after recrystallization from glacial acetic acid. The hydrobromide was very hygroscopic.

Anal. Calcd. for $C_{18}H_{21}O_3N_2Br$: Br, 20.32. Found: Br, 19.75.

The free peptide was obtained from the hydrobromide by the usual silver carbonate–hydrogen sulfide method. After crystallization from a 1:2 methanol–water mixture, it melted at 232–233° with decomposition.

Anal. Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.25; H, 6.41; N, 8.97. Found: C, 69.23; H, 6.41; N, 8.75.

β-Phenyl-β-alanine ethyl ester hydrochloride, prepared in quantitative yield by treatment of an absolute ethanol solution of the acid with hydrogen chloride,[20] separated from 1:4 absolute ethanol–ether solutions as silky needles, m. p. 137–138°.[21]

Anal. Calcd. for $C_{11}H_{16}O_2NCl$: N, 6.10. Found: N, 6.02.

β-Phenyl-β-alanine Hydrobromide.—Crystals from glacial acetic acid, m. p. 182–183°.

Anal. Calcd. for $C_9H_{12}O_2NBr$: N, 5.69; Br, 32.48. Found: N, 5.65; Br,[22] 32.25.

Summary

Three dipeptides of β-phenyl-β-alanine are described. The synthesis of β-phenyl-β-alanylglycine and of β-phenyl-β-alanyl-β-phenyl-α-alanine was accomplished by the carbobenzoxy method, that of β-phenyl-α-alanyl-β-phenyl-β-alanine by the azlactone method. The instability of carbobenzoxy-β-phenyl-α-alanine has been noted.

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[20] Posner recorded the failure of this reaction with sulfuric acid as a catalyst [*Ber.*, **38**, 2321 (1905)].

[21] Houben and Pfankuch prepared this substance [*ibid.*, **59**, 1604 (1926)], but did not give the melting point.

[22] Analysis by Betty H. Whitenack.

NEWARK, DELAWARE RECEIVED OCTOBER 25, 1940

[CONTRIBUTION FROM THE C. F. KETTERING FOUNDATION FOR THE STUDY OF CHLOROPHYLL AND PHOTOSYNTHESIS ANTIOCH COLLEGE, AND FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

Porphyrin Studies. IV.[1] The Synthesis of α,β,γ,δ-Tetraphenylporphine

BY PAUL ROTHEMUND AND AMEL R. MENOTTI[2]

The subject of this report represents an application of the general reaction between pyrrole and aldehydes, reported some time ago.[3]

A systematic study of some of the many possibilities of this reaction is in progress in order to secure more information on the chemical properties of porphine and the substituted porphine ring system, especially in connection with the study of chlorophyll and photosynthesis.

In the preceding paper[1] a table was given summarizing some of the experimental results obtained. α,β,γ,δ-Tetraphenylporphine (Fig. 1), the synthesis of which is being reported here, was mentioned, and characterized by hydrochloric acid number 13.5, and 8.5, respectively.

When we condensed pyrrole and benzaldehyde, in pyridine solution, in sealed tubes at 220° for forty-eight hours, α,β,γ,δ-tetraphenylporphine $C_{44}H_{30}N_4$ was formed. It crystallized from the reaction mixture in beautiful lustrous deep-blue needles and had a hydrochloric acid number of 13.5.[4] If, however, pyrrole, benzaldehyde and pyridine were refluxed in methanol solution at atmospheric pressure for several days, two porphyrins were obtained. Their separation could be accomplished by fractionation of an ether solution with hydrochloric acid of different concentration, and yielded the above-mentioned α,β,γ,δ-tetraphenylporphine of hydrochloric acid number 13.5, and, in smaller amount, a porphyrin of hydrochloric acid number 8.5.

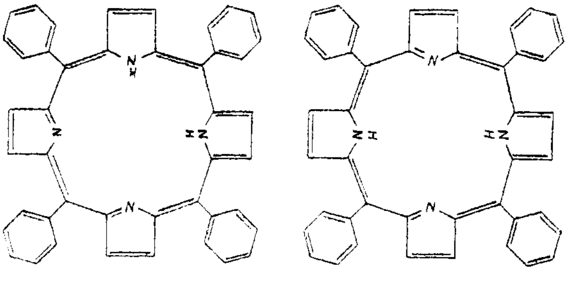

Fig. 1.—α,β,γ,δ-Tetraphenylporphine.

