*Anal.* Calcd. for $C_{17}H_{16}O_4NI$: I, 29.81. Found: I, 29.77.

**N-(β-Phenylethyl)-2-ethoxy-5-carbethoxypyridinium Iodide (VII).**—One gram (0.0041 mole) of N-(β-phenylethyl)-5-carboxy-2-pyridone (III) was mixed with 7 ml. of phosphorus oxychloride in 10 ml. of dry xylene and heated for two hours at 135°. The reaction mixture was worked up as in the preceding example to give 0.25 g. of the iodide salt, m.p. 109–110° dec. The compound decomposed after standing a few weeks.

*Anal.* Calcd. for $C_{18}H_{22}O_3NI$: C, 50.60; H, 5.19. Found: C, 50.43; H, 5.32.

**Ultraviolet Absorption Data.**—Ultraviolet absorption measurements were made with a Beckman DU ultraviolet spectrophotometer using 1.00-cm. silica cells and hydrogen and tungsten discharge lamps as light sources. The compounds were measured in 95% ethanol solution. The authors are indebted to Miss LaVerne Duckwall for these measurements.

LOUISVILLE, KENTUCKY

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

# New Methods for Porphyrin Synthesis[1]

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The synthesis of etioporphyrin I from dipyrrylmethane-metal complexes has been studied and new complexes of the porphyrin have been prepared. Most favorable results were obtained with the copper complex. Mildly basic media proved unsatisfactory for porphyrin synthesis unless metallic atoms were present to aid the condensation. By the use of cuprous chloride it has proved possible to prepare the copper complex of 1,3,5,7-tetramethyl-2,4,6,8-tetracarbethoxyporphyrin and it has been found that concentrated sulfuric acid will remove the copper from this complex, yielding the free porphyrin.

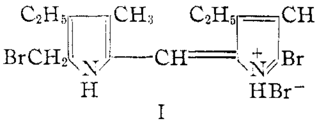
Attempted synthesis of porphyrins containing carbethoxy groups from bromomethenes have led to little or no porphyrin product in the standard acid melts. A recent communication[2] has shown that this is not due to any inherent instability of this type of porphyrin and records relatively good yields of 1,4,5,8-tetramethyl-2,3,6,7-tetracarbethoxyporphyrin. The present paper deals with modifications of porphyrin syntheses designed to obtain both alkyl and carbethoxy substituted porphyrins.

Linstead's[3] synthesis of metal-phthalocyanines in the presence of metal salts and Helberger's[4] synthesis of metal-tetrabenzoporphyrins indicated that the presence of a metal capable of forming square planar bonds might have a beneficial effect upon the synthesis. Since metallic complexes of dipyrrylmethenes are not stable in acids, such a synthesis should be performed in neutral or mildly basic media. Previous attempts at alkaline porphyrin syntheses from methenes have not led to good results[5] although basic porphyrin condensations of other types have been successful.[6]

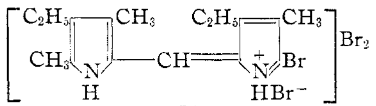
It was first determined that etioporphyrin II could be recovered from its copper complex in 96–99% yield, thus opening the way to a complete porphyrin synthesis through the metal complex as an intermediate.

The effect of added cupric acetate on the yield of etioporphyrin II was found to be negligible in the formic acid–dipyrrylmethane synthesis. Similarly the condensation of 3,3′-dicarbethoxy-4,4′-dimethyldipyrrylmethane was not improved by cupric acetate. The free porphyrin was first formed and the copper complex appeared only after continued heating.

Attempts to prepare the free base or metallic complexes of 3,4′-dimethyl-4,3′-diethyl-5-bromomethyl-5′-bromodipyrrylmethane hydrobromide (I) were unsuccessful. From 3,5,4′-trimethyl-4,3′-diethyl-5-bromodipyrrylmethene hydrobromide perbromide (II) the free base and copper, cadmium, zinc and ferrous complexes were readily prepared.



