in the reaction of α-ethoxycarbonyl-substituted pyrroles with compounds **48** containing chloromethyl and cyanovinyl (or cyanoacryl) groups in the α-positions. The latter deactivate pyrrole **48** and prevent its self-condensation. The condensation is carried out in inert solvents, *e.g.*, dichloromethane, dichloroethane, benzene, *etc*. The dipyrrolylmethanes of the type **49** are often decarboxylated upon heating with alkalis.[46] It should be noted that the cyanoacryl group which is hydrolysed more readily than the cyanovinyl group provides more efficient protection.



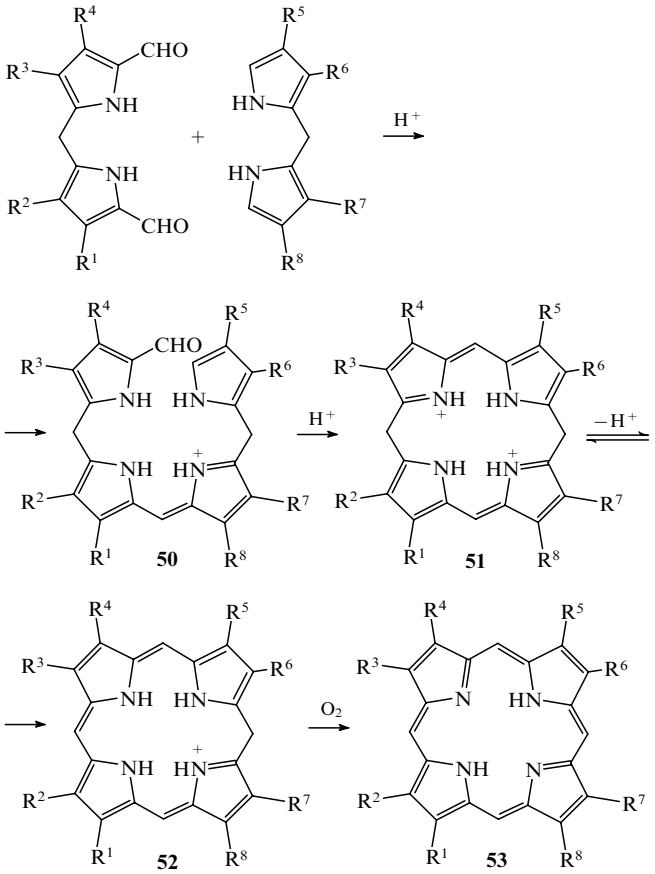
The common disadvantage of the syntheses based on monoformyl derivatives of dipyrrolylmethanes is the necessity to protect the aldehyde groups prior to chemical transformations.[46] Removal of protecting groups may provoke side reactions.

IV. Synthesis of porphyrins

Dipyrrolylmethanes have been widely used in the synthesis of porphyrins since 1960. McDonald *et al*.[39] developed a procedure for the condensation of bis(5-formylpyrrol-2-yl)methanes with 5,5′-unsubstituted dipyrrolylmethanes under mild conditions. This reaction is carried out in glacial acetic acid in the presence of hydroiodic acid in a highly dilute solution (Scheme 7).

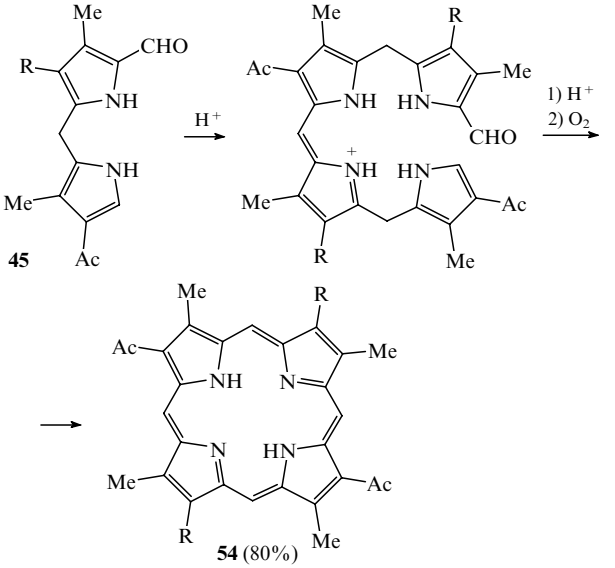
This process involves the formation of *b*-bilene **50** and porphodimethene **51** which is partially converted into phlorine **52**. Both the intermediate products and the phlorine **52** can be oxidised with atmospheric oxygen to yield porphyrin **53**. In some cases, self-condensation of the original bis(5-formylpyrrol-2-yl)methanes may occur to a certain extent. The yields of the porphyrins **53** prepared by condensation of symmetrical dipyrrolylmethanes by the method of McDonald are given in Table 2.

Scheme 7



The condensation of bis(3-butyl-4-methylpyrrol-2-yl)methane with bis(3-butyl-5-formyl-4-methylpyrrol-2-yl)methane in ethanol in the presence of hydrobromic acid and subsequent oxidation of the reaction mixture with *o*-tetrachloroquinone results in 3,7,13,17-tetrabutyl-2,8,12,18-tetramethylporphyrin in 24% yield.[9]

A method for the synthesis of porphyrins from 5-formyl-5′-unsubstituted dipyrrolylmethanes has been proposed.[45] Self-condensation of compound **45** in glacial acetic acid in the presence of small quantities of acetic anhydride and hydrobromic acid gives 2,6-diacetyldeuteroporphyrin-II **54**.



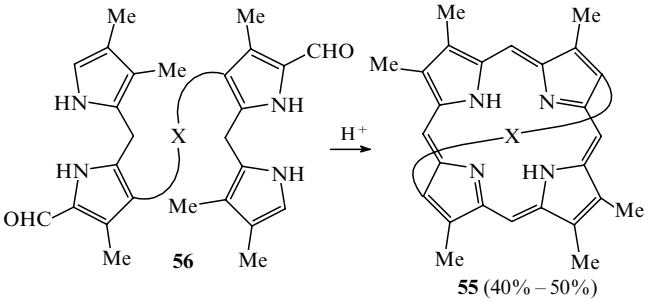
R = $(CH_2)_2CO_2Me$.

Table 2. The porphyrins **53** synthesised by the McDonald method.[39,47,48]

R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Yield (%)
$(CH_2)_2CO_2Me$	CH_2CO_2Me	CH_2CO_2Me	$(CH_2)_2CO_2Me$	$(CH_2)_2CO_2Me$	CH_2CO_2Me	CH_2CO_2Me	$(CH_2)_2CO_2Me$	65
$(CH_2)_2CO_2Me$	CH_2CO_2Me	CH_2CO_2Me	$(CH_2)_2CO_2Me$	CH_2CO_2H	$(CH_2)_2CO_2H$	$(CH_2)_2CO_2H$	CH_2CO_2H	55
Me	CO_2Et	CO_2Et	Me	Me	CO_2Et	CO_2Et	Me	66
$(CH_2)_2CO_2Me$	CH_2CO_2Me	CH_2CO_2Me	$(CH_2)_2CO_2Me$	Me	CO_2Et	CO_2Et	Me	40
Me	$CH=CH_2$	Me	$CH=CH_2$	Me	$(CH_2)_2CO_2Me$	$(CH_2)_2CO_2Me$	Me	45
Me	$CH(OH)CH_2CO_2Me$	Me	$CH(OH)CH_2CO_2Me$	Me	$(CH_2)_2CO_2Me$	$(CH_2)_2CO_2Me$	Me	29 [a]
Et	Me	Et	Me	$(CH_2)_2CO_2Me$	CH_2CO_2Me	CH_2CO_2Me	$(CH_2)_2CO_2Me$	36 [a]

Note. The reaction was carried out in glacial acetic acid containing HI. [a] HCl was used instead of HI.

