SYNTHESES OF PORPHYRINS THROUGH OPEN TETRAPYRROLE STRUCTURES

(REVIEW)

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Methods for the preparation of porphyrins through 1-methyl-19-formyl(H)-bil-b-enes and 1-methyl-19-H-bila-a,c-dienes are examined. Principal attention is directed to a discussion of the effect of electron-acceptor substituents on the formation of open polypyrrole compounds and cyclization of the latter to porphyrins.

Synthetic studies of porphyrins are carried out by means of investigations of the biosynthesis and catabolism of these compounds [1-5] in order to ascertain the mechanism of the action of chromoproteides [6, 7] and to create biologically active substances [8]. Porphyrins and their metal complexes are studied extensively both within a theoretical framework [9] and in order to arrive at practical applications of them [10-12]. In particular, porphyrins are used as markers in geochemistry in the determination of the level of life on the earth in various historical epochs [13, 14]; they are detected in meteorites and on the moon's surface [15].

The development of the synthesis of porphyrins began with the fundamental research of the Fischer school [16]. The culmination of this research was the synthesis of hemin. Despite the low yield of the final product (0.1%), this event was an important advance in synthetic organic chemistry. Of the later studies, one should undoubtedly note the total synthesis of chlorophyll *a*, accomplished by Woodward [17] in 1960.

At present, methods that include the synthesis of intermediate "linear" tetrapyrrole compounds are among the most successful of the various methods for the preparation of porphyrins. Molecular models show that such structures exist in a spiral loop conformation due to repulsion of the adjacent β substituents [18]; the extreme A and D pyrrole rings prove to be drawn together in this case, and this is an important factor in the case of closing to form macrocyclic compounds. Depending on the oxidation state of the tetrapyrrole compounds, the existing methods can be divided into two principal groups. The first group includes the synthesis of bilene structures, and the second group includes the synthesis of biladiene structures. Within each of the above-indicated groups, individual methods are in turn distinguished by the modes of construction of the polypyrrole chain and also by the presence of various substituents in the 1 and 19 positions. The latter circumstance to a considerable degree determines the method of cyclization of the bilenes and biladienes to porphyrins.

Despite undoubted advances, the synthesis of complex porphyrin structures and, in particular, porphyrins with electron-acceptor substituents has been fraught up to now with certain difficulties [19]. A number of reviews devoted to research on porphyrins has been published in recent years [18, 20-24]. However, these reviews usually encompass a broad range of problems, and this does not make it possible to consider all of the available studies in detail. The aim of the present review was a discussion of the results of a portion of our studies on the synthesis of porphyrins. We deliberately limited our examination of methods for the preparation of porphyrins, singling out a group of syntheses through linear tetrapyrrole compounds, inasmuch as this method enabled us to solve some difficult problems in the synthesis of porphyrins.

Synthesis of Porphyrins through 1-Methyl-19-formyl(H)-bil-b-enes

In developing this method we proceeded from the fact that a symmetrical dipyrrole structure (dipyrrolylmethene C-D in porphyrin molecule 1) can be isolated in most natural porphyrins of the protoporphyrin

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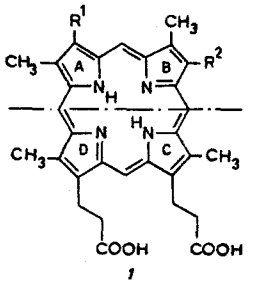
IX* and coproporphyrin III types. We therefore decided to realize synthesis of bil-b-ene on the basis of dipyrrolylmethane fragments A-B and C-D. Symmetrical dipyrrolylmethanes 2a [26] and 2b [27, 28] were the key compounds in our method for the preparation of porphyrins through bil-b-enes [29].



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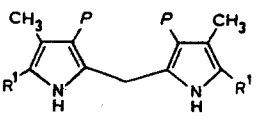
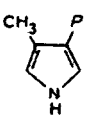


2a, b

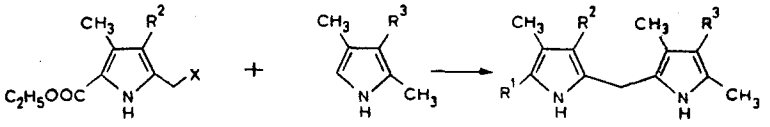


3

2 a R¹=H; b R¹=CHO; P=$CH_2CH_2COOCH_3$

The most complicated problem in the preparation of dipyrrolylmethane 2a was decarboxylation of the corresponding 5,5'-dicarboxylic acid. Only strict observance of the reaction conditions makes it possible to obtain 2a in high yield; if such conditions are not observed, the dipyrrolylmethane undergoes decomposition, and the chief product is pyrrolecarboxylic acid 3.

Dipyrrolylmethanes of the 6 type, which are considerably more accessible than the corresponding α,α'-unsubstituted derivatives [30], were selected as the second dipyrrole fragment (A-B).