We are continuing the study of the porphyrin with the lower hydrochloric acid number and hope to report on our findings shortly. Figure 2 shows the great similarity of the absorption spectra of the two porphyrins and of their hydrochlorides. This property leads to the assumption that a close structural relationship exists between the two compounds, most likely isomerism in the porphine ring system as indicated in

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[1] Paper III, THIS JOURNAL, **61**, 2912 (1939).

[2] From the dissertation submitted by Amel R. Menotti to the Faculty of the Graduate School of the Ohio State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[3] Rothemund, THIS JOURNAL, **57**, 2010 (1935).

[4] Determination by the method of Willstätter in the improved form suggested by Fischer and Kirstahler, *Z. physiol. Chem.*, **198**, 47 (1931).

Fig. 1. The existence of this kind of ring isomerism has been demonstrated already for the case of porphine and isoporphine.[1]

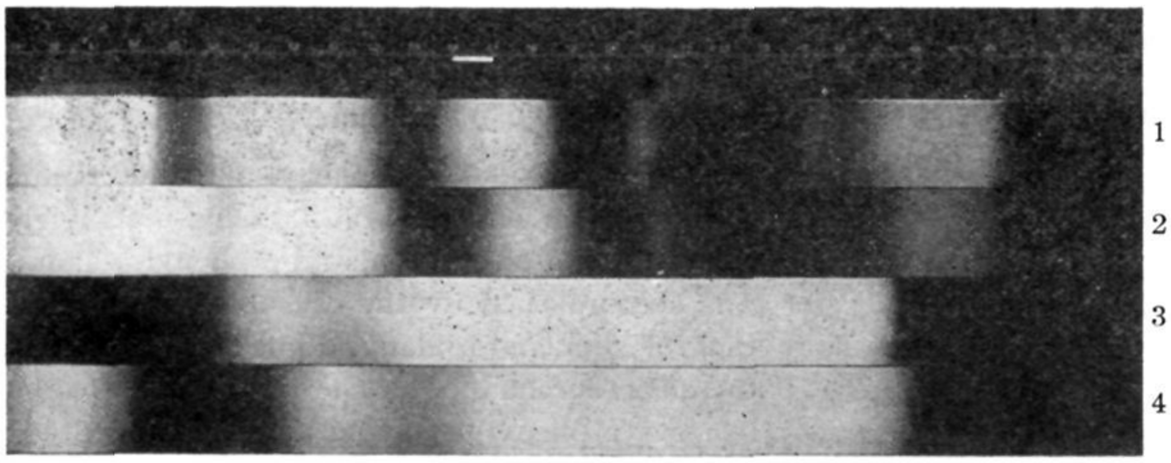

Fig. 2.—1, $\alpha,\beta,\gamma,\delta$-Tetraphenylporphine, HCl no. 13.5, in ether; 2, $\alpha,\beta,\gamma,\delta$-tetraphenylporphine, HCl no. 8.5, in ether; 3, hydrochloride of $\alpha,\beta,\gamma,\delta$-tetraphenylporphine, HCl no. 13.5, in chloroform; 4, hydrochloride of $\alpha,\beta,\gamma,\delta$-tetraphenylporphine, HCl no. 8.5, in chloroform.

The present paper deals with the $\alpha,\beta,\gamma,\delta$-tetraphenylporphine of hydrochloric acid number 13.5 only. The visible absorption spectrum of this porphyrin in ether solution had six bands. Measurements of the molecular absorption coefficients showed[5] the order IV, III, II, I, for the intensity of the four principal bands in the visible region of the spectrum. According to this intensity distribution the spectrum of $\alpha,\beta,\gamma,\delta$-tetraphenylporphine must be classified as an "Etio Type" spectrum[6] although one should have expected that the spectrum of a porphyrin with substituents in all four *ms*-positions would resemble the type of the known *ms*-mono- and *ms*-disubstituted porphyrins. The intensity distribution for the γ-methyl substituted phylloporphyrin has been found to be IV, II, III, I ("Phyllo Type"[7]); in some cases a variation of this type to IV, II, I, III could be observed. $\alpha,\beta,\gamma,\delta$-Tetraphenylporphine represented a very interesting exception to this spectrum type classification: phenyl groups as substituents in the four *ms*-positions did not have a cumulative effect, emphasizing the Phyllo Type, but changed the spectrum type entirely.

