

by Larsen and Heyl⁹ and by Simpson⁷ when they attempted to brominate α -spinasterol.

Summary

1. The unsaponifiable fraction of alfalfa seed

oil has been separated into a crystalline substance and an oily mixture.

2. The crystalline substance is believed to be α -spinasterol.

EAST LANSING, MICHIGAN

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[CONTRIBUTION FROM THE C. F. KETTERING FOUNDATION FOR THE STUDY OF CHLOROPHYLL AND PHOTOSYNTHESIS]

Porphyrin Studies. III.¹ The Structure of the Porphine² Ring System

BY PAUL ROTHMUND

The importance of the porphine ring system is evident from the fact that it is the fundamental ring system of all the porphyrins. "Chlorins" are dihydroporphines, and the—thus far hypothetical—"Phorbine" ring, which is present in the chlorophylls, differs from chlorin only by the addition of an isocyclic ring in 6, γ -position.

Some time ago the author reported the synthesis of porphine by the interaction of pyrrole and formaldehyde.³ It was found that many aldehydes can be condensed with pyrrole to yield porphines, in which the four *meso* (*ms*-) positions α , β , γ , and δ , carry the residue from the corresponding aldehyde as substituent. The reaction seems to be a general one of aldehydes, for more than 25 aliphatic, aromatic, and heterocyclic aldehydes gave positive results in this porphyrin formation. In this synthetic work a number of facts relating to the structure of the porphine ring have been observed.

In the second publication quoted above³ it was mentioned that under certain conditions the reaction mixture from the porphine synthesis contained, in addition to porphine, a porphyrin with a hydrochloric acid number much lower than that of porphine. In comparison with porphine the two main absorption bands of this porphyrin were shifted about 100 Å. toward the red region of the spectrum. The new porphyrin formed only in small quantities, while porphine of hydrochloric acid number 3.3 was the main product.

(1) Paper II, *THIS JOURNAL*, **58**, 625 (1936).

(2) In preceding papers we spelled "Porphin," because the term was introduced in this form into the chemical literature by H. Fischer for the—at that time hypothetical—fundamental ring system of porphyrins [H. Fischer and P. Halbig, *Ann.*, **448**, 193 (1926)]. Dr. Austin M. Patterson, member for the United States of the Committee on Organic Nomenclature of the International Union of Chemistry, and Chairman of the American Committee, recommended strongly to change the spelling in English to "Porphine," the final *e* signifying the basic character of the compound. He recommended further that the spelling of porphyrin be maintained.

(3) Rothmund, *THIS JOURNAL*, **57**, 2010 (1935); **58**, 625 (1936).

The hydrochloric acid number was 0.5, and the elementary analysis checked with that of porphine within the limits of analytical error. Each of the two porphyrins formed complex metal salts with magnesium ("phyllin"), iron ("hemin"), and copper. The low yields of the porphyrin with hydrochloric acid number 0.5 have prevented the preparation of complex metal salts other than the ones mentioned above so far, but from the component of hydrochloric acid number 3.3 the silver, zinc, cadmium, cobalt and nickel salt were prepared.

The direct determination of the molecular weight of the two porphyrins met with failure so far, but from analytical and spectroscopic data of the free compounds and of their metal complex salts, the author assumes that the new porphyrin isolated in the synthesis of porphine from pyrrole and formaldehyde is the isomer of porphine, and he suggests the term "isoporphine" for it. Two structural formulas may represent the difference in structure of the two compounds: formula I with hydrogen atoms linked to the nitrogen atoms in rings I and II (adjacent rings), and formula II, in which these hydrogen atoms are attached to nitrogen in rings II and IV (opposite rings).

There is, at present, no possibility of assigning one configuration absolutely to either compound, hence the use of the name porphine for structure I, and isoporphine for structure II is still arbitrary.

These structural formulas are drawn to show a double bond between carbon atom γ and the α carbon atom of ring IV (nomenclature of H. Fischer⁴). The presence of a double, not a single, bond between these carbon atoms has been postulated from physicochemical data by Stern.⁵

(4) Fischer, Halbig and Walach, *Ann.*, **452**, 268 (1927); Fischer, Moldenhauer and Süss, *ibid.*, **486**, 107 (1931).

