Convenient Synthesis of Porphine

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Porphine formation from pyrrole and formaldehyde was examined in detail. Under optimized conditions, 9 mg of crystalline porphine was obtained per 1 ml of pyrrole.

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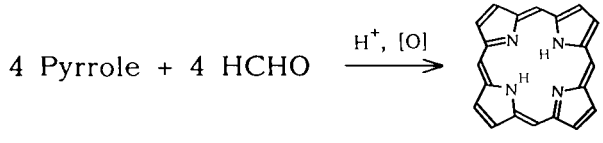
Porphyrins are biological pigments identified as the prosthetic group of various hemoproteins. The most familiar porphyrin, ordinarily found in hemoglobin and myoglobin, is protoporphyrin IX with several peripheral substituents. The parent nucleus of porphyrin is an elementary tetrapyrrole called porphine. Owing to the unique structure, porphine has become increasingly important for chemical and biological investigations. Although porphine is a simple compound, its preparation in any quantity is still difficult [1]. Several commercial samples are available, but they are quite expensive. The most efficient synthesis hitherto known is that of Longo *et al.* [2]. After adding 2 ml of 2-hydroxymethylpyrrole over 2 weeks to 3 ℓ of chromatographed ethylbenzene at 100°, they obtained 8-10% yield of porphine. In 1936, Rothemund [3] reported porphine formation with pyrrole and formaldehyde in methanol/pyridine in an anaerobically sealed glass tube. He obtained 1 mg of porphine from 1 ml of pyrrole. Despite the inferior yield (0.08%), the Rothemund porphine synthesis appears still attractive in view of availability of the starting materials. During our myoglobin reconstitution work with iron porphine, a relatively large amount of porphine became necessary. We have developed the porphine production with pyrrole and formaldehyde (Scheme) to a practical level under modern concepts of general porphyrin synthesis.

Scheme



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In the preliminary experiments carried out in acetic acid, we could not obtain even a trace amount of the product. We employed propionic acid, rather than acetic acid or basic methanol [3], as the reaction medium because the synthesis of *meso*-tetraphenylporphyrin is known to be much improved in this solvent [4]. However, addition of equimolar amounts of formaldehyde and pyrrole in one portion to refluxing propionic acid, afforded only a trace amount of the product. In the porphine synthesis with 2-hydroxymethylpyrrole, Longo *et al.* [2] emphasized the importance of high dilution conditions to prevent random oligomerization of the reactants. Addition of pyrrole and formaldehyde under dilute conditions was essential in our synthesis as well. Table I compares several results of the present porphine synthesis. Our highest yield was obtained when 0.9 ml of pyrrole and 0.9 ml of formalin were concomitantly added at 10 minute intervals to 1 ℓ of propionic acid at 90°. The reagent titration at shorter intervals or with increased amounts resulted in decreased yield. Changes in the pyrrole/formaldehyde ratio also did not improve the reaction. Considerable amounts of side-products were formed even under the optimized conditions. Fortunately, these were insoluble black polymers readily removable by simple filtration to allow much easier separation of porphine. The crude product was often contaminated with a small amount (about 2%) of chlorin, a hydrogenated product of porphine. The chlorin could be oxidized into porphine with high-potential quinone. Subsequent chromatographic purification followed by crystallization afforded pure porphine. We routinely obtained 9 mg of porphine from 1 ml of pyrrole, which is about 9-fold larger than that of Rothemund [3] and seems acceptable. The present yield (0.9%) is even inferior to those of Longo *et al.* (8-10%) [2], Eisner and Linstead (3.9%) [5], and Krol (5%) [6], who used precursory 2-hydroxymethylpyrrole or 2-dimethylaminomethylpyrrole derived from pyrrole with substantial amounts of synthetic efforts and time. Lower yields in the present synthesis appears not discouraging because pyrrole and formalin are by far the more common

Table I

Porphine Synthesis with Pyrrole and Formalin

Entry	Modification [a]	Yield [b]
1	None	9.6
2	Reaction at 140°	0.2
3	Reaction at 80°	1.5
4	Reagent addition in one portion	2.5
5	Reagent addition at 5 minute intervals	4.9
6	Reagent addition at 20 minute intervals	8.0

[a] Other conditions are the same as those described in the Experimental. [b] Mg of porphine/ml of pyrrole.

reagents and least expensive. In addition, the separation and purification procedures are very easy to perform even for those who are not familiar with organic synthesis.

A variety of metalloporphine complexes can be derived with the method of Adler *et al.* [7]. Iron porphine is very unique of all metallo derivatives to induce drastic modification of the highly specific heme-globin contacts in myoglobin [8].

EXPERIMENTAL

The proton nmr spectrum was recorded at 300 MHz on a Varian XL-300 spectrometer with tetramethylsilane as an internal reference. Mass spectral and elemental analyses were performed by the Department of Analytical Chemistry, Kyoto Pharmaceutical University. Pyrrole, formalin (37% aqueous solution of formaldehyde stabilized with 8% methanol), propionic acid, and pyridine were purchased from Nakalai Tesque Inc., Kyoto. Silica gel (Wakogel C-200, 100-200 mesh) was from Wako Pure Chemical Industries, Ltd., Osaka.

Porphine (**1**).

In a 1 ℓ three-necked round-bottom flask equipped with thermometer, reflux condenser, and stirring bar, 1 ℓ of propionic acid and 10 ml of pyridine were heated to 90° in an oil bath. To the efficiently stirred solution, 0.9 ml (13 mmoles) of pyrrole and 0.9 ml (12 mmoles) of formalin were simultaneously added at 10 minute intervals. Porphine formation was identified on a silica gel plate in 60 minutes. After total addition of 13.5 ml of pyrrole and 13.5 ml of formalin, the mixture was heated for further 60 minutes followed by bubbling air into the hot solution over 5 minutes. The cooled solution was filtered on a Buchner funnel to remove a large amount of insoluble black polymers. After adding 400 ml of chloroform, the mixture was washed with water (0.8 ℓ x 2), 0.1 *N* sodium hydroxide (0.5 ℓ x 2) and water (0.5 ℓ x 2) to separate propionic acid. The resultant chloroform solution was filtered to eliminate residual insoluble impurities, dried with anhydrous magnesium sulfate, and evaporated to dryness. The residue, washed with methanol until colorless, was chromatographed on a silica gel column (2.7 cm x 15 cm) with chloroform as the eluent. Porphine developed as the most mobile purple band. The visible spectrum of the porphine fraction often showed a 638-nm band from a small amount (about 2%) of contaminating chlorin [5]. To the eluted chloroform solution (about 300 ml) in a 500 ml round-bottom flask with reflux condenser and stirring bar, 8 mg of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 20 ml of chloroform was added at 50° and allowed to stand for 30 minutes at this temperature to oxidize residual chlorin. The cooled solution was passed through a short silica gel column (2.7 cm x 3 cm) equilibrated with chloroform to remove quinone derivatives. To the concentrated chloroform solution, 20% by volume of methanol was added. Slow evaporation under low heating afforded 130 mg of reddish-brown porphine crystals (yield, 0.9%). The visible [6] and proton nmr [9] spectra were identical with those in the literature. The mass spectrum was consistent with the expected structure.

Anal. Calcd. for $C_{20}H_{14}N_4$ (310.4): C, 77.40; H, 4.55; N, 18.05. Found: C, 77.25; H, 4.61; N, 17.93.

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