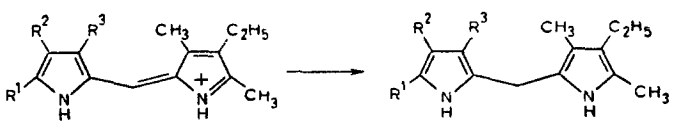


4 5 6 a-c

4—6 R^2=Et, $CH_2CH_2COOCH_3$, CH=CHCOOH, Ac, COEt, COBu, COBu-*i*, COPh, $COC_{15}H_{31}$; R^3=H, Me, Et, $CH_2CH_2COOCH_3$, CH=CHCOOH, Ac, $CH_2CH_2NEt_2$, 6 a R^1=H; b R^1=CHO; c R^1=COOEt

Compound 6c ($R^2=R^3$=Ac) and the isomeric dipyrrolylmethanes were prepared by heating α-chloromethylpyrrole 4 with pyrrole 5 in alcohol [31]. A number of dipyrrolylmethanes 6c (R^2=acyl, R^3=alkyl) was obtained by refluxing the reagents with triethylamine in chloroform [32, 33]. In the case of 6c (R^2=Et, R^3=Ac) better results are obtained when acetoxymethyl derivative 4 (X=OAc) and pyrrole 5 are heated in aqueous alcohol [34]. Dipyrrolylmethanes 6c ($R^2=R^3$=P and $R^2=R^3$=CH=CHCOOH) were obtained from acetoxymethyl derivative 4 and pyrrole 5 in dimethylformamide (DMF) [28]. No difficulties are usually encountered in the conversion of the resulting dipyrrolylmethanes to the corresponding α-unsubstituted compounds and formylation of the latter.

In our discussion of the synthesis of dipyrrolylmethanes it would be particularly desirable to dwell on two instances. The first is associated with the preparation of dipyrrolylmethanes that do not have stabilizing electronegative groups and, because of this, are extremely labile. With this end in mind, we used the accessible dipyrrolylmethenes 7a,b [30], which were reduced with sodium borohydride. This method can be used for the preparation of α-unsubstituted dipyrrolylmethanes, although the principle product usually contains a small amount of pyrroles. For this reason, dipyrrolylmethene carboxylic acid 7c, which is in turn obtained in practically quantitative yield [16], was subsequently reduced. The yield of 8c was 88%. The accessibility of the starting dipyrrolylmethenes and their easy reduction with sodium borohydride makes it possible to hope that this method will find application in the synthesis of alkyl-substituted dipyrrolylmethanes [35].



7 a-c 8 a-c

7, 8 a R^1=Br; R^2=CH_3; R^3=C_2H_5; b R^1=H; R^2=C_2H_5; R^3=CH_3; c R^1=COOH; R^2=CH_3; R^3=C_2H_5

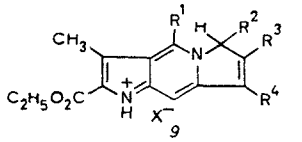
*The nomenclature proposed by H. Fischer [16] is used for porphyrins in this review, whereas the IUPAC system [25] is used for polypyrrole compounds.

TABLE 1. Porphyrins Synthesized through Bil-b-enes*

Porphyrin	Starting dipyrrolylmethanes				Variant	Yield, %
	2	6				
	R^1	R^1	R^2	R^3		
2-Ethyl-4-acetyldeuteroporphyrin IX	CHO	H	Et	Ac	A	26
	H	CHO	Et	Ac	B	28
2-Acetyl-4-ethyldeuteroporphyrin IX	CHO	H	Ac	Et	A	11
Diacetyldeuteroporphyrin IX	CHO	H	Ac	Ac	A	3,3
	H	CHO	Ac	Ac	B	9,5
Mesoporphyrin IX	CHO	COOH	Et	Et	A	26
Protoporphyrin IX + 2,4-bis(1-hydroxy-2-carbomethoxyethyl)-deuteroporphyrin IX	CHO	COOH	CH=CH | COOH	CH=CH | COOH	A	5,0+6,7

*All of the porphyrins presented in this table are the dimethyl esters.

The second instance involves the synthesis of 3-acyldipyrrolylmethanes. As a result of intramolecular condensation, dipyrrolylmethanes of this sort in acidic media are rapidly converted to 6H-pyrrolo-[3,2-f]indolizines (9) [36, 37]. A similar reaction was observed in the dipyrrolylmethene series [38]. Pyrroloindolizines 9 constitute a new class of heterocyclic compounds and are of undoubted interest [39].



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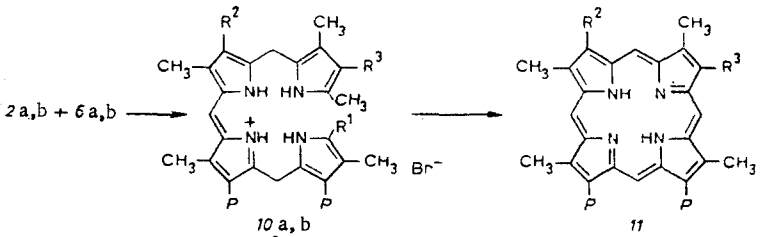
In developing a method for the preparation of porphyrins [40] we started from the fact that bil-b-enes, in contrast to bil-a-enes and bil-c-enes [41, 42], are sufficiently flexible systems. In addition, the presence of a methyl group in the 1 position and of hydrogen or a formyl group, which can be split out [43], in the 19 position makes it possible to close this system to a porphyrin. In order to facilitate the cyclization we used copper salts. It might have been expected that the formation of a bilene complex with divalent copper ions would facilitate the drawing together of the extreme pyrrole rings [44, 45], and, in addition, Cu^{2+} may act as an oxidizing agent.

