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IMPROVED METHOD FOR SYNTHESIS OF SUBSTITUTED TETRAPHENYLPORPHINS

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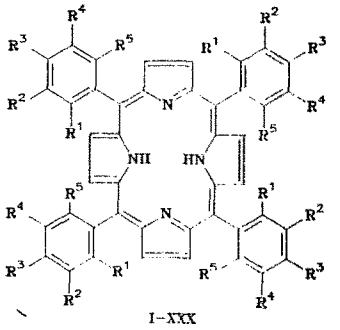
Condensation of pyrrole with benzaldehydes in a mixture of xylene and chloroacetic acid gives a series of substituted tetraphenylporphins with yields exceeding the yields of porphyrins synthesized according to known preparative methods.

The development of practicable methods for the synthesis of porphyrins having the most varied properties and stable to the action of aggressive media and reagents is an urgent necessity [1]. Included among such porphyrins are meso-tetraphenylporphins substituted in the phenyl rings, which are obtained by a one-stage condensation of pyrrole with substituted benzaldehydes.



I–XXX

II $R^1=CH_3$; III $R^2=CH_3$; IV $R^3=CH_3$; V $R^1=OCH_3$; VI $R^2=OCH_3$; VII $R^3=OCH_3$; VIII $R^1=F$; IX $R^2=F$; X $R^3=F$; XI $R^1=Cl$; XII $R^2=Cl$; XIII $R^3=Cl$; XIV $R^1=Br$; XV $R^2=Br$; XVI $R^3=Br$; XVII $R^1=I$; XVIII $R^2=I$, XIX $R^3=I$; XX $R^1=R^2=CH_3$; XXI $R^1=R^3=CH_3$; XXII $R^1=R^4=CH_3$; XXIII $R^1=R^5=CH_3$; XXIV $R^2=R^3=CH_3$; XXV $R^2=R^4=CH_3$; XXVI $R^1=R^2=OCH_3$; XXVII $R^2=R^3=OCH_3$; XXVIII $R^2+R^3=OCH_2O$; XXIX $R^2=R^4=$ = t-Bu; $R^3=OH$; XXX $R^2=R^4=CH_3$, $R^3=OH$; not stated R^1, R^2, R^3, R^4, $R^5=H$

The existing preparative methods for the synthesis of tetraphenylporphins have made it possible for these porphyrins to be obtained with yields not usually exceeding 20-25% [2, 3]. The yield reaches 30-35% only when benzaldehydes with certain electron-seeking substituents are used in the condensation reaction [4, 5]. The best results are achieved when the condensation is carried out in organic solvents containing an acid. A mixture of pyridine and acetic acid (with bp 135°C) [2] and propionic acid (bp 141°C) [3] are the most suitable solvents. The use of acetic acid (bp 118°C) as solvent considerably slows down the rate of reaction in comparison with the reaction in propionic acid (up to 10 h), while in butyric acid (bp 163°C) porphyrins are not formed [6]. The use of mixtures containing strong mineral acids as the medium for conducting the condensation also does not give positive results.

The yield of porphyrins in the condensation reaction decreases if there is water in the reaction medium, whereas the addition to the reaction medium of weak dehydrating agents such as acetic anhydride leads to some increase in yield [6].

The isolation of porphyrins that are very soluble in the reaction mixture and do not crystallize after carrying out the reaction is difficult. Methods of treating the reaction mass under these conditions are protracted and complicated, and are accompanied by considerable losses of porphyrins [2].

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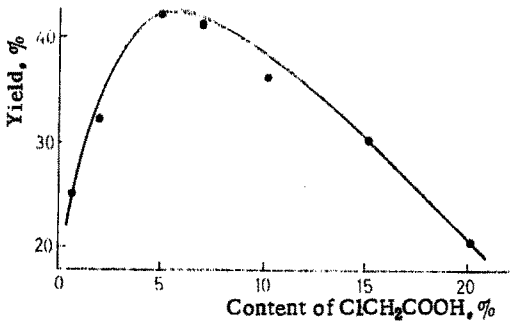

Fig. 1

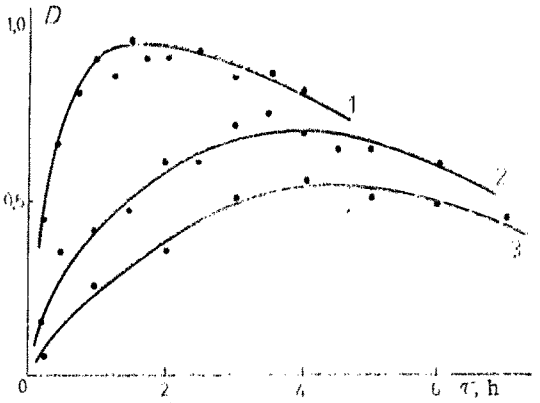

Fig. 2

Fig. 1. Dependence of yield of tetra(4-methoxyphenyl)porphin on concentration of chloroacetic acid in the reaction mixture.