The reaction mechanism by which pyrrole and benzaldehyde give porphyrin has not been definitely proved. In the light of numerous syntheses of porphyrins from dipyrrylmethenes and dipyrrylmethanes[7] one can postulate the formation of an intermediate phenyldipyrrylmethene and the subsequent reaction of two molecules of the methene with two molecules of benzaldehyde to produce the porphyrin.

In hydrochloric acid $\alpha,\beta,\gamma,\delta$ - tetraphenylporphine formed a hydrochloride; the analysis of this water-soluble material offered considerable difficulties. Bromination of the free porphyrin in glacial acetic acid with elementary bromine led to two brominated porphyrins; concentrated sulfuric acid yielded a porphyrin trisulfonic acid. Further studies of these materials are under way.

The preparation of $\alpha,\beta,\gamma,\delta$-tetraphenylporphine described above is at present the simplest method of synthesizing a porphyrin in satisfactory yield. It can be recommended as a laboratory synthesis to acquaint students with this important class of compounds, the spectroscopic properties, and the formation of complex salts. The numerous complex salts of $\alpha,\beta,\gamma,\delta$-tetraphenylporphine, which we have prepared, will be the subject of a forthcoming publication.

Experimental

I. Synthesis of $\alpha,\beta,\gamma,\delta$-Tetraphenylporphine.—For this synthesis special sealing tubes were prepared, since the capacity of standard Carius tubes did not allow of heating relatively large quantities of reaction mixture. These sealing tubes were made of Pyrex tubing of 24 mm. diameter (wall thickness 2 mm.) and about 300 mm. length; one end of the tube was closed and to the other end a piece of tubing, of 10 mm. diameter and 150 to 200 mm. length, was joined in order to facilitate sealing, opening, and repeated use of the tube. The tube was filled through a long-stem funnel with 10 ml. of pyrrole, 20 ml. of benzaldehyde, and 20 ml. of pyridine.[8] The air in the tube was replaced by nitrogen, the tube was sealed and heated in a large Carius furnace to 220° for forty-eight hours. The dimensions of the protective iron tube in the furnace were: length 800 mm., diameter approximately 75 mm. Slow cooling of the tube over a period of about ten hours caused the porphyrin to crystallize in beautiful needles of blue luster directly in the tube. The reaction mixture was

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

(6) Stern and Wenderlein, *Z. physik. Chem.*, **A170**, 345 (1934).

(7) Fischer and Orth, "Die Chemie des Pyrrols," Akademische Verlagsgesellschaft m. b. H., Leipzig, 1937 (3 volumes).

(8) The pyrrole used was prepared according to "Organic Syntheses," Vol. IX, p. 78. The pyridine was distilled from Pyridine (Pract.), Eastman Kodak Co., the benzaldehyde was commercial C. P. material.

filtered on a Buchner funnel and the tube and crystals washed with a mixture of 10 volumes of ether and 1 volume of acetone, until the wash liquid came through clear pink. Occasionally the black, tarry reaction mixture was too viscous to filter directly. In such a case it was diluted with 50 ml. of the above ether–acetone mixture before filtering. Benzoic acid, which at times accompanied the crystals, could be removed with hot methanol or hot water, in which solvents the porphyrin was insoluble.

Sufficient pyridine is required in the reaction tube to keep the impurities in solution, otherwise the separation of the crystalline porphyrin is very difficult. The water formed favors the complete removal of the porphyrin from the solution. The use of too much pyridine will dissolve the porphyrin, causing difficulties in working up the reaction mixture. The impurities are insoluble in ether, but extremely soluble in acetone; the porphyrin is only slightly soluble in ether, and dissolves easily in acetone.