In the first synthetic variant (A) we used aldehyde 2b and unsymmetrical dipyrrolylmethane 6a. In the second variant (B) dipyrrolylmethanes 2a and 6b were condensed (Table 1).

It is expedient to examine the peculiarities of this method in the case of 2-ethyl-4-acetyldeuteroporphyrin IX [34]. In this case the key moment in the synthesis is condensation of the starting dipyrrolylmethanes. Of the various factors involved (the ratio of the dipyrrolylmethanes, dilution, order of addition of the mineral acid, temperature, etc.) the chief factor is the amount of acid used (or, more precisely, its concentration). When the condensation is carried out via variant A in methanol with HBr, the yield of bilene 10b initially increases as the amount of acid is increased, reaching 75% when 30% excess acid is present, after which the yield decreases smoothly (63% when a fourfold excess is present and 56% when a 20-fold excess is present).



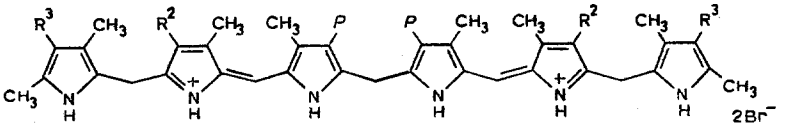
10 a, b

10 a R^1=H; b R^2=CHO

11

It was shown that dipyrrrolylmethanes can be condensed both to bil-b-enes and to side product hexapyrrodiene 12a. In contrast to the bilene, the yield of the latter increases as the excess amount of the acid increases (42% in the case of a 20-fold excess of HBr).

The simultaneous formation of bilene and hexapyrrodiene is evidently due to reaction between bilene and the as yet unchanged dipyrrolylmethane 6a. In fact, when a 25% excess of 2b is used, the yield of bilene increases. This sort of method of carrying out the condensation seems of interest, inasmuch as, in addition to increasing the yield of bilene, it restricts the formation of hexapyrrodiene, which gives a mixture of various porphyrins in the next step, hindering isolation of the desired porphyrin.



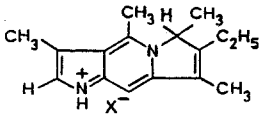
12 a-e

12 a $R^2=C_2H_5$, $R^3=Ac$; b $R^2=R^3=Ac$; c $R^2=CO_2C_2H_5$, $R^3=Ac$; d $R^2=R^3=P$; e $R^2=R^3=C_2H_5$

The cyclization of bilene 10b ($R^2=Et$, $R^3=Ac$) was carried out in methanol with acetic acid in the presence of copper acetate. The yield of the copper complex of the dimethyl ester of 2-ethyl-4-acetyldeuteroporphyrin IX (11, $R^2=Et$, $R^3=Ac$) was 39%, and other porphyrins were not detected.

In a preparative respect, it is more advantageous to synthesize the porphyrins directly from dipyrrolylmethanes without isolation of the bilenes. In the first case (variant A) when a small amount of HBr was used, the yield of the desired products was 27%, as compared with only 6% in the case of a high acid concentration (the reaction mixture also contained a number of porphyrins). In the second case (B) the formation of hexapyrrodiene 12a was not observed, and the yield of porphyrin reached 28%. The conversion of 19-unsubstituted bilene 10a to hexapyrroldiene 12a evidently proceeds more slowly than the corresponding reaction with 19-formylbilene 10b. The different reactivities of the bilenes are associated with the fact that the α-unsubstituted position in bilene 10a is somewhat deactivated because of the effect of the conjugated dipyrrolylmethene structure, whereas this effect is not observed in the case of 19-formylbilene.

In order to ascertain the effect of the position of the acetyl group in the dipyrrolylmethane on the formation of bilene and cyclization of the latter to porphyrin we synthesized an isomeric porphyrin – 2-acetyl-4-ethyldeuteroporphyrin IX (11, $R^2=Ac$, $R^3=Et$) [46]. Considering what was stated above, it would be more expedient to synthesize this porphyrin by method B. However, we were unable to introduce a formyl group into α-unsubstituted dipyrrolylmethane. In the presence of acid reagents dipyrrolylmethane is converted to pyrroloindolizine 13.



13

The synthesis of the porphyrin was therefore accomplished only via variant A. The lability of 6a ($R^2=Ac$, $R^3=Et$) required thorough checking of the reaction conditions. Best results were obtained when the condensation was carried out in acetic acid with a small amount of acetic anhydride [47] and a fourfold excess of hydrobromic acid. In this case hexapyrrodiene is not formed even at high HBr concentrations. An increase in the reaction time leads to the formation of coproporphyrin. The oxidative cyclization of bilene gave 2-acetyl-4-ethyldeuteroporphyrin IX in 11% yield. As seen from this synthesis, the presence of an acetyl group in the pyrrole ring adjacent to the methene bridge of bil-b-ene considerably hinders the preparation of the porphyrin.