Fig. 2. Dependence of optical density of protonated tetra(4-methoxyphenyl)-porphin (λ 700 nm) on reaction time in a mixture of: 1) 5% $ClCH_2COOH$ + isomeric xylenes; 2) 5% $ClCH_2COOH$ + toluene; 3) 5% $ClCH_2COOH$ + benzene.

Based on what has been said about conducting the condensation reaction, we chose a solvent possessing the merits of the reaction media already known and lacking some of their inherent shortcomings. Such a solvent turned out to be a mixture of isomeric xylenes (bp ~ 140°C) with the addition of a strongly acid component with low volatility — chloroacetic acid [7]. In the course of condensation water separating out from the reaction mixture was removed. On formations of porphyrins very soluble in the given reaction mixture, the latter were neutralized with a solution of ammonia, and the organic layer after washing with water was chromatographed on a suitable adsorbent. This considerably simplifies the more complex methods used earlier for isolation and purification of such porphyrins [2].

TABLE 1. Yield and Certain Properties of Tetraphenylporphins

Compound	R_f	Electronic absorption spectra in pyridine, λ_{max}, nm (log ε)				
		I	II	III	IV	Soret
I	0,15 (A)	646 (3,71)	591 (3,71)	549 (3,96)	515 (4,27)	420 (5,73)
II	0,61 (A)	648 (3,54)	592 (3,73)	547 (3,76)	514 (4,29)	419 (5,64)
III	0,55 (A)	648 (3,71)	592 (3,67)	550 (3,89)	516 (4,21)	421 (5,64)
IV	0,47 (A)	652 (3,80)	595 (3,72)	554 (4,01)	517 (4,25)	422 (5,68)
V	0,28 (B)	648 (3,53)	590 (3,73)	546 (3,79)	513 (4,27)	420 (5,62)
VI	0,45 (B)	649 (3,73)	591 (3,74)	549 (3,86)	515 (4,28)	422 (5,66)
VII	0,33 (B)	651 (3,79)	595 (3,66)	556 (4,04)	518 (4,16)	424 (5,65)
VIII	0,69 (C)	653 (3,62)	593 (3,89)	546 (3,81)	512 (4,33)	419 (5,93)
IX	0,57 (C)	647 (3,56)	591 (3,86)	552 (3,92)	518 (4,37)	421 (5,37)
X	—	647 (3,62)	591 (3,85)	552 (3,94)	517 (4,30)	421 (5,39)
XI	0,7 (D)	656 (3,54)	590 (3,89)	546 (3,74)	514 (4,38)	420 (5,20)
XII	0,35 (C)	648 (3,52)	592 (3,76)	550 (3,85)	515 (4,29)	421 (5,65)
XIII	—	651 (3,65)	593 (3,68)	551 (4,10)	517 (4,34)	422 (5,46)
XIV	0,44 (C)	648 (4,09)	592 (4,33)	548 (4,26)	515 (4,69)	422 (5,99)
XV	0,64 (C)	650 (3,76)	591 (3,95)	549 (4,24)	515 (4,39)	421 (5,74)
XVI	0,70 (C)	652 (3,74)	595 (3,77)	553 (3,97)	517 (4,30)	422 (5,69)
XVII	0,55 (C)	659 (3,58)	597 (3,98)	555 (3,91)	520 (4,46)	427 (5,76)
XVIII	0,66 (D) 0,57 (C)	653 (3,72)	593 (3,81)	552 (3,96)	518 (4,33)	423 (5,66)
XIX	0,69 (D)	649 (3,82)	590 (3,84)	551 (4,07)	517 (4,35)	423 (5,70)
XX	0,73 (A)	657 (3,84)	592 (3,81)	547 (3,91)	515 (4,30)	420 (5,61)
XXI	0,72 (A)	650 (3,77)	592 (3,79)	548 (3,88)	516 (4,29)	422 (5,55)
XXII	0,75 (A)	651 (3,77)	592 (3,81)	548 (3,84)	516 (4,30)	420 (5,63)
XXIII	0,76 (A)	649 (3,75)	591 (3,73)	546 (3,76)	514 (4,18)	420 (5,43)
XXIV	0,55 (A)	651 (3,80)	595 (3,82)	555 (4,06)	518 (4,30)	424 (5,76)
XXV	0,72 (A)	650 (3,80)	594 (3,81)	553 (4,01)	518 (4,29)	423 (5,74)
XXVI	0,08 (B)	653 (3,78)	590 (3,77)	545 (3,77)	513 (4,33)	420 (5,68)
XXVII	0,19 (B)	653 (3,80)	595 (3,72)	558 (4,05)	520 (4,22)	428 (5,58)
XXVIII	0,49 (B)	652 (3,57)	594 (3,63)	557 (3,90)	520 (4,12)	428 (5,47)
XXIX	0,56 (E)	658 (4,17)	599 (3,94)	564 (4,39)	525 (4,35)	430 (5,86)
XXX	0,66 (F)	654	596	562	522	429