(5) Stern and Wenderlein, *Z. physik. Chem.*, **A175**, 405 (1936).

The structures of porphine and isoporphine given above seem to be the best patterns not only for writing the formulas of nuclear-isomeric porphyrins, but also for the representation of the more complicated, partially hydrogenated compounds with porphine or isoporphine ring, as encountered in the chlorophylls and their derivatives.

Examples of this type of isomerism had been unknown so far. The author and his co-workers were, therefore, greatly interested in checking the synthesis of meso-(= α , β , γ , δ)-tetrasubstituted porphines³ with respect to a possible formation of two isomers. These syntheses yielded indeed in many cases two porphyrins with different hydrochloric acid numbers; their separation by fractionation with hydrochloric acid usually worked satisfactorily, and the isolated porphyrins showed characteristic differences in their spectra in ether.

The table gives some of the experimental results in abbreviated form; publication of the details will follow soon.⁶

TABLE I

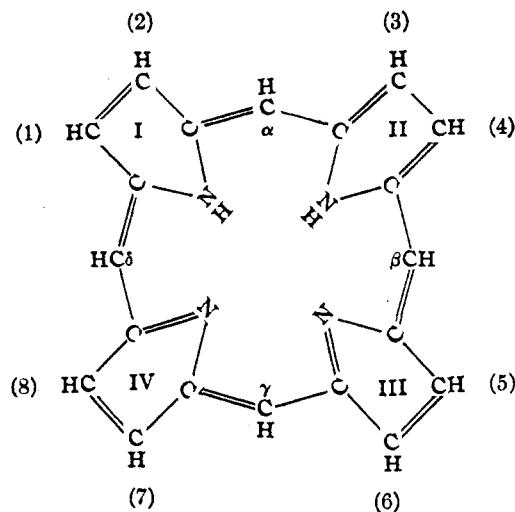
A question mark in a column indicates that the porphyrin has been found in the reaction, but that the purification has not been sufficient to determine its hydrochloric acid number.

Porphyrin	Hydrochloric acid number	
Porphine	3.3	0.5
$\alpha, \beta, \gamma, \delta$ -Tetramethylporphine	0.5	0.075
$\alpha, \beta, \gamma, \delta$ -Tetrapropylporphine	Near 8	2.3
$\alpha, \beta, \gamma, \delta$ -Tetra- <i>n</i> -butylporphine	Near 14	7.0
$\alpha, \beta, \gamma, \delta$ -Tetraisobutylporphine	?	5.2
$\alpha, \beta, \gamma, \delta$ -Tetraphenylporphine	13.5	8.5
$\alpha, \beta, \gamma, \delta$ -Tetrakis-3-methoxy-4-hydroxyphenylporphine	1.04	0.45
$\alpha, \beta, \gamma, \delta$ -Tetrakis- <i>o</i> -hydroxyphenylporphine	15.7	?
$\alpha, \beta, \gamma, \delta$ -Tetrakis- <i>m</i> -hydroxyphenylporphine	6.0	12.2
$\alpha, \beta, \gamma, \delta$ -Tetrakis- <i>p</i> -methoxyphenylporphine	4	16.8

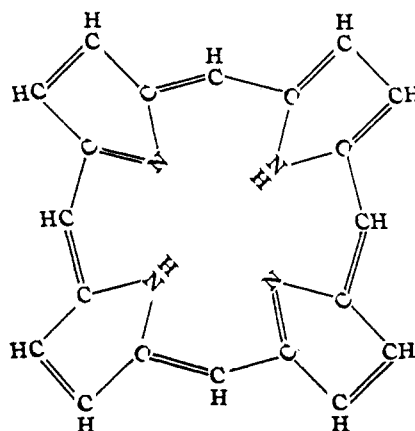
In Fig. 2 the absorption spectra of porphine, isoporphine and of their magnesium complex salts ("phyllins") are given diagrammatically. The characteristic spectroscopic differences are not very large, but they are sufficient to recognize an admixture of about 10 to 20% of one isomer to a solution of the other by visual spectroscopy.

The curve of the molecular absorption coefficient of porphine in ether solution throughout the visible region of the spectrum has been published

(6) Theses in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Graduate School, The Ohio State University (of Th. Londergan, A. Menotti and J. Van Cleve).