We also synthesized a porphyrin with two electronegative groups. We used diacetyldeuteroporphyrin IX as the subject [29, 48]. This choice was due to the fact that this compound is an intermediate in the preparation of hemato- and protoporphyrins IX [49, 50]. In the course of our research diacetyldeuteroporphyrin was synthesized in [51] extremely low yield on the order of 0.1% based on the starting dipyrrolomethenes.

Diacetyldeuteroporphyrin IX has been synthesized by two methods [27, 52]. Better results are obtained by variant B. A study of the two processes made it possible to conclude that the principal difference is associated with the formation of the corresponding bil-b-enes. When aldehyde 6b ($R^2=R^3=Ac$) was used, the yield of the bilene was close to quantitative. At the same time, the bilene is formed only in insignificant amounts in variant A. These results were also obtained at low HBr concentrations and when a large excess of HBr was present. Just as in the previously considered synthesis [46], hexapyrrodiene is not

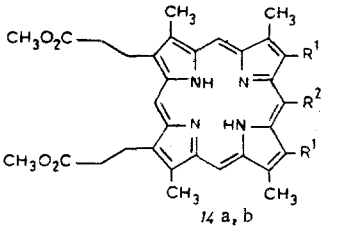
formed in the case of variant A. On the other hand, an increase in the amount of mineral acid in variant B leads to the formation of side product hexapyrrodiene 12b. In addition, at high HBr concentrations, coproporphyrin II is formed in considerable quantities along with diacetyldeuteroporphyrin IX [27]. The cyclization of bilene 10a ($R^2 = R^3 = Ac$) under the usual conditions gives the copper complex of diacetyldeuteroporphyrin IX in 9.5% yield.

Mesoporphyrin IX is the traditional subject in the development of new methods for the preparation of porphyrins [53-55]. We also accomplished the synthesis of this compound [35, 52]. Because of the difficulty involved in the preparation of dipyrrolylmethane 6b ($R^2 = R^3 = Et$), we checked only variant A. A peculiarity in the synthesis in this case was the fact that α-carboxydipyrrolylmethane was used in the reaction. Considerable quantities of mineral acid were necessary to effect decarboxylation. This led to the formation of hexapyrrodiene 12e. We were able to reduce this reaction to a minimum by using acetic acid as the solvent. The reasons for such a specific effect of acetic acid are as yet unclear. Mesoporphyrin IX was obtained in 26% yield as a result of closing of the bilene [35].

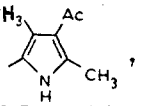
The method under examination for the preparation of porphyrins was also used for the synthesis of the porphyrin most widespread in nature – protoporphyrin IX [28]. Acrylic acid was used as the precursor of the vinyl group. A number of pyrroles and dipyrrolylmethanes with acrylic acid residues was synthesized [56]. Unsymmetrical dipyrrolylmethane 6 ($R^1 = COOH$, $R^2 = R^3 = CH = CHCOOH$) under decarboxylation gave a mixture of two compounds, viz., 6a ($R^2 = R^3 = CH = CHCOOH$ and $R^2 = R^3 = CH = CH_2$), which were used, without separation, for the synthesis of the porphyrin. The condensation of the dipyrrolylmethanes was carried out in methanol with a considerable excess of HBr. The formation of the bilene was monitored spectrophotometrically, after which it was cyclized to the porphyrin. As a result we obtained protoporphyrin IX in ~ 5% yield, as well as another porphyrin, which was found to be deuteroporphyrin IX – 2,4-di-(2-hydroxypropionic acid) (6.7%).

The latter compound [57] is the biogenetic precursor of protoporphyrin IX. We realized the conversion of deuteroporphyrin IX – 2,4-di(2-hydroxypropionic acid) – to protoporphyrin IX. With allowance for this transformation and the fact that the yields of the porphyrins were calculated not on the basis of starting dipyrrolylmethane 6a but rather on the basis of its carboxylic acid, the yield of protoporphyrin IX should be considered to be satisfactory.

In conclusion let us say a few words regarding the side reactions that occur during the synthesis of porphyrins through bil-b-enes, above all, the formation of hexapyrrodienes. In order to study these compounds and their conversion to porphyrins we realized the specific synthesis of a number of hexapyrrodienes (12a-e). The yields of these compounds usually exceed 90%. Heating the hexapyrrodienes in methanol with acetic acid in the presence of copper acetate leads to various porphyrins. When electronegative substituents are present in the extreme pyrrole rings, meso-pyrrolylporphyrins are formed [34]; meso-unsubstituted porphyrins are formed when substituents of this type are absent [35, 58], and porphyrin-like compounds, the structure of which has not been definitively ascertained, are formed when electron-acceptor groups are present in the two extreme pyrrole rings. The first type of cyclization of hexapyrrodienes under different conditions was described by Clezy and Liepa [59]. Cyclization of 12a leads to α-(2,4-dimethyl-3-acetyl-5-pyrrolyl)mesoporphyrin III (14a), and mesoporphyrin III (14b) is also formed in small amounts [34]. The presence of these compounds in the reaction mixture markedly hinders the isolation and purification of the principal porphyrin formed from the bilene, and the formation of a hexapyrrodiene during the synthesis of the bilene is therefore extremely undesirable. The cyclization of hexapyrrodiene 12e leads to mesoporphyrin III (14b) in 65% yield [35].