*Yield for condensation in a xylene–chloroacetic acid mixture is given in brackets.

†For condensation in a mixture of pyridine and acetic acid.

We investigated the possibility of using a binary acid mixture of xylene–chloroacetic acid for the synthesis of porphyrins on the model condensation of pyrrole with anisaldehyde, which results in the formation of tetra(4-methoxyphenyl)porphin. This porphyrin is sparingly soluble in a mixture of xylenes ($1.3 \cdot 10^{-4}$ moles/liter at 25°C), which makes its isolation in a pure form possible by filtration of the reaction mixture after it has been neutralized with a solution of ammonia followed by washing of the precipitate of tetra(4-methoxyphenyl)porphin with methanol.

The highest yield of porphyrin (42%) is observed when the reaction is carried out between equimolar quantities of pyrrole and anisaldehyde in the xylene–chloroacetic acid mixture with the content of the latter at ∿5% (Fig. 1) and for a reaction time of 1.5 h (Fig. 2). The reaction was conducted with air bubbled through and water removed from the reaction mixture with the aid of a Dean–Stark attachment.

When the synthesis of tetra(4-methoxyphenyl)porphin is carried out without removal of water the yield decreases to 36%, and without bubbling air through it decreases to 34%. The use of benzene or toluene instead of xylene leads to a sharp increase in the reaction time and a considerable decrease in the yield of porphyrin (Fig. 2). The use of isomeric xylenes in the reaction does not affect the yield of porphyrin.

The proposed method was used to obtain a series of methyl- (II-IV, XX-XXV), methoxy- (V-VII, XXVI-XXVIII), halogeno- (VIII-XIX), and hydroxy- (XXIX, XXX) substituted tetraphenylporphins.

On separation of one or another porphyrins from the reaction mixture, specific properties determined by their differing solubilities in xylene are observed.

EXPERIMENTAL

Electronic absorption spectra of the compounds were recorded in pyridine on a Specord UV-Vis spectrophotometer. The identity of each compound obtained was established using TLC on Silufol in the following systems: toluene–hexane, 1:1 (A); chloroform (B); chloroform–hexane, 3:2 (C); chloroform–hexane, 2:1 (D); chloroform–hexane, 1:1 (E); and acetone–hexane, 1:1 (F).