A series of sterically hindered (strapped) porphyrins **55** were synthesised by condensation of bisformyldipyrrolylmethanes **56** in a dichloromethane – methanol mixture (30 : 1) in the presence of *p*-toluenesulfonic acid.[27]



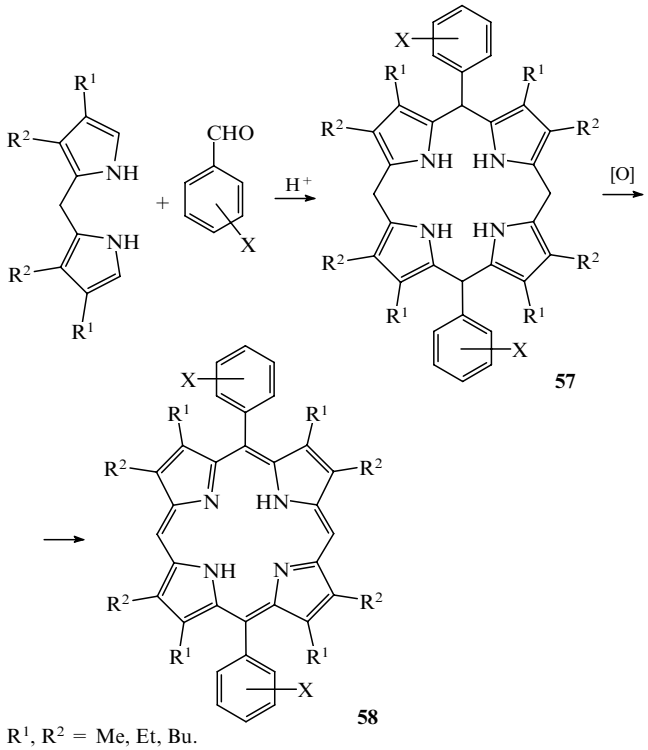
X is the residue of a saturated or an aromatic hydrocarbon.

Monoformyldipyrrolylmethanes have not found wide application in the synthesis of porphyrins due to their unavailability and the necessity to perform multistep syntheses.

The condensation of a symmetrical 5,5′-unsubstituted dipyrrolylmethane with triethyl orthoformate in formic acid was carried out.[9] In this reaction, first the formylation of dipyrrolylmethane occurs followed by formation of the porphyrin. As this reaction occurs under drastic conditions, it can be accompanied by rearrangements of dipyrrolylmethane resulting in a mixture of isomeric porphyrins.

The condensation reactions of 3,3′4,4′-tetraalkyl-5,5′-unsubstituted dipyrrolylmethanes with aldehydes resulting in 5,15-dialkyl- and 5,15-diaryl derivatives of porphyrins are well documented in the literature.[7–10] Initially, the oxidative condensation was carried out in one step, as in the case of synthesis of *meso*-tetraphenylporphyrins, *viz*., in a boiling solvent in the presence of atmospheric oxygen.[33] In a pyridine – acetic acid mixture, the yield of porphyrins was rather low (~ 3%), but it was increased when the reaction was performed in benzene in the presence of TFA with high dilution of the reagents. It was shown [49–52] that the use of a two-step procedure gives better results. The reaction of dipyrrolylmethane with benzaldehyde results in porphyrinogen **57**, which is further oxidised by benzoquinone derivatives to porphyrin **58**.

The yields of porphyrins **58** synthesised by this method are given in Table 3. The yield of porphyrin **58** (R^1 = Me, R^2 = Bu^n, X = 2-OMe) does not depend on the solvating properties of the solvent (Table 4), which suggests high complexity of the reaction mechanism.[52] The strength of the organic acid used as a catalyst only slightly affects the yield of the target product but the nature of the oxidant is a critical factor (Table 4). If the condensation is performed in a boiling solvent, the rate of the reaction is naturally increased with no decrease in the yield.[50]



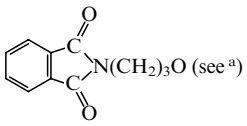
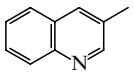
R^1, R^2 = Me, Et, Bu.

It is of note that rearrangements in dipyrrolylmethanes and/or intermediate tetrapyrroles in acid media result in the formation of monoarylporphyrins in addition to diarylporphyrins.[33] In some cases, the monosubstituted porphyrin is the main or even the only reaction product, especially at elevated temperatures. The nature of the substituent in the original dipyrrolylmethane and the presence of a *para*-substituent in the benzaldehyde molecule have little effect on the yield of the target porphyrins (Table 5).

The reaction of 5,5′-unsubstituted dipyrrolylmethanes with an equimolar mixture of two aromatic aldehydes gives unsymmetrical 5,15-diphenyloctaalkylporphyrins and a mixture of all the three feasible products, which have to be further separated by chromatography or, in some cases, by chemical modification. The closer are the electronic effects of the substituents in the aldehydes, the higher are the yields of unsymmetrical porphyrins.[33,53]

The condensation of the dialdehydes **59** with 5,5′-unsubstituted dipyrrolylmethanes affords 'capped' porphyrins **60** in sufficiently high yields.[14] This method can be used for the synthesis of other complex systems containing octamethylporphyrin and etioporphyrin fragments.[13–16,18,22] Unfortunately, porphyrins containing methyl or ethyl groups in the β-positions of the macrocycle

Table 3. The conditions of synthesis and the yields of 5,15-diaryl(hetaryl)octaalkylporphyrins **58**.