14 a, b

a $R^1 = C_2H_5$, R^2 =  , 2,4-dimethyl-3-acetyl-5-pyrrolyl

b $R^1 = C_2H_5$, $R^2 = H$

Coproporphyrin II is formed as a side product when there is an electronegative substituent in the A ring of the unsymmetrical dipyrrolylmethane and the mineral acid concentration is high [27, 46].

In concluding this section, it would be desirable to state some fundamental observations.

1. The utilization of the method is expedient for the synthesis of porphyrins of the protoporphyrin IX type in view of the accessibility of the starting pyrroles and dipyrrolylmethanes.

2. The method makes it possible to synthesize porphyrins with both electron-donor and electron-acceptor substituents.

3. Of the two variants for the synthesis of the bilene, better results are obtained when an unsymmetrical formyldipyrrolylmethane is used. In this case the yield of the hexapyrrodiene side product is a minimum. The formation of the latter also is reduced when excess symmetrical dipyrrolylmethane is used. When a symmetrical diformyldipyrrolylmethane is used, it is better to use the carboxylic acid form of the second component. In this case one can also avoid the formation of the hexapyrrodiene. This is apparently associated with the low rate of decarboxylation of the dipyrrolylmethanecarboxylic acid, as a consequence of which the chief reaction proceeds practically when a large excess of the symmetrical component is present.

4. The cyclization of bil-b-enes proceeds successfully in a mixture of methanol and acetic acid, and 1-methyl-19-formylbilenes undergo closure more readily than the corresponding 19-unsubstituted bilenes.

Synthesis of Porphyrins through Bila-a,c-dienes

Continuing our search for new methods for the preparation of unsymmetrical porphyrins and considering that for most natural compounds these methods should include the use of the readily accessible dipyrrolylmethane 2, we developed a new method for the synthesis of porphyrins through bila-a,c-dienes [60, 61]. The method includes the preparation of 1-methyl-14-unsubstituted tripyrrene-a (16), conversion of it to biladiene 18, and cyclization of the latter to porphyrin 19. The key moment in the synthesis of the porphyrin is the step involving the preparation of the tripyrrene. As in the synthesis of bil-b-enes, in the condensation of formylpyrroles 15 with symmetrical dipyrrolylmethane 2a, one may observe, in addition to the formation of the tripyrrene, a side reaction leading to a symmetrical biladiene. We chose conditions that made it possible to practically exclude the formation of the biladiene [62]. These conditions include the use of aprotic solvents, vigorous stirring of the reaction mixture, and slow addition of stoichiometric amounts of the mineral acid. The development of the tripyrrene structure during the addition of a molecule of pyrrole 15a to dipyrrolylmethane 2a leads to partial deactivation of the second α position. This is the reason for the fact that addition of a second formylpyrrole molecule is not observed at low mineral acid concentrations. The yield of 1-methyl-14H-tripyrrenes reaches 95%.

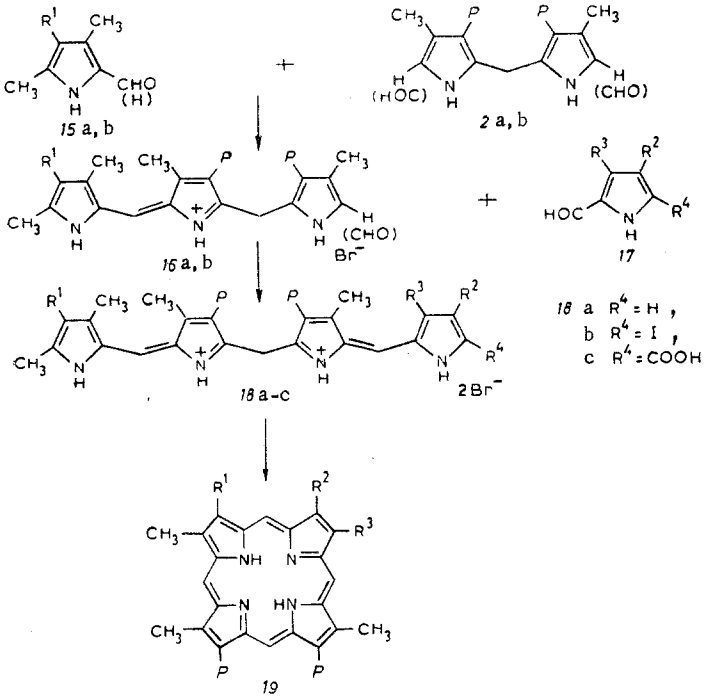
We also studied the possibility of the preparation of tripyrrenes from α,α'-diformyldipyrrolylmethane 2b and α-unsubstituted pyrroles 15b. In this case the addition of the first pyrrole molecule does not