From the above quantities of starting material between 1.7 to 2.0 g. of lustrous blue needles was obtained. Needle-shaped crystals up to 2 cm. long could be prepared by cooling over a period of eighteen hours. The larger crystals were easily filtered and washed, while the fine material was more difficult to filter, and dissolved appreciably in the ether–acetone wash liquid.

The crude, crystallized α,β,γ,δ-tetraphenylporphine was extracted from a thimble with benzene. The small crystals thus obtained were of analytical purity.

Properties of α,β,γ,δ-Tetraphenylporphine.—The hydrochloric acid number was 13.5; the porphyrin was soluble in chloroform, dichloroethane, benzene, anisole, pyridine, tetralin, camphor, slightly soluble in ether, dioxane, acetone, ligroin, insoluble in aliphatic alcohols, and in water. It also dissolved in glacial acetic acid (35 mg./100 ml.), formic acid (90%, approximately 250 mg./100 ml.), and to some extent in solutions of inorganic acids. The acid solutions were bright green and exhibited a characteristic acid porphyrin spectrum, while the solutions in the other solvents were of magenta-red color with red fluorescence.

The melting point was 450°. Sublimation to long, thin, bluish-red needles of unchanged porphyrin took place above 400°. Some decomposition occurred, and the oil which distilled over with the sublimate gave a positive test with Ehrlich reagent, *p*-dimethylaminobenzaldehyde, indicating an α-free pyrrole.

Anal. Crystals from reaction tubes recrystallized twice by extracting from a Soxhlet thimble with benzene. The air-dried material gave no appreciable loss when further dried at 105°. Calcd. for $C_{44}H_{30}N_4$ (614.71): C, 85.96; H, 4.92; N, 9.12. Found: C, 85.8; H, 4.8; N, 9.1.

II. Hydrochloride of α,β,γ,δ-Tetraphenylporphine.—The hydrochloride formed when solutions of the porphyrin were shaken with hydrochloric acid of concentration above 4%. A hydrochloride was isolated by passing dry hydrogen chloride through a saturated solution of the porphyrin in chloroform. When twice the volume of anhydrous ether was added to the chloroform an amorphous green precipitate formed, which was filtered off. The hydrochloride was reprecipitated by dissolving in chloroform and again following the above procedure. The dry hydrochloride slowly decomposed on standing; in the presence of moisture the decomposition was rapid. Analysis of the amorphous hydrochloride proved difficult and showed an indefinite composition. Upon drying *in vacuo* in a Pregl block at 80–90°, it lost up to 15% of its weight before acquiring a constant weight, and this material when analyzed indicated between three and four attached hydrogen chloride molecules.

The hydrochloride was only slightly soluble in hydrochloric acid solutions. This property made the fractionation of ether solutions of the porphyrin with hydrochloric acid difficult. Upon shaking a concentrated ether solution of the porphyrin with 15% hydrochloric acid, the green hydrochloride immediately formed; it dissolved somewhat in the acid layer, but most of it precipitated at the ether–acid interface. On standing, the amorphous green compound mentioned above precipitated from the acid layer. In the fractionation of impure mixtures of the porphyrin, it was found advantageous to filter off the hydrochloride mixed with precipitated impurities, and to extract with a mixture of ethanol and 21% hydrochloric acid (1:1