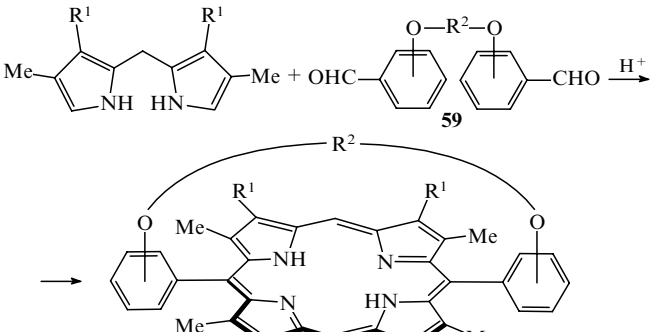
X	R^1	R^2	Yield (%)	Solvent	Catalyst	Oxidant	Ref.
H	H	H	3	Py	AcOH	air	54
H	Me	Me	58	MeOH	CCl_3CO_2H	*p*-tetrachloroquinone	55
H	Me	Et	56	MeOH	CCl_3CO_2H	"	55
H	Et	Et	30	PhH	CF_3CO_2H	air	56
H	Me	Bu	11	MeOH	TsOH	*o*-tetrachloroquinone	32
2-Me	H	H	81	CH_2Cl_2	CF_3CO_2H	*p*-tetrachloroquinone	55
2-Me	Et	Et	40	PhH	CF_3CO_2H	air	56
3-Me	H	H	86	CH_2Cl_2	CF_3CO_2H	*p*-tetrachloroquinone	55
3-Me	Et	Et	30	PhH	CF_3CO_2H	air	56
4-Me	H	H	89	CH_2Cl_2	CF_3CO_2H	*p*-tetrachloroquinone	55
4-Me	Me	Me	54	MeOH	CCl_3CO_2H	"	33
4-Me	Me	Et	56	MeOH	CCl_3CO_2H	"	33
4-Me	Me	Et	58	MeOH	TsOH	*o*-tetrachloroquinone	33
4-Me	Et	Et	30	PhH	CF_3CO_2H	air	56
3-Et	Me	Et	77	CH_2Cl_2	CF_3CO_2H	DDQ	33
2-OMe	H	H	86	CH_2Cl_2	CF_3CO_2H	*p*-tetrachloroquinone	55
2-OMe	Et	Et	30	PhH	CF_3CO_2H	air	56
3-OMe	Et	Et	40	PhH	CF_3CO_2H	"	56
4-OMe	H	H	83	CH_2Cl_2	CF_3CO_2H	*p*-tetrachloroquinone	55
4-OMe	Me	Me	50	MeOH	CCl_3CO_2H	"	33
4-OMe	Me	Et	56	MeOH	CCl_3CO_2H	"	33
4-OMe	Et	Et	40	PhH	CF_3CO_2H	air	56
2,6-$(OMe)_2$	Me	Et	6	MeCN	CCl_3CO_2H	*p*-tetrachloroquinone	57
	H	H	87	CH_2Cl_2	CCl_3CO_2H	"	55
4-OH	Me	Et	62	CH_2Cl_2	CF_3CO_2H	"	58
2-Cl	H	H	80	CH_2Cl_2	CF_3CO_2H	"	55
2,4-$(Cl)_2$	H	H	79	CH_2Cl_2	CF_3CO_2H	"	55
2-NO_2	H	H	73	CH_2Cl_2	CF_3CO_2H	"	55
4-NO_2	Me	Me	69	MeOH	CCl_3CO_2H	"	55
4-NMe_2	Me	Me	46	MeOH	CCl_3CO_2H	"	9
 (see [a])	Et	Et	55	MeOH	TsOH	*o*-tetrachloroquinone	59
 (see [a])	Et	Et	44	MeOH	TsOH	"	59

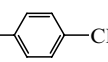
Note. DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; [a] *meso*-substituent.

Table 4. The dependence of the yield of 5,15-diaryloctaalkylporphyrin **58** (R^1 = Me, R^2 = Bu^n, X = 2-OMe) on the nature of the solvent, the catalyst and the oxidant.[33, 50]

Solvent	Catalyst	Oxidant	Yield (%)
C_6H_{14}	CF_3CO_2H	*o*-tetrachloroquinone	44
CCl_4	CF_3CO_2H	"	24
PhH	CF_3CO_2H	"	27
$CHCl_3$	CF_3CO_2H	"	40
MeCN	CF_3CO_2H	"	24
Et_2O	CF_3CO_2H	"	34
MeOH	CF_3CO_2H	"	37
Me_2CO	CF_3CO_2H	"	29
$CHCl_3$	CCl_3CO_2H	"	44
$CHCl_3$	CH_2ClCO_2H	"	44
$CHCl_3$	CH_2ClCO_2H	*p*-tetrachloroquinone	32
$CHCl_3$	CH_2ClCO_2H	*p*-tetrabromoquinone	28
$CHCl_3$	CH_2ClCO_2H	DDQ	42

are poorly soluble in organic solvents, which significantly restricts their investigation and practical application.[60–66]



R^1 = Me, Bu; R^2 = CH_2——CH_2.

Some attempts were undertaken to synthesise porphyrins with bulky alkyl substituents in the β- and *meso*-positions starting from

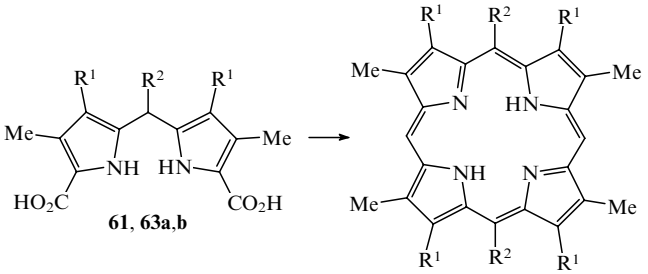
Table 5. The effects of substituents on the yields of 5,15-diaryloctaalkylporphyrins **58**.[33,50]

X	R^1	R^2	Yield (%)
Solvent — MeOH			
H	Me	H	66
H	Me	Me	64
H	Me	Et	64
4-OMe	Me	Me	59
Solvent — $CHCl_3$			
H	H	Me	61
H	Me	Me	68
H	Et	Me	33

5,5′-unsubstituted dipyrrolylmethanes aimed at enhancement of their solubilities.[7–10,24,32,67,68] The yields of porphyrins in the reaction of bis(4-butyl-3-methylpyrrol-2-yl)methane with benzaldehyde in *o*-xylene–TFA, methanol–*p*-toluenesulfonic acid, chloroform–acetic acid systems and in acetic acid do not exceed 2.2%, 3%, 10% and 4.1%, respectively. In condensation of bis(dimethyl- and butylmethylpyrrol-2-yl)methanes with aliphatic aldehydes RCHO [R = Alk(C_2–C_7), $C_{11}H_{23}$] in TFA-containing chloroform followed by oxidation of the resulting porphyrinogens with *p*-tetrachloroquinone, the yield of porphyrins did not exceed 5%.[9]

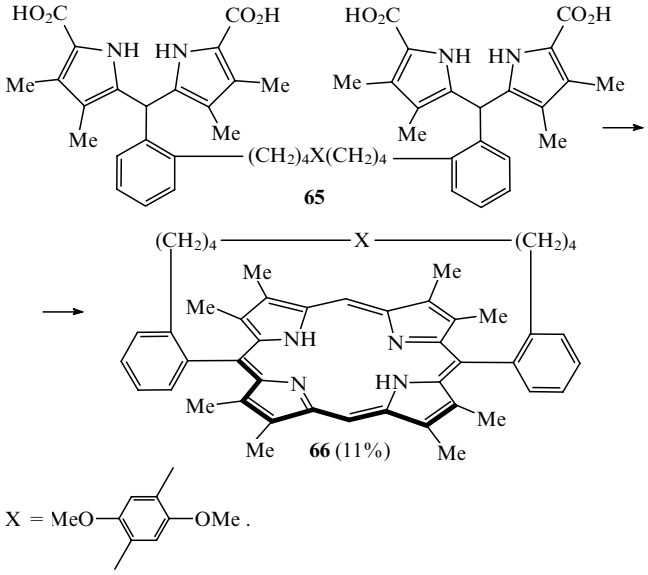
The synthesis of porphyrins from 5,5′-dicarboxy derivatives of dipyrrolylmethanes, the synthetic precursors of 5,5′-unsubstituted compounds and 5,5′-diformyldipyrrolylmethanes, appeared to be more efficient. 5,5′-Dicarboxylic acids are far more stable than 5,5′-unsubstituted derivatives, and porphyrins are formed from them in higher yields and the amounts of poorly separable admixtures are much less than in the synthesis of porphyrins from the corresponding unsubstituted and formyl derivatives of dipyrrolylmethanes.