Porphine



Isoporphine

Fig. 1.

by Dr. Albers and Dr. Knorr of this Laboratory.⁷

In accordance with the formulas in Fig. 1, we write the structures of the metal complex salts, *e. g.*, the phyllins, in the following manner (Fig. 3).

Haurowitz⁸ could not find any connection between ion radius and absorption bands in porphyrins and their metal complex salts, and he concluded that a formula of type I (Figs. 1 and 3) with linkage of the metal to the nitrogen of adjacent rings, is improbable. He formulates the porphine ring as a biradical with ten conjugated double bonds. Stern⁹ has set forth several objections to this assumption. It is hoped by the author of this paper that further studies, especially the comparative evaluation of absorption and fluorescence spectra, and the determination of the magnetic susceptibilities, of the porphines and the mesotetrasubstituted porphines will elucidate this matter. The röntgenographic investigation of these porphyrins and their com-

(7) Albers and Knorr, *J. Chem. Phys.*, **4**, 422 (1936).

(8) Haurowitz, *Ber.*, **68**, 1795 (1935); *ibid.*, **71**, 1404 (1938).

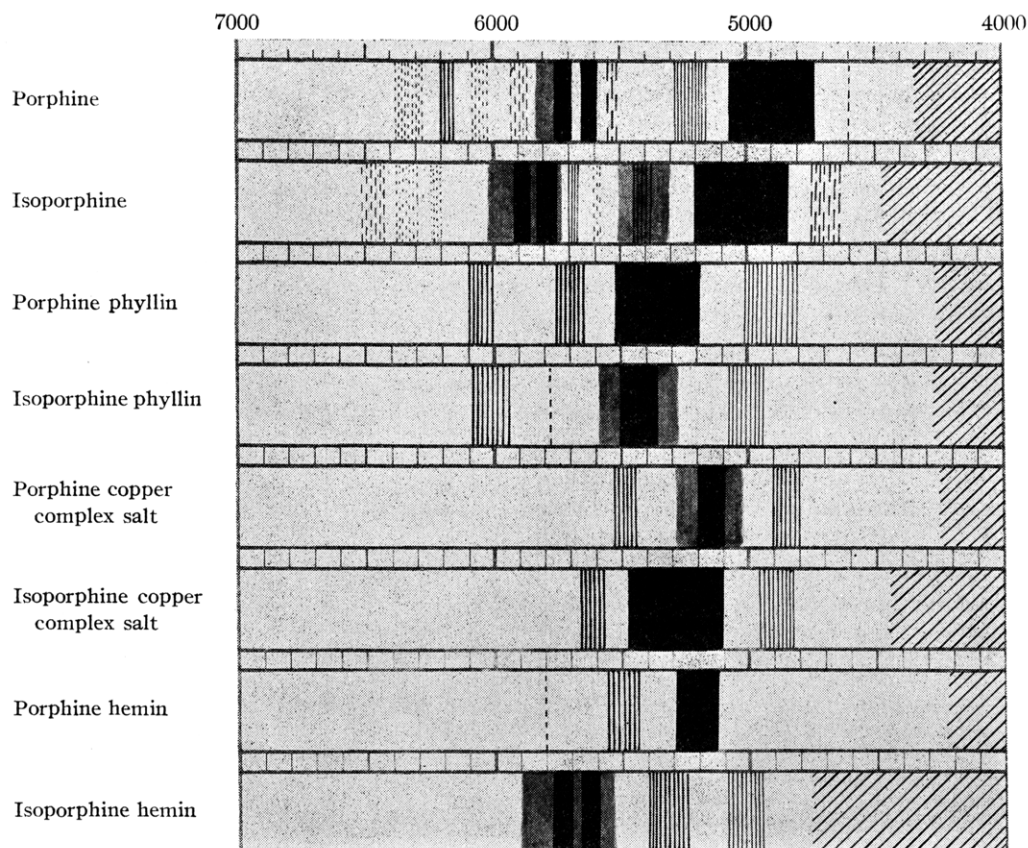


Fig. 2.

plex salts has been started by Professor Blake, Department of Physics, The Ohio State University.