TABLE 2. Porphyrins Obtained through Biladienes*

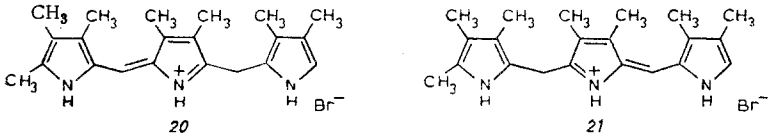
Porphyrin	Starting biladiene 18				Yield, %
	R^1	R^2	R^3	R^4	
Mesoporphyrin IX	Et	Me	Et	H	91
	Et	Me	Et	COOH	72
Mesoporphyrin III	Et	Et	Me	H	86
Coproporphyrin III	*P*Me	Me	*P*Me	I	76
	*P*Me	Me	*P*Me	COOH	53
2-(2-Carbomethoxyethyl)-4-methyldeuteroporphyrin IX	*P*Me	Me	Me	H	82
2-Ethyldeuteroporphyrin IX	Et	Me	I	I	67
4-Methyldeuteroporphyrin IX	H	Me	Me	H	30
2-Ethyldeuteroporphyrin III	H	Et	Me	H	76
Deuteroporphyrin IX	H	Me	I	I	30
2-Ethyl-3-(2-diethylaminoethyl)-deuteroporphyrin III	$CH_2CH_2NEt_2$	Et	Me	H	51
2-Acetyl-4-methyldeuteroporphyrin IX	Me	Ac	Me	H	61
	Ac	Me	Me	H	41
2-Ethoxycarbonyl-3-ethyldeuteroporphyrin III	Et	CO_2Et	Me	H	69
	CO_2Et	Et	Me	H	32
2-Ethyl-4-ethoxycarbonyldeuteroporphyrin IX	Et	Me	CO_2Et	I	41
2-Cyano-4-methyldeuteroporphyrin IX	CN	Me	Me	H	56
2-Ethoxycarbonyl-4-methyldeuteroporphyrin IX	CO_2Et	Me	Me	H	63

*All of the compounds were obtained as the dimethyl esters.

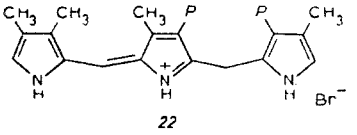
hinder subsequent reaction, and, as a result, tripyrrene 16b contains a symmetrical biladiene impurity [63].



Tripyrrene-a 20 and tripyrrene-b 21 were synthesized in order to study the reactivities of isomeric tripyrrenes [64]. It was shown that the 14 position in tripyrrene-b is markedly deactivated, and compounds of this sort give biladienes only under severe conditions.



We therefore prepared 1,14-unsubstituted tripyrene-a 22, which, in some cases, made it possible to simplify the synthesis of the porphyrins [65, 66].



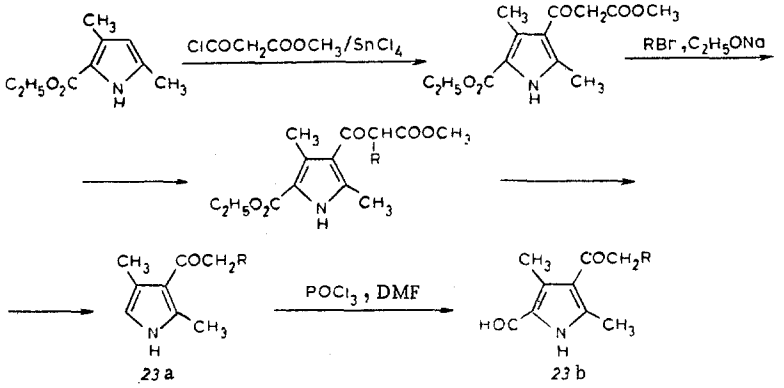
The condensation of tripyrrene-a 16a with formylpyrroles 17 makes it possible to obtain biladienes 18a-c containing hydrogen or iodo or carboxyl groups in the 19 position in up to 96% yields.

The cyclization of biladienes to porphyrins (Table 2) is accomplished in o-dichlorobenzene; it is best to use iodine as the oxidizing agent in this case [63], whereas it is best to use a mixture of iodine and bromine in the synthesis of porphyrins with electron-acceptor groups [66]. Higher yields are obtained for porphyrins with electron-donor substituents. Porphyrins with one β-unsubstituted position are obtained in somewhat poorer yields. The presence of two β-unsubstituted positions in the biladiene hinders cyclization even more. Thus, in the well-known Johnson method the yield of deuteroporphyrin IX from 1-methyl-19-bromobiladiene was 9.7% [67]. We synthesized this porphyrin in 30% yield [63]. A porphyrin containing a β-diethylaminoethyl group, which was proposed in our laboratory for the preparation of vinylporphyrins [68-71], was also synthesized. The cyclization of 1-methyl-19-carboxybiladienes proceeds with somewhat greater difficulty than the cyclization of 19H-biladienes; however, considering that biladienes of this sort are more accessible in a number of cases, this method also is worthy of attention.

