A New Synthesis of Porphin

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Porphin was synthesized by Fischer and Gleim[2] by prolonged boiling of pyrrole α-aldehyde with formic acid. It was also obtained by Rothemund[3] by heating pyrrole and formaldehyde in the presence of methanol in a sealed tube. Yields were below 0.1%

As porphobilinogen, 5-(aminomethyl)-4-(carboxymethyl)-3-pyrrolepropionic acid, can be readily transformed into uroporphyrins by boiling with dilute acid (Cookson and Rimington[4]) and ready formation of aetioporphyrins from hydroxymethylpyrroles (later shown to be acetoxymethyl derivatives[5]) has been demonstrated (Siedel and Winkler[6]), it seemed possible that either 2-aminomethylpyrrole or 2-hydroxymethylpyrrole might be similarly convertible into porphin.

Eisner and Linstead[7] have reported the synthesis of chlorin in 3.9% yield from 2-dimethylaminomethylpyrrole and its conversion to porphin.[8] They were unable to prepare porphin or any other macrocyclic pigment from 2-hydroxymethylpyrrole.

In this laboratory, porphin has been obtained in a one-step synthesis in yields of up to 5% by treating dilute solutions of 2-hydroxymethylpyrrole with potassium persulfate or a similar peroxidizing agent in glacial acetic acid. Porphin has also been obtained directly from 2-dimethylaminomethylpyrrole by treatment in ethereal solution with magnesium and methyl iodide in the presence of air.

In preliminary experiments, 2-dimethylaminomethylpyrrole methiodide was refluxed with sodium ethoxide and small quantities of porphin were obtained. Treatment of the solution at 50–60° with potassium persulfate resulted in a large increase of fluorescence. Of other oxidizing agents investigated, benzoyl peroxide proved equally effective, but hydrogen peroxide and Caro's acid were much less efficient. The presence of magnesium in the reaction mixture increased the yield of porphin (Eisner and Linstead[8]).

These experiments indicated that 2-hydroxymethylpyrrole might be implicated and further investigations were conducted with this substance. Porphin was produced with either water or benzene as solvent and best yields were obtained when the 2-hydroxymethylpyrrole was present in high dilution (*ca.* 0.01*M*). Other conditions favoring porphin production were slow addition of the 2-hydroxymethylpyrrole to a stirred solution of the oxidizing agent and magnesium dissolved in glacial acetic acid at 50° (Table I). The porphin was purified chromatographically and was characterized by analysis and spectrophotometry. Light absorption data is summarized in Table II. (See also Rimington, Mason, and Kennard[10]).

Conclusion: The synthesis of porphin described in this paper constitutes the best preparative method yet recorded. Yields much in excess of 5% would seem unlikely in a reaction of this type in which polymerization of macromolecules and cyclization in 4-ring units are equally possible.

TABLE I

YIELDS OF PORPHIN

	Without Mg Acetate			With Mg Acetate			
Time taken to add R·OH′ soln. (minutes)	5	10	15	5	10	15	25
μg R·OH	157	314	471	157	314	471	785
μg Porphin	0.79	1.20	1.71	4.25	11.77	19.85	33.86
Per cent yield	0.63	0.47	0.45	3.35	4.64	5.22	5.33

TABLE II

LIGHT ABSORPTION DATA FOR PORPHIN IN BENZENE

This Preparation		Eisner and Linstead[8]		Stern, Wenderlein and Molvig[9]	
λ_{max} (mμ)	$\epsilon \times 10^{-3}$	γ_{max} (mμ)	$\epsilon \times 10^{-3}$	λ_{max} (mμ)	$\epsilon \times 10^{-3}$
616.5	0.853	616	0.89	634	0.16
569	4.170	568.5	4.40	615	0.80
563.5	4.978	563	5.20		
519.5	2.640	520	3.00	562	4.74
489.5	15.750	489.5	16.00	519	2.55
396.5	264.000	395	261.00	489	14.80

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(2) H. Fischer and W. Gleim, *Liebig's Ann.*, **521**, 157 (1936).

(3) P. Rothemund, *J. Am. Chem. Soc.*, **58**, 625 (1936).

(4) G. H. Cookson and C. Rimington, *Biochem. J.*, **57**, 476 (1954).

(5) E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958).

(6) W. Siedel and F. Winkler, *Liebig's Ann.*, **554**, 162 (1943).

(7) U. Eisner and R. P. Linstead, *J. Chem. Soc.*, 3742 (1955).

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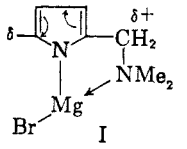
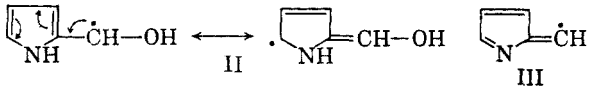
(10) C. Rimington, S. F. Mason, and O. Kennard, *Spectrochim. Acta*, **12**, 65 (1958).