Jackson *et al.*[69] were the first to carry out the condensation of dipyrrolylmethane **61** with triethyl orthoformate in dichloromethane in the presence of trichloroacetic acid. This reaction gives coproporphyrin-II **62** in 25% yield. A series of *meso*-disubstituted porphyrins were synthesised[7,8] by a modified Jackson–Kenner method.[69] In the condensation of 3,3′-dibutyl derivatives of *meso*-aryldipyrrolylmethanes **63a** with triethyl orthoformate in chloroform in the presence of TFA, the yield of porphyrins **64a** was the highest (~ 35%). The substitution of monochloroacetic acid for TFA decreases the yield to 17% and in the chloroform–acetic acid system the yield is 10%. The yield of porphyrins **64b** in the reaction of 3,3′-dimethyl derivatives of *meso*-alkyldipyrrolylmethanes **63b** with triethyl orthoformate in chloroform in the presence of TFA is 20%–25%.[8,10]

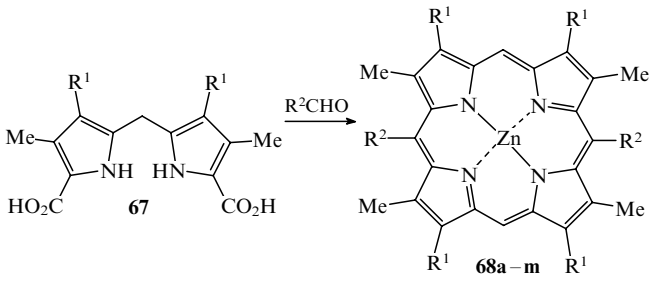


R^1 = $(CH_2)_2CO_2Me$, R^2 = H (**61**, **62**);
R^1 = Bu: R^2 = Ph, C_6H_4OMe-2, C_6H_4OMe-3, C_6H_4OMe-4, $C_6H_4NO_2$-3, $C_6H_4NO_2$-4 (**63a**, **64a**); R^1 = Me: R^2 = Alk(C_1–C_7), $C_{11}H_{23}$ (**63b**, **64b**).

This method is widely used in the synthesis of 'capped' porphyrins.[11,27] For example, the cyclisation of bisdipyrrolylmethane **65** results in porphyrin **66**.[11] The methoxy groups in the substituent X in compound **66** were converted into the carbonyl groups by demethylation with boron tribromide in dichloromethane with subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (the yield of the target product is 54%).



As noted above, octamethyl derivatives of porphyrins manifest low solubility. However, the yield of porphyrins decreases drastically if the methyl groups are substituted by bulkier alkyl groups in order to increase the solubility. It was found[32] that condensation of 5,5′-dicarboxy derivatives of dipyrrolylmethanes with aldehydes in pyridine in the presence of zinc acetate can increase the yield up to 20%. The highest yields are obtained with nitrobenzoaldehydes, which can be attributed to the oxidising ability of the nitro group. Evidence in favour of this hypothesis can be derived from the increase in the yield of 5,15-diphenylporphyrin **68a** after addition of small quantities of nitrobenzene. The optimum ratio of the reagents (dipyrrolylmethane **67** : PhCHO : $PhNO_2$) is 1 : 3.6 : 3.6 (Fig. 1).



Compound **68**	R^1	R^2
a	Bu	Ph
b	Bu	C_6H_4OMe-4
c	Bu	C_6H_4OMe-3
d	Bu	C_6H_4OMe-2
e	Bu	$C_6H_4NO_2$-4
f	Bu	$C_6H_4NO_2$-3
g	Me	Me
h	Me	Et
i	Me	Pr
j	Me	Bu
k	Me	C_5H_{11}
l	Me	C_6H_{13}
m	Me	$C_{11}H_{23}$

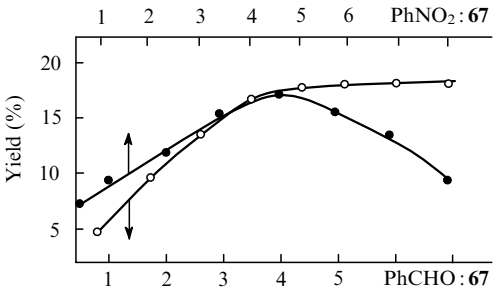
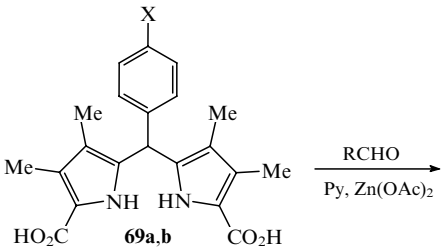


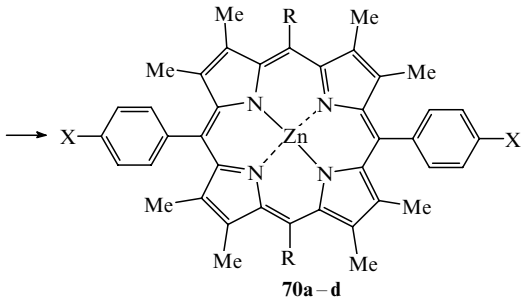
Figure 1. The dependence of the yield of porphyrin **68a** on the molar ratio of the reaction mixture components.

This method was used in the synthesis of 2,8,12,18-tetrabutyl-3,7,13,17-tetramethyl-5,15-diphenylporphyrin (**68a**) and its derivatives **68b**–**f** containing different substituents in the benzene rings.[9, 32, 65] The yields of porphyrins (~ 20%) practically do not depend on the nature of the substituent in the benzaldehyde. 2,8,12,18-Tetrabutyl-5,15-di(2-methoxyphenyl)-3,7,13,17-tetramethylporphyrin (**68d**) is an exception; its lower yield (10%) can be attributed to steric hindrance in the condensation of dipyrrolylmethane with 2-methoxybenzaldehyde. This porphyrin exists in the form of two atropoisomers (α,α and α,β), which differ in relative positions of substituents in the phenyl fragments relative to the macrocycle plane.

