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A Stepwise Porphyrin Synthesis[1]

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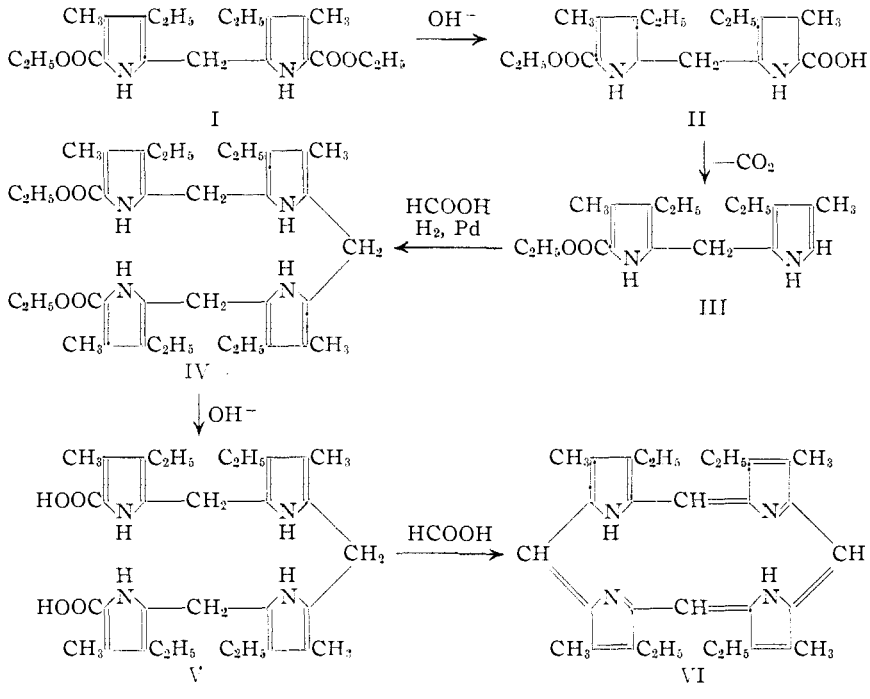
A stepwise synthesis of etioporphyrin II has been accomplished by the monohydrolysis, decarboxylation and formic acid coupling of 3,3′-diethyl-4,4′-dimethyl-5,5′-dicarbethoxydipyrrylmethane to give 1,4,5,8-tetramethyl-2,3,6,7-tetraethyl-1′,8′-dicarbethoxybilane, followed by hydrolysis, decarboxylation and a second formic acid coupling.

In the usual porphyrin synthesis, a critical reaction involves prolonged treatment of properly substituted dipyrrylmethene fragments with concentrated organic acid at elevated temperatures.[2] It is evident that this reaction must involve several steps, including coupling of two such fragments to form a linear tetrapyrryl molecule, juncture of the two ends of this intermediate to form the requisite cyclic structure, and oxidation to the stable resonating porphyrin system. The yields by this method are low and the conditions sufficiently rigorous to preclude the possibility of employing starting materials with sensitive substituent groups. Evidence exists demonstrating the ease with which polypyrryl compounds can cleave and recombine into new combinations,[3] making the reliability of structural proofs based upon the acid melt method surprising. Less drastic procedures involving dipyrrylmethanes have been described by Fischer and Halbig[4] and by Andrews, Corwin and Sharp.[5]

The present paper describes a more nearly stepwise porphyrin synthesis and suggests the possibility that further refinement of this method may furnish a new general porphyrin synthesis in which every intermediate can be isolated and every step elucidated.

In a previous paper[6] the successful monohydrolysis of a 5,5′-dicarbethoxydipyrrylmethane was described, as were the limitations imposed by the presence of an ester group in the 3- or 3′-position. To avoid these complications, 3,3′-diethyl-4,4′-dimethyl-5,5′-dicarbethoxydipyrrylmethane (I) was selected as the starting point, despite the later verified prediction that its alkyl substituents in the β-positions would decrease the stability of the system.[7] On treatment with one mole of sodium hydroxide it gave the monoacid (II), which was decarboxylated by vacuum distillation from glycerol solution to the α-free dipyrrylmethane (III).