I



II

With boiling tributylamine as the solvent and condensing medium, little or no porphyrin could be prepared from the mixture of methenes I and II, from either separately or from the free base of II. On the addition of cupric acetate to these reaction mixtures, the copper complex of etioporphyrin I was obtained in small yields with methene I giving the best yield. Even higher yields were obtained from the metallic complexes of methene II. These diminished in the following order: Cu > Zn > Cd. The ferrous complex gave no porphyrin. We thus conclude that in this case, mildly basic conditions are not satisfactory for porphyrin synthesis unless certain metallic atoms are present to aid the condensation.

After numerous trials it was found that the copper complex of 1,3,5,7-tetramethyl-2,4,6,8-tetracarbethoxyporphyrin (IV) could be prepared from 3,5,4′ - trimethyl - 4,3′ - dicarbethoxy - 5′ - bromo-

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(1) Porphyrin Studies XI. Paper X, A. H. Corwin and E. C. Coolidge, THIS JOURNAL, **74**, 5196 (1952). Taken from the doctoral dissertation of Virginia L. Sydow, The Johns Hopkins University, Baltimore, Md. Presented at the Buffalo Meeting of the American Chemical Society, April, 1952.

(2) J. S. Andrews, A. H. Corwin and A. G. Sharp, *ibid.*, **72**, 491 (1950).

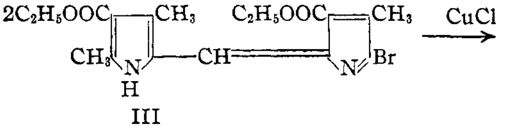
(3) R. P. Linstead, *et al.*, *J. Chem. Soc.*, 1016 (1934).

(4) J. H. Helberger, *Ann.*, **529**, 205 (1937); J. H. Helberger and A. von Rebay, *ibid.*, **531**, 279 (1937); J. H. Helberger, A. von Rebay and D. B. Hever, *ibid.*, **533**, 197 (1938).

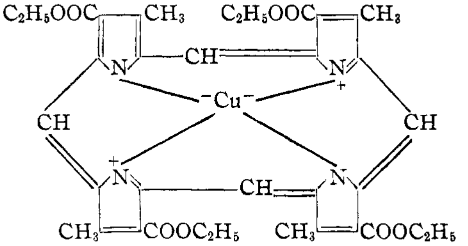
(5) H. Fischer, H. Friedrich, W. Lamatsch and K. Morgenroth, *ibid.*, **466**, 164 (1928).

(6) P. Rothemund, THIS JOURNAL, **57**, 2010 (1935); **58**, 625 (1936); S. Aronoff and M. Calvin, *J. Org. Chem.*, **8**, 205 (1943); R. H. Ball, G. D. Dorough and M. Calvin, THIS JOURNAL, **68**, 2278 (1946).

dipyrrylmethene (III) in hot naphthalene, using cuprous chloride as the metal donor. Addition of bases, such as tributylamine, completely prevented the reaction. No product was obtained when the copper complex of the methene was used nor when cupric acetate was substituted for cuprous chloride.



III



IV

It is concluded that in this case copper successfully serves as a condensing center for the porphyrin synthesis, thus making available for the first time a derivative of porphyrin (IV). The success of the cuprous salt and the failure of the cupric are matters for conjecture. Since a "*cis*" and a "*trans*" form of the cupric complex of III can be formulated, it might be assumed that the wrong one for porphyrin formation is more readily produced. Because of its smaller steric interference with planarity, it would ordinarily be assumed that the "*trans*" form should be produced more rapidly and should be the more stable, in addition to being the better suited for porphyrin formation. The suitability of the cuprous salt might also be explained on steric grounds. Porter[7] has shown that in a closely similar case groups in the $\alpha$-positions interfere with the planarity of the cupric complex. Such an interference would not occur in a tetrahedral cuprous complex, if it were formed as an intermediate. Moreover, this complex would exist in only one form which would automatically lend itself to porphyrin formation upon simultaneous twisting of the two planar methene structures with respect to each other, elimination of bromine and oxidation of tetrahedral cuprous to planar cupric.