The reaction of dipyrrolylmethane **67** with aliphatic aldehydes in pyridine in an inert atmosphere (180 °C, 0.5–2 h) resulted in 5,15-dialkyl derivatives of octamethylporphyrin **68g**–**m**.[65] The presence of a coordinating reagent (zinc acetate) in the reaction mixture markedly facilitates the cyclocondensation. The yields of porphyrins **68g**–**m** are maximum at the $Zn(OAc)_2$: dipyrrolylmethane **67** : RCHO molar ratio of 1.5 : 1 : 1.25. It is noteworthy that depending on the chain length of alkyl substituents, the yields of porphyrins vary in the range of 15%–33%, *i.e.*, are relatively high (*cf.* tetraalkyl-substituted porphyrins, which are obtained by condensation of monopyrroles in 5% to 15% yields [33]). A salient advantage of this method is that reaction products do not contain even trace amounts of *meso*-monosubstituted porphyrins.

The condensation of *meso*-aryl-substituted dipyrrolylmethanes **69a**,**b** with aliphatic aldehydes was used in the synthesis of 5,15-dialkyl-10,20-diaryl-β-octamethylporphyrins **70a**–**d**.[24] These compounds are characterised by high solubility due to the presence of *meso*-alkyl substituents; their aryl fragments can be subject to chemical modification.





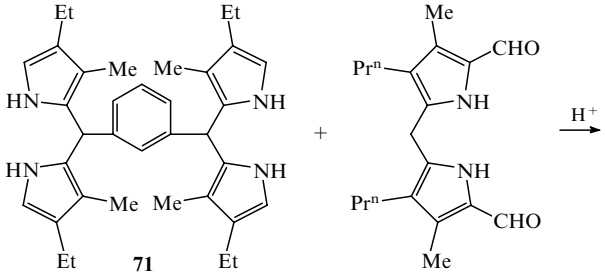
69: X = H (**a**), 4-OMe (**b**); **70**: X = H, R = Me (**a**), Et (**b**), C_6H_{13} (**c**); X = 4-OMe, R = C_6H_{13} (**d**).

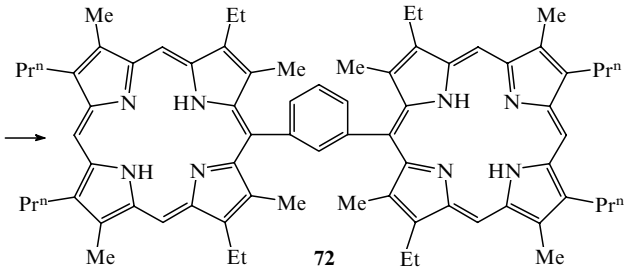
The condensation of compounds **69a**,**b** with acetaldehyde and heptanal was carried out in pyridine at elevated temperatures and high pressures. The yields of *meso*-tetrasubstituted porphyrins **70a**,**c**,**d** are low (3% to 5%), which can be ascribed to steric hindrance in the cyclocondensation, and do not depend on the chain length of the alkyl substituent. Similarly, the yields of porphyrins obtained by the condensation of 5,5′-unsubstituted *meso*-aryldipyrrolylmethanes with benzaldehyde and formaldehyde are 5%–6% and do not depend on the nature of the aldehyde.[24]

It may thus be concluded that 5,5′-dicarboxy derivatives of dipyrrolylmethanes are promising reagents in the synthetic chemistry of porphyrins. They compare favourably with 5,5′-unsubstituted dipyrrolylmethanes and formyl derivatives by relative accessibility and, which is particularly important, by their resistance to oxidation. These compounds can be used in the synthesis of porphyrins of complex structure, including position isomers.

V. Synthesis of bisporphyrins

A vast variety of bisporphyrins with different spatial arrangement of macrocycles have been synthesised from dipyrrolylmethanes. Such syntheses are typically performed by a modified McDonald method.[11, 13, 15, 16, 70] Sessler *et al.*[12] were the first to synthesise the so-called 'gable' bisporphyrins the porphyrin fragments in which are linked through the *meta*-positions of the benzene ring. This synthesis involves the formation of intermediate dipyrrolyl structures. The reaction of compound **71** with 5,5′-diformyl derivatives of dipyrrolylmethane in methanol in the presence of *p*-toluenesulfonic acid and subsequent oxidation of the condensation product with tetrachloroquinone result in bisporphyrin **72**.[15]



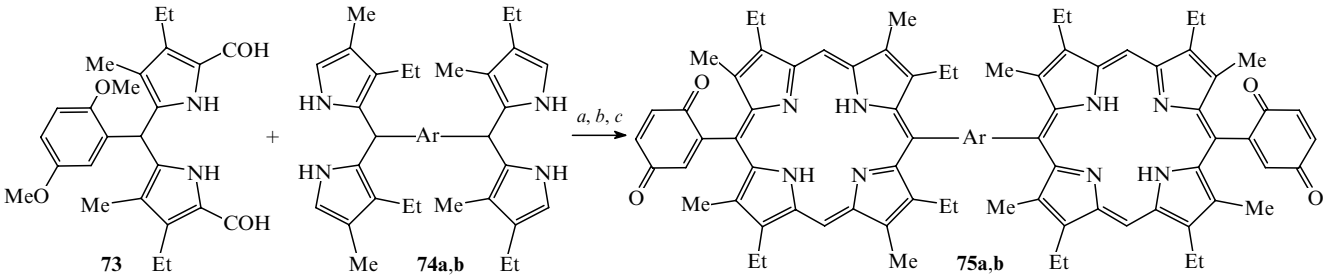


In order to construct models which are geometrically identical to the active centres involved in photosynthesis, Sessler *et al.*[16] carried out the condensation of the 5,5′-diformyl derivative of dipyrrolylmethane **73** with bisdipyrrolylmethanes **74a**,**b** to yield bisporphyrin **75a** with spatially approximated porphyrin nuclei and its linear analog **75b**. The same procedure was used in the synthesis of a bisporphyrin in which the porphyrin macrocycles were linked through a quinone fragment. The yield of porphyrins in the first stage of this reaction was ~ 5% (Scheme 8).

The synthesis of compounds in which porphyrin fragments are linked by aromatic bridges, which stabilise their spatial structure has been described.[13] This synthesis consisted in the condensation of bisdipyrrolylmethanes **76** with bis(5-formyl-3,4-dimethylpyrrol-2-yl)methane and resulted in bisporphyrins **77** (Scheme 9).

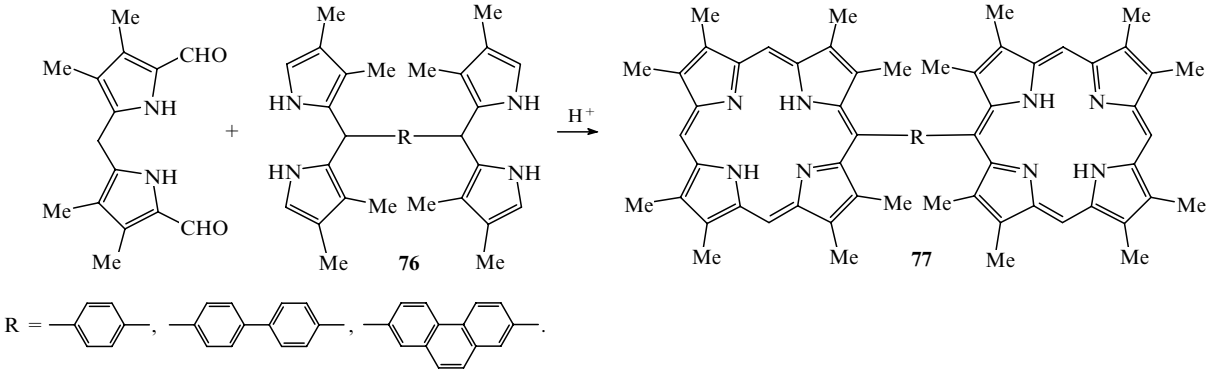
The reaction of bis(5-formyl-3,4-dimethylpyrrol-2-yl)methane with stereoisomeric bisdipyrrolylmethanes **78** in methanol in the presence of *p*-toluenesulfonic acid and subsequent oxidation