In the issue of *Liebigs Annalen* of June 23, 1939, which has just been received, Helberger⁹ described the synthesis of an isomer tetrabenzoporphine, which he named isotetrabenzoporphine. It was obtained from an oxygen-containing "Hydrogenation product 1," which in turn had been prepared by catalytic hydrogenation of *o*-cyanacetophenone. This isomer is especially interesting in connection with our synthesis of $\alpha,\beta,\gamma,\delta$ -tetraphenylporphine, and $\alpha,\beta,\gamma,\delta$ -tetraphenylisoporphine from benzaldehyde and pyrrole.¹⁰

(9) Helberger and Von Rebay, *Ann.*, **539**, 187 (1939). In the nomenclature given above (Fig. 1) Helberger's isotetrabenzoporphine would be called tetrabenzoisoporphine; we should like to suggest strongly the adoption of the latter name, *i. e.*, naming the fundamental rings porphine, and isoporphine, respectively, with the necessary prefixes. This method simplifies cataloging, and will avoid difficulties in cases of substances as mentioned in the table: $\alpha,\beta,\gamma,\delta$ -tetraisobutylporphine, and its isomer $\alpha,\beta,\gamma,\delta$ -tetraisobutylisoporphine.

(10) Reported at the 95th meeting of the American Chemical Society, Dallas-Fort Worth, Texas, April 19, 1938, by Rothmund and Menotti, and at the 49th Annual meeting of the Ohio Academy of Science in Cincinnati, Ohio, April 14, 1939, by A. Menotti. See also footnote 6.

Experimental¹¹

For the experimental part reference is made to paper II.¹ The filling of the reaction tubes was the same; the sealed tubes were heated to 140–150° for twenty-four hours, and then worked up as described. Most of the isoporphine formed entered the 1% hydrochloric acid fraction (500 ml.), although a small amount was present in the 3% fraction, which was the main fraction for the isolation of porphine. From the 1% hydrochloric acid fraction isoporphine was transferred into 1 liter of ether by addition of saturated sodium acetate solution. The ether was washed with water to neutral reaction, and fractionated with 0.5% hydrochloric acid; the transfer from hydrochloric acid to ether was repeated for the purpose of further purification. After washing with water, and drying with sodium sulfate the ether was filtered and evaporated. The residue was dissolved in hot pyridine to make a saturated solution, and then ether was added, first drop by drop, and then in larger amount, until about ten times the volume of the original pyridine solution was obtained. Isoporphine crystallized in dark brown needles; its hydrochloric acid number was 0.5. It was soluble in pyridine, chloroform, or acetic acid; the solubility in pure ether was small, but ether containing acetic acid dissolved the substance much better. The substance did not melt, but decomposed upon heating above 250°.

(11) With the cooperation of Mr. B. Patterson.

Anal. Material recrystallized from pyridine-ether (1 vol. + 9-10 vols.) as described above, dried to constant weight over phosphorus pentoxide *in vacuo* at the temperature of boiling chloroform (drying pistol). Calcd. for $C_{30}H_{14}N_4$ (310.3): C, 77.40; H, 4.55; N, 18.05. Found: C, 77.5; H, 4.4; N, 17.7.

Magnesium Complex Salt of Isoporphine (Isoporphine Phyllin).—A solution of 6 mg. of isoporphine in 5 ml. of pyridine, 50 mg. of magnesium oxide, and 25 ml. of 30% methanolic potassium hydroxide were heated in a sealed tube for five hours to 150°. The solution was worked up exactly as described for the porphine phyllin.

Anal. Calcd. for $C_{30}H_{12}N_4Mg$ (332.6): C, 72.22; H, 3.64; N, 16.83; Mg, 7.31. Found: C, 72.0; H, 3.8; Mg, 7.3. (N not determined.)

The phyllin is not stable, when heated on a steam-bath with 5% hydrochloric acid. The complexly linked magnesium is eliminated and the free porphyrin regenerated.

Hemin and Copper Complex Salt of Isoporphine.—These two compounds were prepared analogously to the preparation of the corresponding porphine compounds.³

Anal. Calcd. for $C_{20}H_{12}N_4Cu$ (371.9): C, 64.59; H, 3.25; N, 15.06; Cu, 17.10. Found: Cu, 17.0 (digestion of the salt with concentrated sulfuric acid, evaporation of the acid and micro electrolysis of the weakly acid solution—Pregl's method—7 ml. electrolyte, 2.8 v., 35 ma., 50 min. boiling).