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## Experimental

**Etioporphyrin II from the Copper Complex.**—Three hundred milligrams of the copper complex of etioporphyrin II was dissolved in the minimum amount of concentrated sulfuric acid. Sodium hydroxide (10%) was added until the mixture was basic to litmus, ice being added as necessary to keep the temperature at about 25°. The mixture was filtered with suction immediately and washed exhaustively with water until the washings gave no test for copper ion with ammonia. The precipitate was recrystallized from chloroform–methanol; yield 258 mg. (96.5%) of etioporphyrin II.

**Effect of Cupric Acetate on the Synthesis of Etioporphyrin II.**—A suspension of 300 mg. of 3,3′-diethyl-4,4′-dimethyl-5,5′-dicarboxydipyrrylmethane and 200 mg. of cupric acetate in 2.5 ml. of formic acid (90%) was heated at 40° for 14 hours and then heated on a steam-bath for 12 hours with air bubbling through slowly. The original volume was maintained by addition of formic acid until the last two hours, when the black mixture was allowed to evaporate to dryness. The reaction mixture was dissolved in 10 ml. of chloroform, filtered, and the filtrate evaporated to 5 ml. Fifteen ml. of hot methanol was added and the solution placed in the refrigerator for 12 hours. The cupric etioporphyrin crystals were collected, washed with cold methanol, recrystallized from chloroform and methanol and dried *in vacuo* over sodium hydroxide and calcium chloride; yield 100 mg., or 39.2%. This is comparable with the yield obtained in the absence of cupric acetate.

**Cupric Acetate in the Synthesis of 1,4,5,8-Tetramethyl-2,3,6,7-tetracarbethoxyporphyrin.**—A suspension of 0.67 g. of 3,3′-dicarbethoxy-4,4′-dimethyldipyrrylmethane, 3.5 g. of methylene iodide, 2 ml. of pyridine and 0.3 g. of cupric acetate in 15 ml. of xylene was refluxed for 8.5 hours. Spectroscopic examination showed the presence of free porphyrin. The porphyrin was extracted with concentrated hydrochloric acid and a little ether. After filtration, the solid material was returned to the reaction flask, 15 ml. of tributylamine added and the mixture refluxed for three hours. A porphyrin-copper complex spectrum was then observed. Fifteen milliliters of ether was added to the hydrochloric acid solution of porphyrin and then water until a solid floated between the layers. The solid was filtered off, dissolved in hydrochloric acid and reprecipitated. It was then redissolved in hydrochloric acid and the porphyrin extracted with chloroform. The chloroform solution was partially dried by passage through two layers of filter paper, evaporated to 2 ml., 8 ml. of hot methanol added and placed in the refrigerator overnight. Seven milligrams of dark red crystalline porphyrin was obtained. The reaction mixture from the second heating was extracted with concentrated hydrochloric acid, leaving a large amount of brown solid which contained the copper-porphyrin. The copper-porphyrin was extracted with chloroform, the solution washed four times with hydrochloric acid and twice with water. It was concentrated to a small volume, four volumes of hot methanol added, and cooled overnight in the refrigerator. Three milligrams of dark red, crystalline porphyrin-copper complex was obtained.

**Metal Complexes of 3,5,4′-Trimethyl-4,3′-diethyl-5′-bromodipyrrylmethene (II).** (a) **Copper.**—Five grams of the methene free base was dissolved in boiling 95% ethanol, and a hot saturated solution of 6.25 g. of cupric acetate in ethanol containing a few drops of ammonia was added with vigorous stirring. Green crystals started to form immediately. The mixture was cooled overnight in the refrigerator, suction filtered and the crystals washed with 2% ammonia to remove excess cupric ions and then with water. The product was dried *in vacuo* over sodium hydroxide and calcium chloride; yield 4.9 g. or 90% of metallic green crystals with a decomposition point of 160–161° were obtained. On attempted recrystallization, a powdery green material with a lower melting point was obtained.