Scheme 8

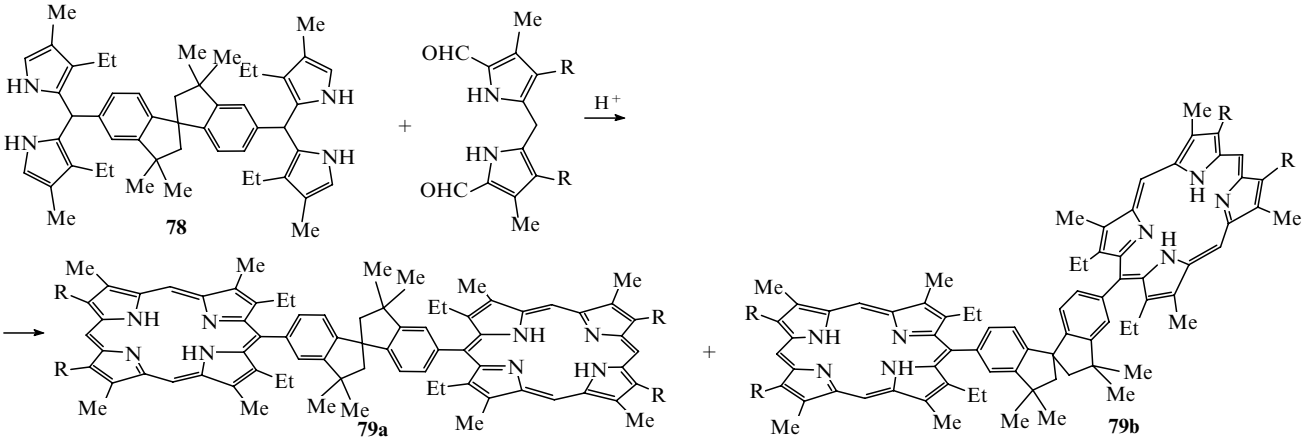


Ar = *m*-C_6H_4 (**a**), *p*-C_6H_4 (**b**); (*a*) H^+; (*b*) BBr_3, CH_2Cl_2; (*c*) [O].

Scheme 9



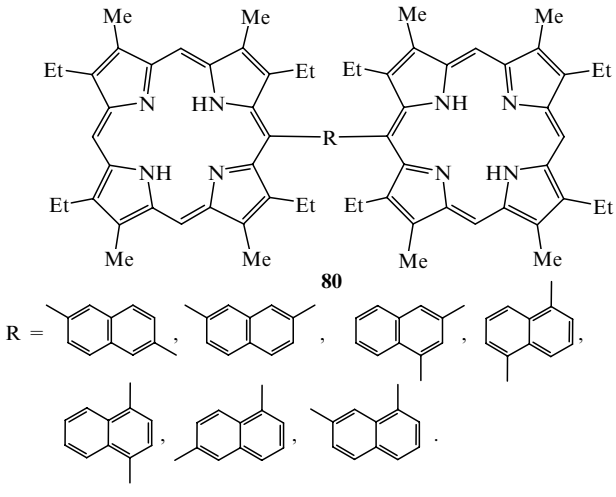
Scheme 10



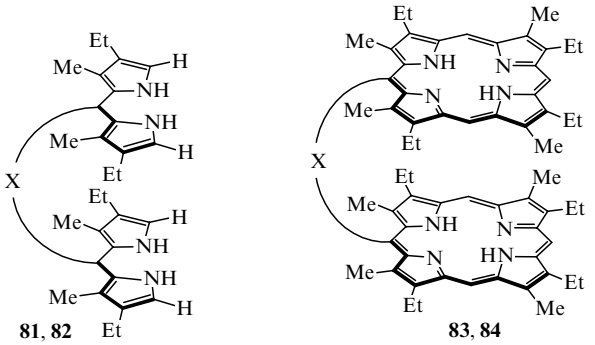
R = C_6H_{13}.

of the reaction mixture with tetrachloroquinone afforded spiro derivatives **79a**,**b** in a total yield of 5% (Scheme 10).[22, 70] Owing to the presence of a rigid spirobisindan bridge between the macrocycles, bisporphyrins acquired fixed spatial orientation. The distances between the centres of the macrocycles are equal to 1.80 and 1.00 nm, respectively; the porphyrin fragments of compound **79b** partially overlap at an angle (see Scheme 10).

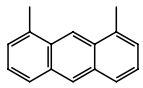
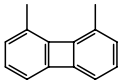
Osuka and Maruyama [71] synthesised a series of bisporphyrins **80** the porphyrin fragments of which were linked through different positions of the naphthalene nucleus. The original 5,5′-unsubstituted bisdipyrrolylmethanes were prepared by the reaction of 5-unsubstituted pyrrole with the corresponding dialdehydes according to the known procedure.[13] The naphthalene fragments ensure rigid binding of porphyrin macrocycles, which are perpendicular to their plane.



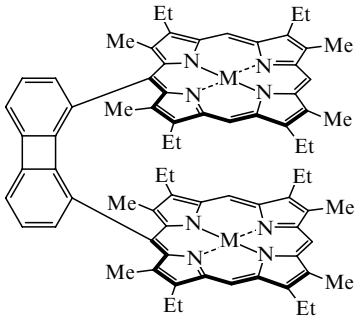
A series of bisporphyrins with a 'face-to-face' orientation of fragments (FTF-porphyrins) containing a conformationally rigid backbone between the macrocycles has been synthesised.[18, 72, 73] The reaction of bisdipyrrolylmethane **81** with bis(3-ethyl-4-methyl-5-methoxymethylpyrrol-2-yl)methane in boiling benzene with its subsequent oxidation with tetrachloroquinone or the reaction of compound **82** with bis(3-ethyl-5-formyl-4-methylpyrrol-2-yl)methane in methanol in the presence of perchloric acid yields bisporphyrins **83** and **84**.



81, **82** **83**, **84**

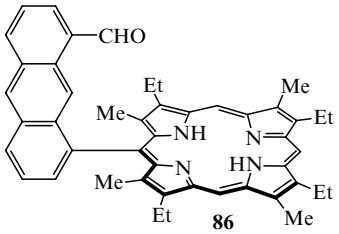
X =  [**83** (10%)],  [**84** (20%)].

It has been noted [18, 72] that bisporphyrins **83** and **84** are devoid of stereoisomers. Spectral data provide evidence in favour of the FTF-orientation of the macrocycles. Collman *et al.*[74] synthesised binuclear ruthenium and molybdenum complexes **85**, which generate coordination compounds with intramolecular metal–metal bonds upon photolysis in pyridine.