The essential feature of many of the reactions described above is that there is no possibility of I,



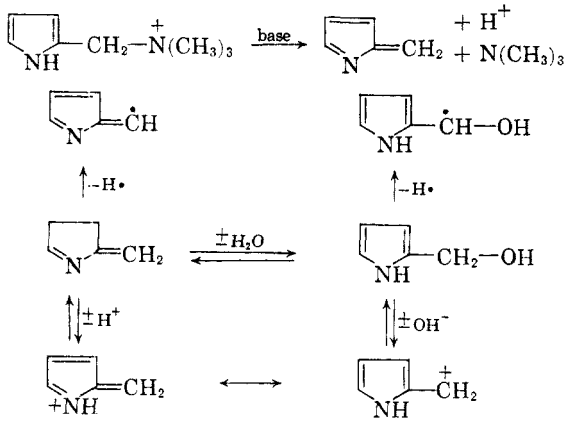
I

postulated by Eisner and Linstead,[7] being formed, as the synthesis involves the use of preformed 2-hydroxymethylpyrrole and it can proceed in the absence of magnesium. The present experimental evidence points either to the ionic mechanism postulated by Cookson and Rimington[4] or to the



II III

free radical mechanism involving secondary radicals such as II and III. Both these radicals or the ionic species of Cookson and Rimington can be derived either from 2-hydroxymethylpyrrole or from the pyrrole-Mannich base as in the following



scheme: This postulate not only accounts for the known lack of alcoholic properties of 2-hydroxymethylpyrrole (*cf.* Silverstein *et al.*[11]) but also brings under one general scheme the apparently diverse conditions capable of resulting in porphin production.

EXPERIMENTAL

2-Dimethylaminomethylpyrrole methiodide. 2-Dimethylaminomethylpyrrole was prepared by the method of Herz, Dittmer, and Cristol.[12] It was converted to the methiodide by adding a slight excess (1.5 g.) of methyl iodide to the Mannich base (1.14 g.) in ethanol (25.0 ml.). The precipitated methiodide was filtered and crystallized from water.

2-Hydroxymethylpyrrole. This was prepared by the method of Silverstein, Ryskiewicz, Willard, and Koehler.[11]

Spontaneous formation of porphin. When 2m*M* ethereal solutions of the methiodide of pyrrole-Mannich base were left standing in the absence of strong sunlight but in contact with air for three weeks at room temperature or at 0°, several red-fluorescing substances were formed. These were separated by extracting the ethereal solutions successively with 5%, 10%, 15%, 20%, and 25% w/v HCl. Porphin was found in the 5% HCl extract.

Experiments with 2-dimethylaminomethylpyrrole in the presence of methyl iodide and magnesium. Magnesium (0.01 mole), 2-dimethylaminomethylpyrrole (0.01 mole), and methyl iodide (0.012 mole) plus a trace of iodine were mixed in ether (100 ml.) and left standing in contact with air at room temperature with occasional shaking. No precautions were taken to exclude moisture. Trimethylamine was evolved and an intense green fluorescence developed within 10–15 min.; in a short time this changed to orange and eventually to strong red. After 90 min. the reaction mixture was extracted with 5% w/v HCl (6 × 5 ml.). The acid extracts were combined, neutralized to Congo red by addition of solid sodium acetate, and extracted with benzene (3 × 40 ml.). The benzene solution was distilled to dryness under reduced pressure, and the residue was redissolved in hot benzene (50 ml.) and applied to a column of MgO (20 × 2 cm.) prepared according to Nicholas.[13] Development of the chromatogram with a benzene–chloroform–methanol mixture (85:10:5) eluted two small bands in advance of the main porphin band. This was collected and concentrated to small bulk. On cooling 3.4 mg. of porphin crystals were obtained.

A green band followed the porphin band. It had an absorption spectrum similar to that of chlorin with maxima at 481, 489, 534, 582, 602.5 and 631 mμ in benzene solution and at 399.5 (Soret band) 515 and 620 mμ in 20% HCl.

Similar experiments were carried out in which the methiodide was refluxed with ethanolic sodium ethoxide or with aqueous sodium hydroxide followed by acidification and oxidation. Porphin was obtained in each case although in small yield.

Experiments with 2-hydroxymethylpyrrole. 0.1 Gm. (approx. 0.001 mole) of hydroxymethylpyrrole and 2.2 gm. (0.01 mole) of benzoyl peroxide were each dissolved in 50 ml. benzene and transferred to burettes discharging into a 500 ml. conical flask containing 150 ml. benzene and immersed in a water bath at 60°. The solutions from the burettes were added simultaneously drop by drop to the vigorously stirred benzene, the rate of addition being approx. 25 ml. per hour per burette. The solution was then transferred to a separating funnel and the porphin extracted as described above. Yield 5%.

The experiment was repeated with addition of magnesium acetate (0.05 ml. saturated Mg acetate in glacial acetic acid per ml. oxidizing solution) to the benzoyl peroxide solution. Yield 5.3%.

Products with higher and lower acid numbers than that of porphin were also present in both reaction mixtures, but no attempt was made to identify them (Rimington, Mason, and Kennard[10]).