*Anal.* (Crude product) Calcd. for $C_{32}H_{40}N_4Br_2Cu$: Cu, 9.03. Found: Cu, 8.92.

(b) **Cadmium.**—The methene-free base was dissolved in boiling ethanol, and a saturated solution of two moles of cadmium acetate in water added. After cooling in the refrigerator for three hours, the product was filtered by suction, washed with water and cold alcohol and dried. After two recrystallizations from alcohol, a 94% yield of brown-red crystals with a decomposition point of 176° was obtained.

*Anal.* Calcd. for $C_{32}H_{40}N_4Br_2Cd$: Cd, 14.94. Found: Cd, 14.77.

(c) **Zinc.**—The zinc complex was prepared by the procedure above; yield 82%.

*Anal.* Calcd. for $C_{32}H_{40}N_4Br_2Zn$: Zn, 9.27. Found: Zn, 9.23.

(d) **Ferrous.**—The ferrous complex was prepared as above except that all reactions were carried out under nitrogen. Red-brown needles decomposing at 142–143° were obtained; yield 46%.

*Anal.* Calcd. for $C_{32}H_{40}N_4Br_2Fe$: Fe, 8.02. Found: Fe, 7.59.

**Attempts to Prepare Etioporphyrin I in Tributylamine without Metals.**—One and one-quarter grams of the crude

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(7) C. R. Porter, *J. Chem. Soc.*, 368 (1938).

mixture of methenes I and II obtained from bromination was dissolved in 10 ml. of tributylamine. The solution was heated under nitrogen at 180° for four hours. After cooling, excess hydrochloric acid was added and the solution extracted with ether. The ether layer was discarded. This was repeated until no more material went into the ether layer. The acid solution containing the porphyrin was diluted by half with water and the extraction repeated. This dilution and extraction was continued until the spectroscope showed that porphyrin was beginning to go into the ether layer. The porphyrin was then extracted with ether, the ethereal solution washed with water, dried over sodium sulfate and evaporated. The residue was dissolved in 2-3 ml. of hot chloroform, and 10 ml. of methanol was added. The solution was cooled overnight in the refrigerator, filtered, dried and weighed; yield 6 mg.

The experiment was repeated using methene I alone. A weak porphyrin spectrum was obtained, but no solid product could be isolated. The same was true when the mixture was refluxed in xylene. A similar result was also obtained when methene II was used alone.

**Condensation Yielding Cupric Etioporphyrin I (a).**—One gram of the crude mixture of methenes I and II and 0.3 g. of cupric acetate were refluxed in 10 ml. of tributylamine for two hours. The reaction mixture was cooled to room temperature, 15 ml. of methanol added and the solution placed in the refrigerator overnight. The product was filtered off and dried; yield 17 mg. of cupric etioporphyrin I.

(b) **From Methene I.**—One gram of the methene, 6 ml. of tributylamine, 0.3 g. of cupric acetate and 8 ml. of xylene were refluxed together for two hours. The mixture was cooled and 40 ml. of 18% hydrochloric acid added. The solution was extracted with ether until no more porphyrin complex dissolved in the ether. The combined ether extracts were washed five times with equal volumes of 18% hydrochloric acid and then twice with water. The solution was dried over sodium sulfate, evaporated and 15 ml. of hot methanol added. After cooling, filtering and drying, 50 mg. of cupric etioporphyrin was obtained.

(c) **From Methene II.**—Following the same procedure as in (b) above, 2 mg. of cupric etioporphyrin was obtained from 1 g. of methene II.

(d) **From the Copper Complex of Methene II.**—Following essentially the same procedure as in (b) above but omitting added cupric acetate, 500 mg. of the cupric complex of methene II yielded 110 mg. (28.6%) of cupric etioporphyrin.