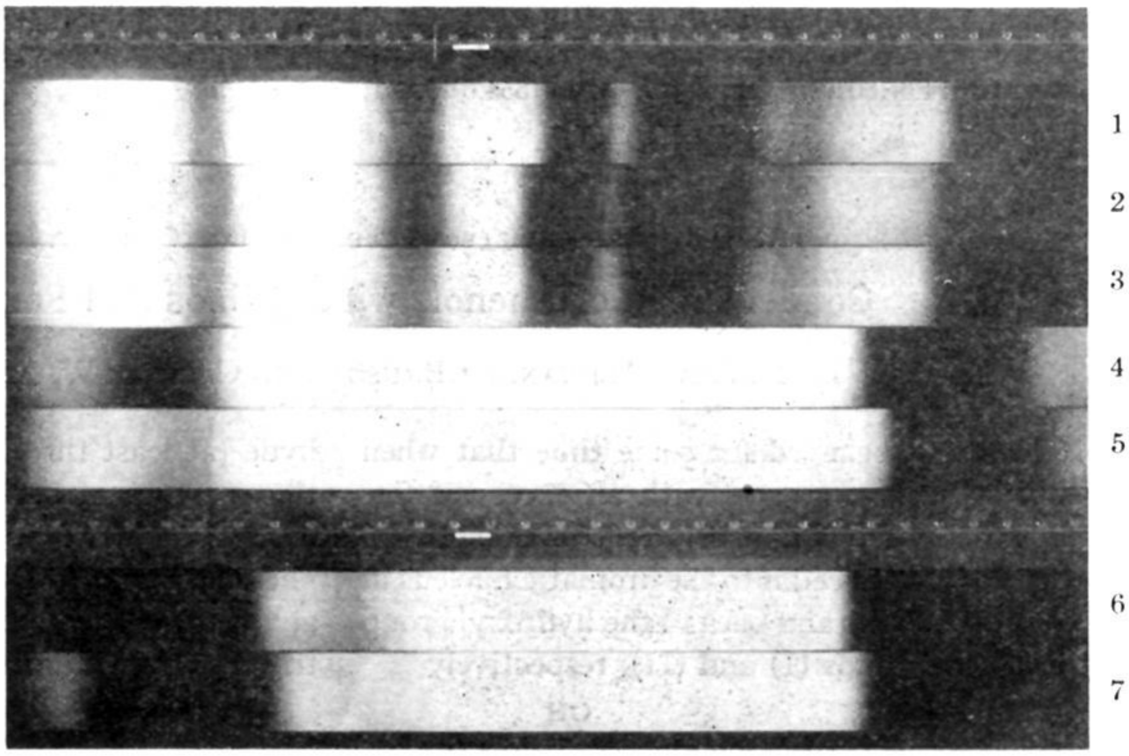


Fig. 3.—Absorption spectra of α,β,γ,δ-tetraphenylporphine: 1, in ether, 0.25 *m;* 2, in chloroform, 0.25 *m;* 3, in pyridine, 0.25 *m;* 4, in chloroform containing hydrogen chloride, 0.12 *m;* 5, in glacial acetic acid, 0.12 *m;* 6, same as 4, but 0.25 *m;* 7, same as 5, but 0.25 *m*.

by volume). In this mixture of solvents the hydrochloride was quite soluble, while much of the accompanying impurities precipitated. This procedure of extracting the impure hydrochloride precipitate was also applied in the attempts to isolate the porphyrin of hydrochloric acid number 8.5 (Fig. 1).

III. Absorption Spectra of $\alpha,\beta,\gamma,\delta$-Tetraphenylporphine. Spectrum in Ether (Fig. 3, No. 1).—I, 654.9-(648.7)-642.6; II, --600.0-(592.6)-585.2--; III, 553.3-(544.9)-536.6; IV, 527.0-(510.5)-494.0; V, 484.6-(478.1)-471.6; VI, 459.7-(454.8)-450.0; E.A. 438.0. Intensity: IV, III, I, II; V; VI.

Spectrum in Chloroform (Fig. 3, No. 2).—I, 657.0-(648.6)-640.2; II, --599.7-(591.5)-583.4; III, 558.2-(550.4)-542.6; IV, 529.5-(514.1)-498.7; V, 487.2-(482.1)-477.0; shadow 458; E.A. 440.4. Intensity: IV, III = I, II, V.

Spectrum in Pyridine (Fig. 3, No. 3).—I, 655.3-(649.3)-643.4; II, 601.2--597.1-(591.6)-586.0; III, 557.8-(549.9)-542.0; IV, 530.0-(514.5)-499.1; V, 487.1-(481.4)-475.7; VI, 461.3-(457.2)-454.1; E.A. 442.0. Intensity: IV, III, I, II; V; VI.