It is well known that the synthesis of porphyrins with electronegative substituents in the ring may proceed ambiguously [72]. Each newly proposed method should therefore be checked for the synthesis not

only of porphyrins with electron-donor groups but also of those with electron-acceptor groups. We have synthesized porphyrins with ester, acetyl, and nitrile groups. In this case we observed that the position of the substituent in the biladiene has a pronounced effect on the yield of the porphyrin. When there is a substituent in the 2 position, the yield of the porphyrin is lower by a factor of 1.5-2 than when there is a substituent in the 18 position [65]. It was found that the degree of conversion of 2-substituted biladienes to porphyrins can be increased if a small amount of bromine is used together with iodine as the oxidizing agent [66]. Thus, the yield of porphyrin 19 (R^1=CN, R^2=R^3=Me) increases from 22 to 56%. The latter circumstance is extremely advantageous, inasmuch as it makes it possible to work with a more accessible biladiene of the first type.

The possibilities of the method were thoroughly demonstrated in the case of a more complex porphyrin – 2-(1-oxohexadecyl)-4-methyldeuteroporphyrin IX [66]. The synthesis of this compound was associated with research on heme *a* and, in particular, with the problem of the incorporation of an unsaturated alcohol residue in the porphyrin molecule. The pyrroles necessary for the synthesis were obtained by Friedel–Crafts acylation of 2,4-dimethyl-5-carbethoxypyrrole [32]. However, this method is not suitable for unsaturated substituents. We therefore developed a different method [73]. The yield of pyrrole 23a was 39%.

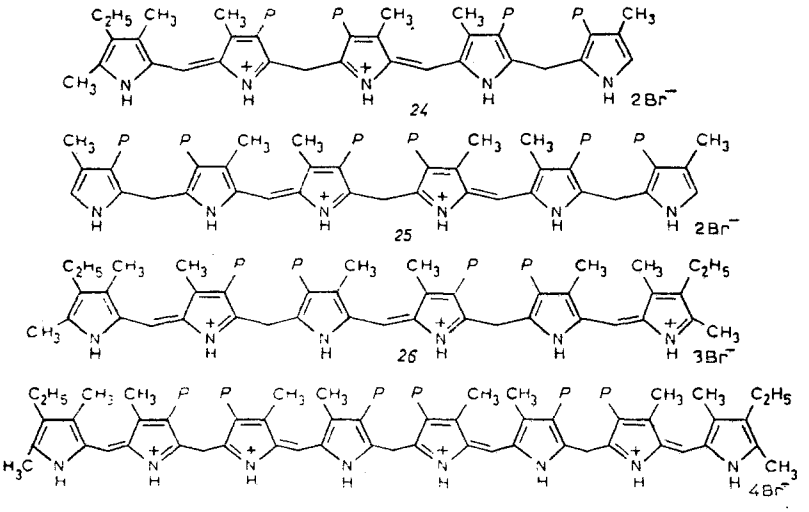


A mixture of iodine and bromine has also been used for the cyclization of a biladiene; this made it possible to raise the yield from 35 to 78% [66].

Thus, our method for the stepwise synthesis of porphyrins through tripyrrenes and biladienes makes it possible to obtain porphyrins with both electron-donor and electron-acceptor substituents in high yields. The low number of synthesis steps, the simplicity of carrying out the reaction, and the high yields in each of the three steps make it possible to suppose that this method is today the most convenient method for the synthesis of porphyrins containing at least one symmetrical dipyrrole structure.

Synthesis of New Types of Linear Polypyrrole Compounds

In order to study the reactivities of tripyrrenes and the side reactions that occur during the synthesis of biladienes, we synthesized a number of linear penta-, hexa-, and octapyrrole compounds with



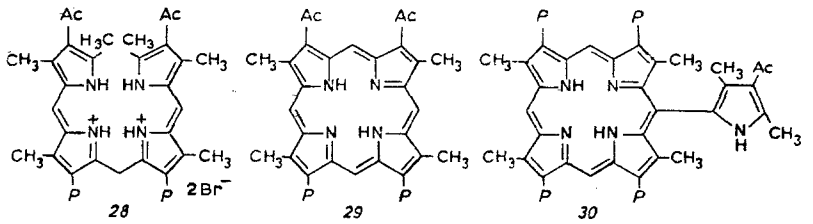
methylene-separated dipyrrolylmethene structures from dipyrrolylmethanes 2a,b and tripyrrenes 16a,b [74, 75]. Compounds 24, 26, 27 are formed in almost quantitative yields, and hexapyrrodiene 25 is formed in 85% yield. Despite the presence of α-unsubstituted positions, penta- and hexapyrrodienes 24 and 25 do not undergo further reaction with formyl derivatives. This sort of deactivation is evidently due to the presence of a biladiene structure in these compounds.