Attempts to link two molecules of this methane with formaldehyde to yield the linear bilane as described by Buc[6] were unsuccessful, due to the inherent instability mentioned above. All such reactions furnished mixed oxidation products, and accordingly formic acid was ultimately employed to accomplish the coupling. The product of the formic acid reaction was then reduced catalytically to the desired 1,4,5,8-tetramethyl-2,3,6,7-tetraethyl-1′,8′-dicarbethoxybilane (IV).

Dihydrolysis of the bilane with excess hydroxide took place in normal fashion but the resulting diacid (V) oxidized too rapidly to permit characterization, doubtless catalyzing its own decomposition. The decarboxylation of this acid could not be achieved and recourse was made to formic acid, which performed this function in combination with coupling of the ends of the molecule to produce etioporphyrin II (VI).

In the synthesis sketched above, the only multiple-step reaction is the last one. The only barrier to a synthesis made up entirely of single steps taking

(1) Porphyrin Studies. X; Paper IX, W. Schlesinger, A. H. Corwin and L. J. Sargent, THIS JOURNAL, **72**, 2867 (1950). This paper was presented at the Boston Meeting of the American Chemical Society, April, 1951. It is from the doctoral dissertation of Edwin C. Coolidge.

(2) H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. II, Akademische Verlagsgesellschaft m. b. H., Leipzig, 1934, p. 176 ff.

(3) A. H. Corwin and K. J. Brunings, THIS JOURNAL, **64**, 2106 (1942).

(4) H. Fischer and D. Halbig, *Ann.*, **450**, 158 (1926).

(5) J. S. Andrews, A. H. Corwin and A. C. Sharp, THIS JOURNAL, **72**, 491 (1950).

(6) A. H. Corwin and S. R. Buc, *ibid.*, **66**, 1151 (1944).

(7) A. H. Corwin and W. N. Quattlebaum, *ibid.*, **58**, 1084 (1936).

place under mild conditions is the last decarboxylation reaction.

Experimental

3,3′-Diethyl-4,4′-dimethyl-5-carbethoxydipyrrylmethane-5′-carboxylic Acid (II).—To a solution of 23.0 g. of the diester (I) in 140 cc. of ethanol at reflux temperature was added, dropwise, a solution of 2.5 g. of solid NaOH in 6 cc. of distilled water. The addition was made through the condenser over a period of seven hours, after which reflux was continued for 1.5 hours. During the early stages of the addition the solution assumed a definite pink tinge, but at the end of the reflux period the color had disappeared, and a pale ivory-colored precipitate was obtained in a colorless solution.

The mixture was immediately evaporated to dryness on the steam-bath under full water vacuum, yielding a light tan soapy mass, stable, if kept cold, for several days. This solid was placed in a flask on the steam-bath, and was twice extracted with 120-cc. portions of boiling distilled water. These were filtered hot, and the filtrates brought to half saturation with solid NaCl. On cooling a sticky tan solid precipitated, which was filtered and washed with 50% aqueous NaCl solution. The filtrate contained the small amount of disodium salt formed, recoverable on acidification. The monosodium salt was suspended in 100 cc. of cold distilled water, brought to *p*H 5 with glacial acetic acid, stirred well, filtered with suction and washed well with water; yield of monoacid (II) 8.3 g. or 39%; of unreacted diester, 10.8 g. or 47%; of diacid, 1.76 g. or 9%. The monoacid can be crystallized with care from warm ethanol, and melts at 148–150°, with decomposition.

Anal. Calcd. for $C_{19}H_{26}O_4N_4$: C, 65.87; H, 7.57. Found: C, 65.94; H, 7.48.

3,3′-Diethyl-4,4′-dimethyl-5-carbethoxydipyrrylmethane (III).—To a large Pyrex test-tube containing 6 cc. of glycerol and one drop of quinoline was added 3.4 g. of the monoacid (II). The test-tube was one-fourth immersed in the steam-bath and gradually heated at 5 mm. to 100°, where it was maintained for four hours. A pure white solid gradually sublimed on the sides of the tube, leaving a tarry residue in the glycerol at the bottom. The product was removed, washed with cold hexane, and dried *in vacuo;* yield 1.8 g. or 61%, melting at 88–89°.