Synthesized

Found, %			Empirical formula	Calculated, %			Yield,* %
C	H	N		C	H	N	
85,4	5,2	9,7	$C_{44}H_{30}N_4$	86,0	4,9	9,1	43,0 (20,0)
84,9	5,2	7,9	$C_{48}H_{36}N_4$	85,9	5,7	8,4	20,0 (11,5)
85,2	6,0	8,4	$C_{48}H_{38}N_4$	85,9	5,7	8,4	30,0 (16,0)
85,7	5,3	8,4	$C_{48}H_{38}N_4$	85,9	5,7	8,4	39,0 (19,5)
76,8	5,1	7,2	$C_{48}H_{38}N_4O_4$	78,5	5,2	7,6	16,0 (9,0)
77,2	5,3	7,8	$C_{48}H_{38}N_4O_4$	78,5	5,2	7,6	25,0 (14,0)
77,8	5,0	7,1	$C_{48}H_{38}N_4O_4$	78,5	5,2	7,6	42,0 (20,0)
76,3	3,5	7,8	$C_{44}H_{26}F_4N_4$	77,0	3,8	8,2	24,0 (10,0)
77,2	3,9	8,0	$C_{44}H_{26}F_4N_4$	77,0	3,8	8,2	10,0
76,2	4,1	8,4	$C_{44}H_{26}F_4N_4$	77,0	3,8	8,2	11,0 (5,0)
69,1	3,9	6,9	$C_{44}H_{26}Cl_4N_4$	70,2	3,5	7,5	16,8 (3,3)
70,4	3,5	7,3	$C_{44}H_{26}Cl_4N_4$	70,2	3,5	7,5	26,8 (17,0)
69,8	3,8	7,6	$C_{44}H_{26}Cl_4N_4$	70,2	3,5	7,5	34,6 (23,3)
57,0	3,1	5,8	$C_{44}H_{26}Br_4N_4$	56,8	2,8	6,0	13,0 (2,5)
57,2	3,1	6,4	$C_{44}H_{26}Br_4N_4$	56,8	2,8	6,0	18,5
56,4	3,0	5,8	$C_{44}H_{26}Br_4N_4$	56,8	2,8	6,0	19,0 (11,0)
45,9	2,0	5,6	$C_{44}H_{26}I_4N_4$	47,3	2,3	5,0	14,7
46,4	2,1	5,2	$C_{44}H_{26}I_4N_4$	47,3	2,3	5,0	21,5
47,7	2,8	4,9	$C_{44}H_{26}\ I_4N_4$	47,3	2,3	5,0	15,5
84,8	6,4	7,5	$C_{52}H_{46}N_4$	85,9	6,4	7,7	10,0
84,5	5,9	7,3	$C_{52}H_{46}N_4$	85,9	6,4	7,7	20,0
84,9	6,0	7,4	$C_{52}H_{46}N_4$	85,9	6,4	7,7	17,0
86,3	6,0	7,6	$C_{52}H_{46}N_4$	85,9	6,4	7,7	0,6
85,5	6,2	7,2	$C_{52}H_{46}N_4$	85,9	6,4	7,7	12,5
85,8	6,1	7,4	$C_{52}H_{46}N_4$	85,9	6,4	7,7	29,0
72,1	5,3	6,1	$C_{52}H_{46}N_4O_8$	73,1	5,4	6,6	14,0
72,5	5,2	6,0	$C_{52}H_{46}N_4O_8$	73,1	5,4	6,6	29,0
73,0	4,0	7,3	$C_{48}H_{30}N_4O_8$	72,9	3,8	7,1	23,0
80,3	8,8	5,2	$C_{76}H_{94}N_4O_4$	81,2	8,4	5,0	37,0 (1,0†)
77,7	5,7	7,3	$C_{52}H_{46}N_4O_4$	78,0	5,8	7,1	11,5

(95:5); for comparison the yield in propionic acid

Properties of the porphyrins obtained are given in Table 1.

Synthesis of Substituted Tetraphenylporphins I-XXX (General Method). Into a 0.5 liter flask with Dean–Stark attachment, reflux condenser, dropping funnel, and air supply was inserted 300 ml of a mixture of isomeric xylenes and 16 g (5%) of chloroacetic acid. The contents of the flask were heated to boiling point and with the constant passage of a flow of air a solution of 72 mmole of the appropriate substituted benzaldehyde and 5 ml (72 mmole) of pyrrole in 50 ml of xylene was added through the dropping funnel over a period of 20 min. The reaction mixture was boiled for a further 1.5 h with air bubbled through. On cooling, the mixture obtained was neutralized with a 25% solution of ammonia until the color changed from green to reddish brown, and three methods of separation were then used depending on the solubility of the porphyrins in xylene.

For isolation of the sparingly soluble porphyrins (VII, X, XXX), the mixture was filtered, and the precipitate washed with methanol until the filtrate was colorless and then dried at 100°C. The dried precipitate of porphyrin was dissolved in chloroform and chromatographed on alumina or recrystallized from a chloroform–methanol mixture.

For isolation of the porphyrins of medium solubility (III, IV, VIII, IX, XII, XIII, XV, XVI, XVIII, XIX, XXIV, XXV, XXVII, XXVIII) the mixture was filtered and the filtrate washed with water and chromatographed on alumina or silica gel. The precipitate was dissolved in benzene and also chromatographed. The fractions containing reaction product were concentrated to a volume of 20 ml and the porphyrin was precipitated from the solution obtained by adding 250 ml of methanol or hexane.

For isolation of the very soluble porphyrins (II, V, XI, XIV, XVII, XX-XXIII) the organic layer was washed with water and chromatographed on alumina or silica gel.

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