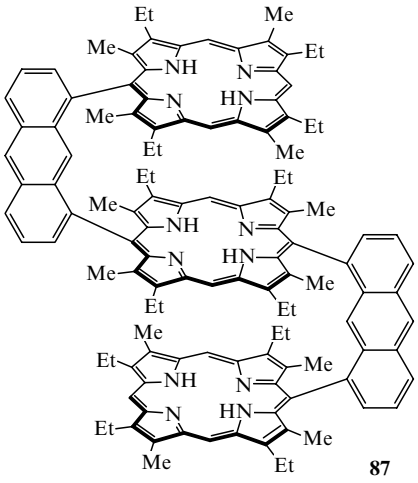


85 (M = Ru, Mo)

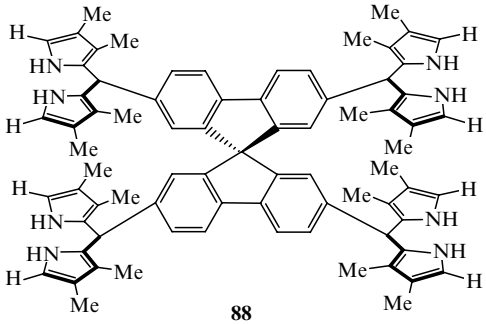
The condensation of formylanthrylporphyrin **86** with bis(3-ethyl-4-methylpyrrol-2-yl)methane has led to a compound of the FTF-type (**87**).[17] Osuka *et al.*[75] carried out the synthesis of tetrakisporphyrin **89** from compound **88** and bis(5-formyl-3-hexyl-4-methylpyrrol-2-yl)methane under identical conditions.



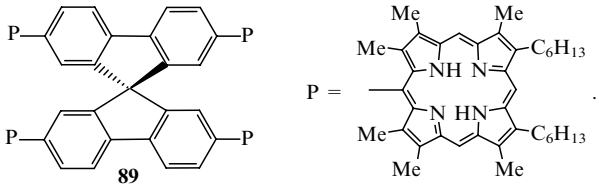
86



87

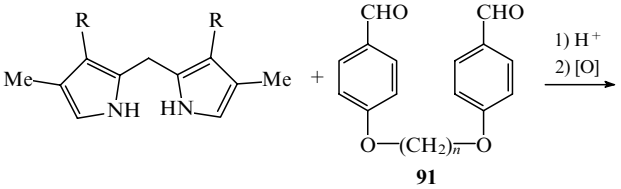


88

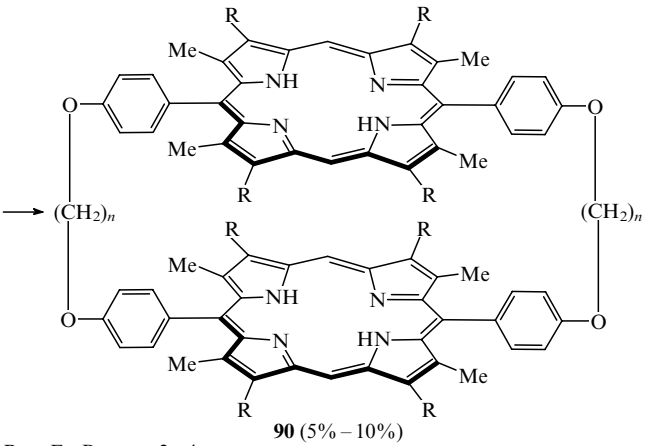


89

A two-step synthesis of cyclophanes **90** containing two bridging $O(CH_2)_nO$ groups connecting the *p*-positions of the benzene nuclei, has been described.[76–78] The condensation of dialdehydes



91

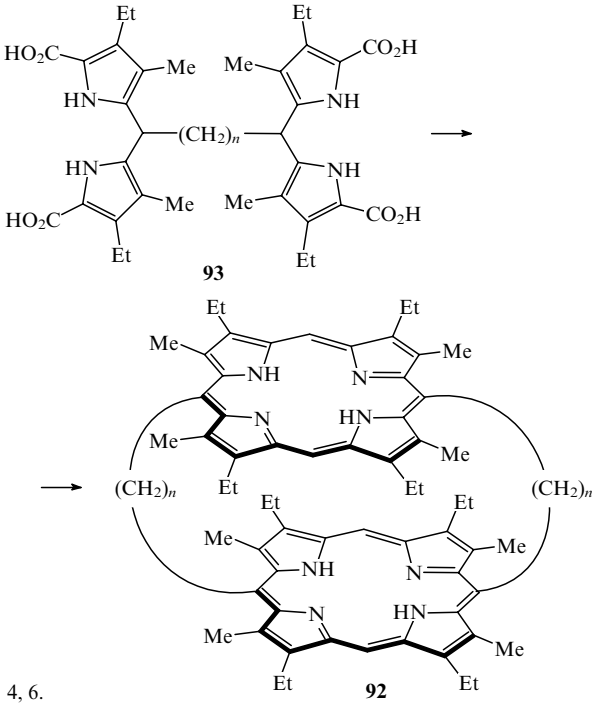


90 (5% – 10%)

R = Et, Bu; *n* = 2–4.

91 with dipyrrolylmethanes was carried out in TFA-containing acetonitrile in an atmosphere of nitrogen. The freely soluble porphyrinogens formed were oxidised *in situ* with *o*-tetrachloroquinone. Cyclophane **90**, the only reaction product, could be easily separated from admixtures by column chromatography.

5,5′-Dicarboxy derivatives of dipyrrolylmethanes were also used in the synthesis of bisporphyrins. The procedure used by Collman [79] in the synthesis of cyclophanes **92** linked with the bridging $(CH_2)_n$ (n = 4, 6) groups through the *meso*-positions is a modification of the Jackson–Kenner synthesis.[69] Heating of bisdipyrrolylmethanes **93** (n = 4, 6) with triethyl orthoformate in dichloromethane in the presence of trichloroacetic acid results in the formation of compounds **92** in very low yields.

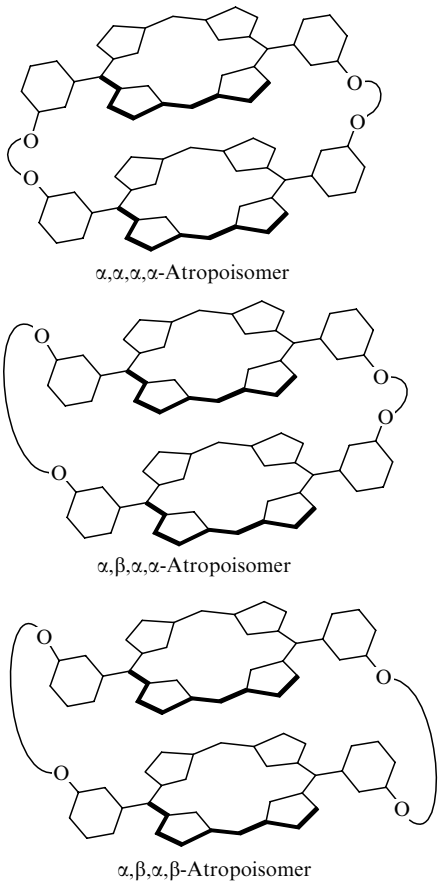


93 → **92**

n = 4, 6.