(e) **Using Cuprous Chloride.**—Procedure (a) for 1,3,5,7-tetramethyl-2,4,6,8-tetracarbethoxyporphyrin (below) was followed, using 1.7 g. of methene I, 1 g. of cuprous chloride and 25 g. of naphthalene. During the course of the reaction it was observed spectroscopically that the free porphyrin was formed before the cupric complex. This was not true in the case of the tetracarbethoxyporphyrin. With the etioporphyrin the free porphyrin was converted into the cupric complex by continued heating of the reaction mixture; yield 6 mg. of cupric etioporphyrin.

**Experiments with Other Metallic Complexes of Methene II.** (a) **Cadmium.**—A suspension of 0.35 g. of the cadmium complex of methene II in 7 ml. of tributylamine was treated as above; yield 10 mg. of red crystals with the characteristic metalloporphyrin spectrum.

(b) **Zinc.**—By the same procedure, 0.5 g. of the zinc complex of methene II gave 15 mg. of metalloporphyrin.

(c) **Ferrous.**—No metalloporphyrin was obtained from the ferrous complex of methene II.

**1,3,5,7-Tetramethyl-2,4,6,8-tetracarbethoxyporphyrin.** (a) **Cupric Complex (IV).**—Three grams of 3,5,4′-trimethyl-4,3′-dicarbethoxy-5′-bromodipyrrylmethene (III) and 2 g. of cuprous chloride were heated in 50 g. of naphthalene on a steam-bath until the naphthalene melted. The mixture was then refluxed over a flame until the vapors were no longer acid to litmus (8 hours). The major part of the solvent was removed by vacuum distillation and the rest by extraction with hexane. A large amount of black solid was obtained from which the copper complex of the porphyrin was eluted with hot chloroform. The chloroform solution was evaporated to 20 ml., 40 ml. of hot methanol was added and the solution allowed to stand overnight in the refrigerator. Red-brown plates were obtained which were difficultly soluble in all ordinary solvents. The product was recrystallized from bromoform and then from nitrobenzene, washed with methanol–chloroform, methanol, and ether; yield 130 mg. (5%) of purplish-red micro-needles.

*Anal.* Calcd. for $C_{36}H_{86}O_8N_4Cu$: C, 60.37; H, 5.07; N, 7.82; Cu, 8.88. Found: C, 60.40; H, 5.04; N, 7.79; Cu, 8.89.

The spectrum of a saturated solution in chloroform was observed by means of a Beckman spectrophotometer; bands at: I, 592 mμ; II, 553 mμ.

(b) **Using α-Bromonaphthalene.**—One gram of methene III and 0.7 g. of cuprous chloride were refluxed in 25 ml. of α-bromonaphthalene for 3.5 hours. The mixture was cooled, 40 ml. of petroleum ether added. A copious black precipitate was obtained which was filtered off, leaving a red solution. The black solid was extracted with chloroform. The chloroform extract showed absorption bands at 550 and 595 mμ, using a hand spectroscope, thus indicating the formation of the cupric complex of the porphyrin. The red solution contained a different compound with bands at 515 and 555 mμ. The amount of material obtained was insufficient for further study.

(c) **The Free Porphyrin.**[8]—The crude product obtained from (a) above after evaporation of the chloroform and addition of methanol, was dissolved in 35 ml. of concentrated sulfuric acid at room temperature. The sulfuric acid solution was filtered into a 250-ml. beaker of ice. The precipitated porphyrin was filtered with suction, washed with water and dried. The crude porphyrin was dissolved in chloroform and run through a chromatographic column, while the red porphyrin band was eluted with chloroform. The chloroform solution was evaporated to a small volume and methanol was added. After cooling and filtering, the product was recrystallized from chloroform–methanol and chloroform–iso-octane. A dioxane solution of the porphyrin showed absorption bands at 526, 556 and 596 mμ.

Material prepared by the procedure given above still retained about 1% ash. To prepare a sample for analysis, the porphyrin was rechromatographed slowly and the eluted solution was carefully filtered on a gravity filter.

*Anal.* Calcd. for $C_{36}H_{38}O_8N_4$: C, 66.05; H, 5.85. Found: C, 66.29; H, 5.70.

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[8] The authors wish to thank Mrs. Marjorie H. Melville for preparing this material.