Anal. Calcd. for $C_{20}H_{12}N_4FeCl$ (399.6): C, 60.11; H, 3.03; N, 14.01; Fe, 13.96; Cl, 8.89. Found: C, 60.0; H, 3.2; N, 13.6; Cl (micro-Carius), 8.5.

Absorption Spectra

Isoporphine. In Dry Neutral Ether.—I, 650.1-(646.2)-642.4; II, 636.7-(632.6)-628.5; III, 624.3-(622.3)-620.5; IV, 601.5---590.2-(587.0)-583.9---581.3-(577.3)-573.4--; V, 569.6-(567.6)-565.7; VI, 560.2-(558.5)-556.9; VII, 551.7---543.9-(540.4)-537.0---531.0; VIII, 520.4-(502.2)-484.1; IX, 474.9-(469.6)-464.4; shadow 447.0; E. A. 431.5. Intensity: VIII, IV (b, a), VII; V, IX, I; VI = II, III.

Isoporphine Phyllin. (a) In Dry Neutral Ether.—I, 609.2-(601.6)-593.9; shadow 578.0; II, 559.3---550.0-(542.7)-535.3---527.0; III, 506.9-(500.4)-493.8; E. A. 428.0. Intensity: II, I, III.

(b) In the Alkaline Reaction Mixture.—I, 613.5-(605.0)-596.5; II, 562.5-(547.8)-533.0; III, maximum approximately 501; E. A. 456.0. Intensity: II; I; (III).

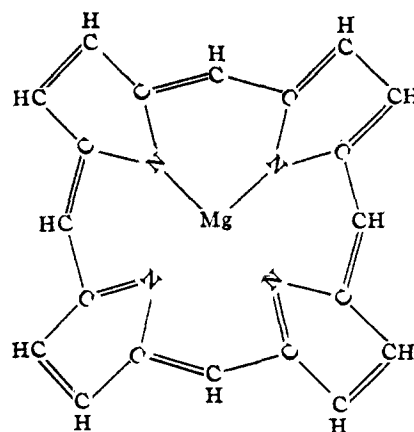
Isoporphine Copper Complex Salt (in Pyridine-Ether).—I, 566.6-(562.4)-558.3; II, 547.1-(529.1)-511.1; III, 496.4-(489.8)-483.2; E. A. 445.0. Intensity: II; I, III.

Isoporphine Iron Chloride (Isoporphine Hemin) (in Pyridine-Ether).—I, 589.7---577.3-(574.0)-570.8---566.6-(563.0)-559.4---554.8; II, 540.3-(532.0)-523.8; III, 509.4-(502.2)-495.1; E. A. 475.5. Intensity: I(b, a), II, III.

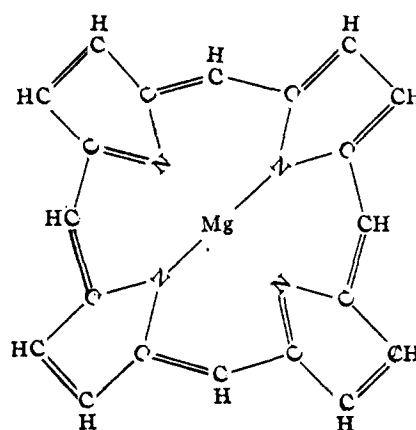
Summary

1. The low hydrochloric acid fraction of the porphine synthesis described previously yielded a new porphyrin of hydrochloric acid number 0.5.

2. Elementary analyses of this porphyrin and of some of its salts lead to the conclusion that this por-



Porphine phyllin



Isoporphine phyllin

Fig. 3.

phyrin is an isomer of porphine: "isoporphine."

3. The phyllin, hemin, and copper complex salt of isoporphine have been prepared.

4. The structures of the porphine and isoporphine ring are discussed.

5. A chart comparing the absorption spectra of porphine, porphine phyllin, porphine hemin, and porphine copper complex salt with those of isoporphine and its corresponding salts is presented.

6. The general synthesis for *meso*-tetrasubstituted porphyrins by the author was tested with respect to the possible formation of two porphyrins instead of one; cases in which two porphyrins have been found are given, and the hydrochloric acid numbers of the new porphyrins are listed.

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