The same procedure was used [80–82] in the synthesis of cyclophanes **94** in which bridging groups connect the *meta*-positions of the benzene nuclei. They were synthesised by the reaction of bisdipyrrolylmethanes **95** with triethyl orthoformate in boiling chloroform containing 2% TFA. The yield of compound **94** was ~ 5%; the monomeric porphyrins were not formed.

Cyclophane **94** exists in the form of three atropoisomers (their structures are shown in Fig. 2). In bisdipyrrolylmethanes, the phenoxy groups easily rotate around the C–C bond of the bridges, thus giving rise to one or another spatial isomer depending on their orientation at the moment of cyclisation. The calculation of the structure of octamethyl analogues carried out by the molecular mechanics method [82] confirmed the possibility of existence of α,α,α,α-, α,β,α,α- and α,β,α,β-atropoisomers. The insufficient length of bridging groups excludes the formation of the α,α,β,β-isomer. Atropoisomers manifest different mobility in thin-layer chromatography (pyridine–hexane, 1:4) which allowed their separation. The assignment of atropoisomers was performed on the basis of ^{1}H NMR data as well as on the basis of analysis of their coordination properties and chromatographic behaviour.[80]



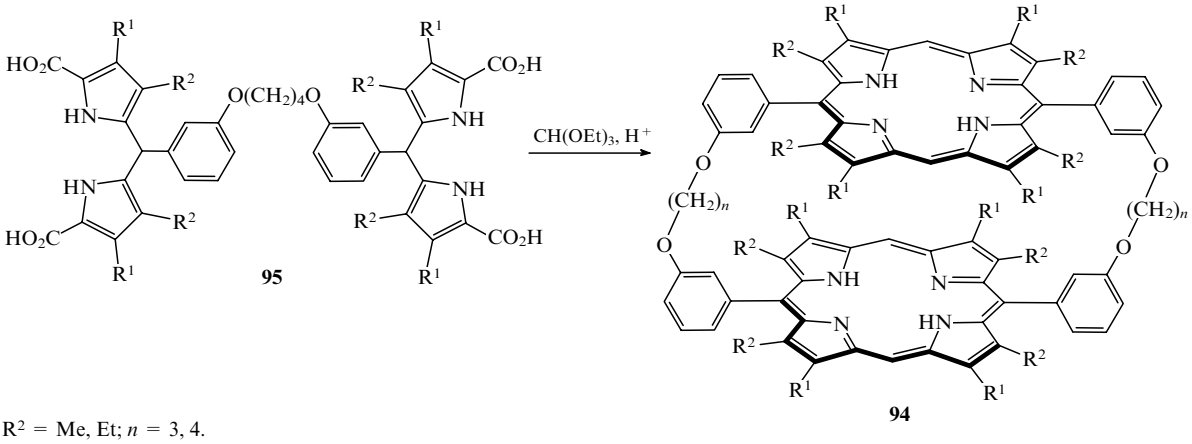
α,α,α,α-Atropoisomer

α,β,α,α-Atropoisomer

α,β,α,β-Atropoisomer

Figure 2. The atropoisomers of cyclophane **94** containing two conformationally active ester bridges.

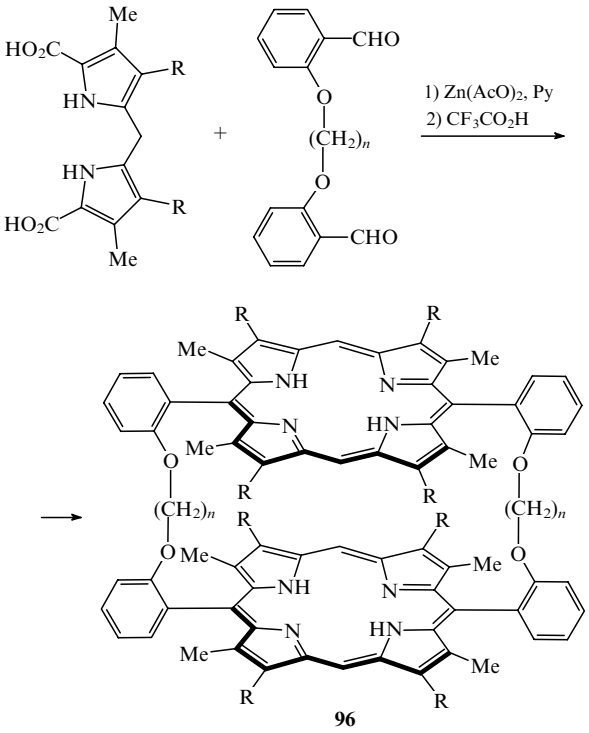
A simpler procedure for the synthesis of analogous compounds has been proposed.[76] The condensation of 5,5′-dicarboxy-substituted dipyrrolylmethanes with dialdehydes in pyridine in the presence of zinc acetate resulted in cyclophanes **96** (which can also exist in the form of three atropoisomers) with



95 → **94**

R^1, R^2 = Me, Et; n = 3, 4.

bridging $O(CH_2)_nO$ ($n = 2-4$) groups connecting the *ortho*-positions of the benzene rings.



R = Et, Bu; $n = 2-4$.

The zinc complexes formed by template synthesis were destroyed *in situ* by treatment with TFA. The molar ratio of the reaction mixture components is critical for the yields of cyclophanes **96**. Using the mathematical simulation method, it was demonstrated that the maximum yield of these compounds varied from 8% to 15% and was reached at the dipyrrolylmethane : dialdehyde : zinc acetate molar ratio of 1 : 2 : 1. These yields decrease regularly with a decrease in the number of methylene units, *n*. The same applies to cyclophanes which contain bridging groups connecting the *meta*- and *para*-positions of the benzene nuclei (compounds **90** and **94**) and may occur as a result of stronger spatial restrictions in cyclocondensation. The optimum duration of the reaction is 2.5 to 3 h. With a drop in temperature from 120 to 80 °C, the reaction products contain only trace amounts of cyclophanes.

It should be noted that the cyclophane **96** containing a shortened bridge $O(CH_2)_2O$ cannot form isomers; all the oxygen atoms of the ether group are arranged inwards towards the interporphyrin cavity.

Cyclophanes containing methyl and ethyl groups in the β-positions of the macrocycles are extremely poorly soluble in the majority of organic solvents; tetrabutyl derivatives are more soluble.

VI. Conclusion

The use of dipyrrolylmethanes opens up good perspectives for the synthesis of different types of mono- and bisporphyrins. At the same time, the potentialities of syntheses based on dipyrrolylmethanes are far from being exhausted. These methods hold a prominent place in the synthetic chemistry of porphyrins. The choice of particular synthetic procedures is largely determined by the symmetry of the porphyrin molecule, the mode and mutual arrangement of substituents in the macrocycle as well as by the availability of the starting compounds.

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