The chief reaction in the preparation of polypyrrole compounds is reaction of formyl- and α-unsubstituted pyrroles. A study of this reaction in the case of carbethoxy-substituted formylpyrroles made it possible to conclude that its occurrence through a dipyrrolylcarbinol [76] or immediately to give the dipyrrolylmethene [77] is associated with the ability of formylpyrroles to undergo protonation [78]. The dipyrrolylmethene is formed by protonation of the aldehyde, bypassing the dipyrrolylcarbinol step. On the other hand, the unprotonated form of the formylpyrrole gives the dipyrrolylcarbinol, which is then converted to the dipyrrolylmethene. The reactions that proceed through dipyrrolylcarbinols may give branched tripyrrolylmethanes [79, 80], which often lead to a mixture of dipyrrolylmethenes [81]. In those cases where the dipyrrolylcarbinol is not formed, the reaction proceeds specifically.

A study of the mass-spectrometric behavior of polypyrrole compounds and primarily tripyrrenes revealed a number of interesting features [82]. Whereas practically individual mass spectra are obtained for the tripyrrenes up to 100°, above 250° the spectra of the porphyrins are observed as a result of thermal cyclization. The biladienes behave similarly.

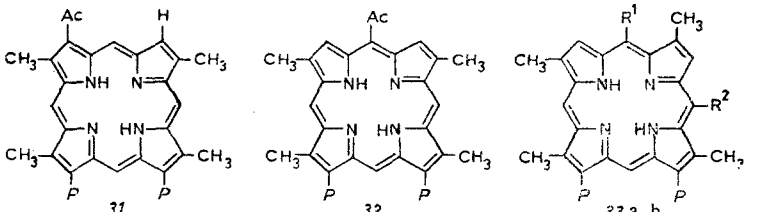
Syntheses of Acetyl- and Formyl-Substituted Porphyrins through 1,19-Dimethylbiladienes

In order to study their spectral and various physicochemical properties we synthesized mono- and diacetyldeuteroporphyrins III and IX. Symmetrical diacetyldeuteroporphyrin III (29) was obtained by cyclization of 1,19-dimethylbiladiene (28) under conditions similar to those in the synthesis of porphyrins through bil-b-enes [83]. β-meso-(2,4-Dimethyl-3-acetyl-5-pyrrolyl)coproporphyrin II (30) was isolated from the reaction mixture along with 29 [84]. In contrast to hexapyrrodienes, the conversion of biladienes to meso-pyrrolylporphyrins was noted for the first time. The PMR, IR, and electronic spectra and the mass-spectrometric behavior of meso-pyrrolyl-substituted porphyrins were examined in [85].



28 29 30

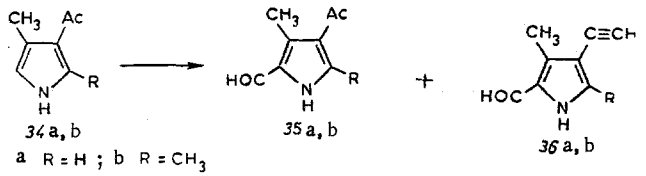
A group of acetylporphyrins (31-33) was also obtained by Friedel–Crafts acylation of copper complexes of deuteroporphyrins III and IX. The most interesting compounds proved to be the meso-acetyl derivatives [86, 87]. The possibility of introduction of an acetyl group in the meso position of the porphyrin ring has not been previously noted [88]. We were able to isolate α-meso-acetyldeuteroporphyrin III (32) and α- and β-meso-acetyldeuteroporphyrins IX (33a,b).



31 32 33 a, b

33 a R^1 = Ac, R^2 = H; b R^1 = H, R^2 = Ac

We obtained the starting acetylformylpyrroles for the synthesis of biladienes by Vilsmeier–Haack formylation. It was observed that pyrrolylacetylene 36 is formed along with pyrrole 35 under these conditions [89].



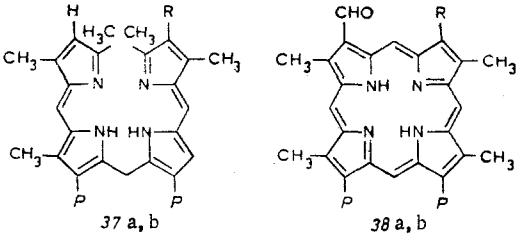
34 a, b
a R = H ; b R = CH_3

35 a, b

36 a, b

The reaction evidently includes attack on the acetyl group in the enol form [90] by phosphorus oxychloride to give an α-chlorovinyl derivative, which is dehydrohalogenated by alkali to pyrrole 36.

A reaction that occurs during the oxidative reaction of 1,19-dimethylbiladiene (in which there are no substituents in the 1 and 18 positions), which we observed in [91, 92], seems of considerable interest. Biladienes 37a,b gave formylporphyrins 38a,b in yields on the order of 15% when they were heated in DMF in the presence of copper chloride.



37 a, b

38 a, b

37, 38 a R = H ; b R = C_2H_5

The use of lead dioxide made it possible to raise the yield in the case of biladiene 37a to 30%. It has been assumed [91] that the formyl group is formed through rearrangement and oxidation of one of the terminal methyl groups.

The possibility of the preparation of formylporphyrins directly by cyclization of biladiene opens up new prospects in connection with research on porphyrin *a* and related compounds.

A comparison of methods for the synthesis of porphyrins through bil-b-enes and bila-a,c-dienes shows that, in most cases, the second method leads to better results; however, it is more expedient to use the first method in the synthesis of porphyrins with electronegative substituents in the 4 position.

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