Anal. Calcd. for $C_{18}H_{26}O_4N_2$: C, 71.49; H, 8.66. Found: C, 71.51; H, 8.69.

1′,8′-Dicarbethoxy-1,4,5,8-tetramethyl-2,3,6,7-tetramethylbilane (IV).—To a large test-tube containing 1.8 g. of the α-free dipyrrylmethane (III) was added 15 cc. of concentrated formic acid. After the mixture had been heated on the steam-bath for ten minutes, 3 cc. of 48% HBr was added. The solution was heated at 100° for 30 minutes more, while particles of red-brown solid were observed to form. The mixture was then cooled thoroughly, and the precipitate filtered and washed with cold ethanol.

The solid was suspended in 50 cc. of ethanol to which was added 1 g. of Norite and 5 drops of 10% $PdCl_2$. The mixture was hydrogenated at atmospheric pressure for 14 hours, immediately made basic with concentrated ammonia, heated to boiling on the steam-bath and the Norite filtered from the hot solution. The Norite was twice washed on the filter with a small amount of boiling ethanol, which was then added to the filtrate. Water was added to the hot solution to turbidity, and the solution was thoroughly cooled. Red-tinted white crystals were filtered off, washed and dried; over-all yield 1.6 g., 86%; recrystallized from ethanol, m.p. 157–159°.

Anal. Calcd. for $C_{37}H_{52}O_4N_4$: C, 72.04; H, 8.50. Found: C, 72.11; H, 8.57.

1,4,5,8-Tetramethyl-2,3,6,7-tetraethylbilane-1′,8′-dicarboxylic Acid (V).—To 0.9 g. of the dicarbethoxybilane (IV) dissolved in refluxing ethanol was added 0.2 g. of sodium hydroxide in saturated aqueous solution. Refluxing was continued for two hours, as a pink-tinted precipitate slowly formed. The mixture was then evaporated to dryness on the steam-bath under water vacuum, suspended in cold distilled water, and acidified to *p*H 5 with 50% aqueous acetic acid. A precipitate of the free diacid formed on the surface of the solution and began darkening toward purple immediately. It was rapidly filtered, washed well with distilled water, and dried *in vacuo* over sodium hydroxide pellets; yield crude, 0.75 g. or 83%. The product was purple in color, due to oxidative impurities, and could not be recrystallized. It melted over a wide range with decomposition. No analysis was undertaken, it being impossible to purify the compound sufficiently for that purpose.

Etioporphyrin II (VI).—A suspension of 0.30 g. of bilane-1′,8′-dicarboxylic acid (V) in 10 cc. of concentrated formic acid was heated on the steam-bath for two hours, to dryness. Chloroform was added to the residue to small volume, then two volumes of hot methanol and the mixture was then cooled and filtered. Black crystals were obtained, which gave in chloroform six spectral lines in the visible range identical with those of a known sample of etioporphyrin II; yield crude, 0.18 g., 60%.

To assay the purity of this material, a portion of it was twice recrystallized from chloroform–methanol, yielding blue-purple crystals with a brilliant metallic sheen. A solution of 5.0 mg. of this pure porphyrin was dissolved in 10.0 cc. of chloroform, and diluted with chloroform to the lowest concentration that would still give visible spectral lines. This was found to be 0.00225 mg./cc. for a test-tube of 12.5 mm. inside diameter.

The process was repeated on a 5.0-mg. sample of the crude porphyrin obtained above and comparison with the pure standard showed it to be 60% pure. The over-all yield of pure material in this reaction was therefore 36%.

Presumably the by-products in this reaction were the result of intermolecular coupling to yield long chain molecules, rather than of intramolecular cyclization to furnish the porphyrin skeleton. To test this hypothesis, 0.30 g. of the diacid (V) was treated exactly as above with formic acid. This time, however, 25 cc. of the latter was employed, on the assumption that greater dilution of the bilane diacid should favor intramolecular reaction; yield crude, 63%. Assayed as above, 70% pure, indicating an over-all yield of 44%.

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