A number of similar experiments were carried out except that benzene solutions of 2-hydroxymethylpyrrole were added to a solution of potassium persulphate in acetic acid at 60°. The addition of magnesium acetate again increased the yield of porphin. A series of experiments was performed using varying quantities of 2-hydroxymethylpyrrole in order to determine the best conditions for porphin formation (see Table I).

Final synthesis of porphin. Ninety-seven mg. of 2-hydroxymethylpyrrole dissolved in 40 ml. water was added slowly over 25 minutes to 200 ml. glacial acetic acid containing 0.2% magnesium acetate, 10 ml. saturated potassium persulphate solution, and maintained at 59–60°. The mixture was then filtered from black amorphous material, 250 ml. water was added and the porphin was extracted into benzene (3 × 150 ml.), the benzene layer was washed twice with 0.35% HCl (50 ml.) and then extracted with 20 ml. portions of 5% w/v HCl until the aqueous layer was almost non-fluorescent. Excess

(11) R. M. Silverstein, E. E. Ryskiewicz, C. Willard, and R. Koehler, *J. Org. Chem.*, **20**, 668 (1955).

(12) W. Herz, K. Dittmer, and S. J. Cristol, *J. Am. Chem. Soc.*, **69**, 1698 (1947).

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sodium acetate was added and the porphin was re-extracted into benzene (3 × 200 ml.). The benzene solution was distilled to dryness under reduced pressure, the residue redissolved in hot benzene (50 ml.) and purified as previously described.

Anal. Calcd. for $C_{20}H_{14}N_4$: C, 77.5; H, 4.5; N, 18.1. Found: C, 77.5; H, 4.7; N, 18.3.

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Substituted Aminobenzacridines

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The preparation of a number of substituted 7-aminobenz[*c*]acridines as potential amoebicides has been reported by Elslager and co-workers[1,2] and by Short and co-workers.[3] The present communication deals with the preparation of a number of substituted 7-aminobenz[*c*]acridines and 12-aminobenz-[*a*]acridines for trials against *Entamoeba histolytica in vitro*.

The compounds were prepared by the interaction of 7-chlorobenz[*c*]acridine and 12-chlorobenz[*a*]-acridine with a slight excess of the appropriate amine in phenol at 120° for 2 hours and isolated as the salicylate as described in an earlier communication by Chatterjee.[4] The compounds were purified by crystallization from 90% ethanol and are shown in Table I.

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(4) A. K. Chatterjee, *J. Org. Chem.*, **24**, 856 (1959).

Attempted Preparation of Benzpinacol Carbonate

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In an endeavor to synthetize benzpinacol carbonate, needed for a kinetic study, two different methods have been attempted: 1) a base-catalyzed ester-interchange between benzpinacol (I) and diethyl carbonate, and 2) the reaction of phosgene with I in presence of antipyrine, according to the method of Ludwig and Piech.[1] Both methods failed to produce the desired cyclic carbonate. Instead, the first method gave a mixture consisting of benzophenone (II), ethyl benzhydryl, and dibenzhydryl carbonates (III and IV), whereas the sec-

(1) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5779 (1951).

TABLE I[a]

Serial No.	Base	Salt	M.p. of Salt, °C.	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	7-benzylaminobenz[*c*]acridine	1.5 $C_7H_6O_3$[b]	202	76.52	76.81	4.99	4.98	5.18	5.10
2	12-benzylaminobenz[*a*]acridine	1.5 $C_7H_6O_3$	216	76.52	76.49	4.99	4.80	5.18	5.15
3	7-(2-phenylethyl)aminobenz[*c*]-acridine	1.5 $C_7H_6O_3$	204	76.76	76.55	5.23	4.92	5.05	4.90
4	12-(2-phenylethyl)aminobenz[*a*]-acridine	1.5 $C_7H_6O_3$	203	76.76	76.91	5.23	4.80	5.05	5.15
5	7-(3-phenylpropyl)aminobenz-[*c*] acridine	1.5 $C_7H_6O_3$	187	76.98	77.21	5.45	5.53	4.92	4.75
6	12-(3-phenylpropyl)aminobenz-[*a*]acridine	1.5 $C_7H_6O_3$	194	76.98	77.15	5.45	5.55	4.92	4.70
7	7-(4-phenoxybutyl)aminobenz-[*c*] acridine	$C_7H_6O_3$	174	76.98	77.00	5.66	5.87	5.28	5.19
8	12-(4-phenoxybutyl)aminobenz-[*a*] acridine	$C_7H_6O_3$	172	76.98	76.75	5.66	5.82	5.28	5.20
9	7-*p*-dimethylaminoanilinobenz-[*c*]acridine	1.5 $C_7H_6O_3$	200	74.74	74.50	5.26	5.00	7.37	7.26
10	12-*p*-dimethylaminoanilinobenz-[*a*] acridine	1.5 $C_7H_6O_3$	196	74.74	74.53	5.26	5.13	7.37	7.42

[a] All melting points are uncorrected. [b] $C_7H_6O_3$, salicylic acid.