Spectrum of Hydrochloride in Chloroform (Fig. 3, No. 4).—I, 689.6-(663.5)-637.5; II, 617.0-(605.1)-593.2; III, 561.9-(552.7)-543.5; Shadow 516; E.A. 468.3. Intensity I; II, III. Diluting resolves another band: IV, 456.5-(446.0)-435.5; E.A. 404.5.

Spectrum in Glacial Acetic Acid (Fig. 3, No. 5).—I, 699.5-(660.3)-621.2; II, 607.5-(598.1)-588.8--578.0; III, 561.0-(550.7)-540.5; IV, 519.1-(510.4)-501.8; E.A. 470.4. Intensity: I; II; III, IV. Upon diluting another band is resolved: V, 448.9-(439.4)-429.9; E.A. 412.5.

Spectrum in 21% Hydrochloric Acid.—I, 697.1-(665.1)-633.2; II, 614.6-(604.3)-594.0; III, 564.8-(554.6)-544.4; E.A. 467.8. Intensity: I; II, III. At great dilution. IV, 448.2-(441.1)-434.0; E.A. 408.2.

Data on the photographic reproduction of the absorption spectra (Figs. 2 and 3): Zeiss Grating Spectrograph for Chemists. Eastman Spectroscopic Plates, Emulsion Type II—F. Length between inside faces of the Corex D glass windows of the cell: 1 cm., concentration 0.25 *m*, except in Fig. 3, nos. 4 and 5 (0.12 *m*), exposure time sixty seconds: Light source ribbon filament lamp, rated at 100 watts at 6 volts, operated at 5.75 volts. Eastman Kodabrom Paper, Glossy, no. 4.

Summary

1. This paper describes the preparation of $\alpha,\beta,\gamma,\delta$-tetraphenylporphine (hydrochloric acid number 13.5) from pyrrole and benzaldehyde in 10% yield (based on pyrrole).

2. A change in reaction conditions led to the formation of $\alpha,\beta,\gamma,\delta$-tetraphenylporphine as main product, and a small amount of another porphyrin, probably its porphine ring isomer (hydrochloric acid number 8.5).

3. The hydrochloride of $\alpha,\beta,\gamma,\delta$-tetraphenylporphine was prepared.

4. The absorption spectra of the porphyrin in different solvents, and of the hydrochloride were measured.

YELLOW SPRINGS, OHIO
COLUMBUS, OHIO

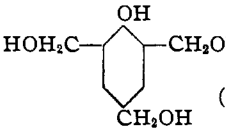
RECEIVED OCTOBER 19, 1940

[CONTRIBUTION FROM RÖHM AND HAAS COMPANY, INC.]

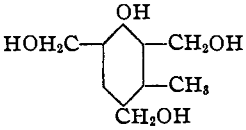
Condensation of Phenols with Amines and Formaldehyde

BY HERMAN ALEXANDER BRUSON AND CLINTON W. MACMULLEN

It has been believed for some time that when phenol or *m*-cresol reacts with an excess of formaldehyde in an alkaline solution, three methylol groups are introduced into the aromatic nucleus in the positions ortho and para to the hydroxyl group to form compounds (I) and (II), respectively



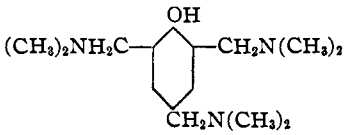
(I)



(II)

but thus far attempts to isolate these trimethylol compounds or any of their derivatives in pure form have led to resinification.[1]

We have observed that an excess of formaldehyde (at least three moles) reacts with phenol in the presence of at least three moles of strongly basic, non-aromatic secondary amines to form phenolic tri-amines. Dimethylamine, for example, gives an almost quantitative yield of 2,4,6-tri-(dimethylaminomethyl)-phenol (III).



(III)

This compound is an oil which exhibits reversed solubility to a striking degree; *i. e.*, it is readily soluble in cold water but only slightly soluble in hot water.

Morpholine, on the other hand, forms a crystalline 2,4,6-tri-(morpholinomethyl)-phenol (IV)

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(1) F. S. Granger, *Ind. Eng. Chem.*, **24**, 442–447 (1932); *ibid.*, **29**, 860–866 (1937); see also Harvey and Baekeland, *ibid.*, **13**, 135 (1929).