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.

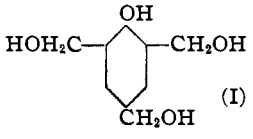
YELLOW SPRINGS, OHIO
COLUMBUS, OHIO
RECEIVED OCTOBER 19, 1940

[CONTRIBUTION FROM RÖHM AND HAAS COMPANY, INC.]

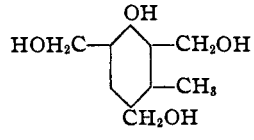
Condensation of Phenols with Amines and Formaldehyde

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



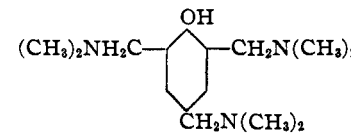
(I)



(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).

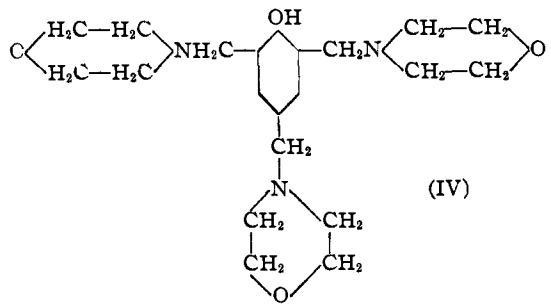


(III)

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)

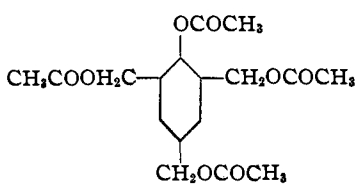
(1) F. S. Granger, *Ind. Eng. Chem.*, **24**, 442–447 (1932); *ibid.*, **29**, 860–866 (1937); see also Harvey and Baekeland, *ibid.*, **13**, 135 (1929).



(IV)

which is soluble in either hot or cold water.

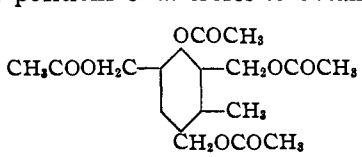
When compounds (III) or (IV) are heated with an excess of acetic anhydride, their tertiary amino groups are completely split off in the form of acetic tertiary amides with the production of the tetra-acetate of (I), namely, 2,4,6-tri-(acetoxymethyl)-phenyl acetate (V).



(V)

This substance is a colorless somewhat viscous oil which can be distilled under reduced pressure without decomposition or resinification. In the presence of alkalies, it resinifies. The position of the acetoxymethyl groups was established by catalytic hydrogenolysis with Raney nickel, to give acetic acid and 2,4,6-trimethylphenyl acetate, which upon saponification yielded 2,4,6-trimethylphenol.

By the same procedure it was possible to introduce three acetoxymethyl groups into the reactive nuclear positions of *m*-cresol to obtain (VI).



(VI)

Experimental

(III) 2,4,6-Tri-(dimethylaminomethyl)-phenol.—A mixture consisting of 94 g. of phenol (1 mole) and 720 g. of 25% aqueous dimethylamine solution (4 moles) was cooled to 20° and stirred while 350 g. of 30% formaldehyde solution (3.5 moles) was added dropwise so that the temperature did not exceed 30° (thirty minutes). The mixture was stirred thereafter for one hour at 25–30° and finally heated with good stirring under reflux on a steam-bath at 90–95° for two hours. To the hot solution 200 g. of sodium chloride was added and the mixture stirred for twenty minutes at 90–95°. The oil layer was then separated from the hot solution and distilled under reduced pressure. The fraction boiling between 130 and 150° at 1–2 mm. was collected. It weighed 228 g. (86% yield) and consisted of a faintly reddish thick oil. Upon redistillation it boiled at 130–135° (1 mm.) and was almost colorless. It was readily soluble in ethanol, benzene, acetone, or cold water but was only slightly soluble in hot water (85–95°): sp. gr. 0.974 at 15°. *Anal.* Calcd. for $C_{15}H_{27}ON_3$: N, 15.84. Found: N, 15.73.

(IV) 2,4,6-Tri-(morpholinomethyl)-phenol.—To a mixture of 94 g. of phenol (1 mole) and 305 g. morpholine (3.5 moles) there was added dropwise while stirring and cooling to 20–25°, 330 g. of 30% formaldehyde solution (3.3 moles). The turbid solution obtained was then stirred for two hours at 20–25° and finally heated for one hour at 85–90° with rapid stirring, during which time it became clear. The clear solution was concentrated in vacuum on a steam-bath until all the water had come off. The product obtained was a viscous yellowish oil which slowly crystallized on standing. After recrystallization from ethyl acetate the product formed large colorless crystals melting at 106–107°. *Anal.* Calcd. for $C_{21}H_{33}O_4N_3$: N, 10.73. Found: N, 10.64%.

(V) 2,4,6-Tri-(acetoxymethyl)-phenyl Acetate.—A mixture consisting of 132 g. of (III) and 255 g. of acetic anhydride was heated at 90–95° on a steam-bath under a reflux condenser for three hours and the reaction mixture fractionated under reduced pressure. The fraction boiling between 175 and 210° at 1–2 mm. was collected. It was washed with warm water to remove traces of acetic acid and acetic dimethylamide, and redistilled at 1–2 mm. The pure compound boiled at 200–205° (1 mm.); yield 154 g. It is a colorless oil of very faint odor. *Anal.* $C_{17}H_{20}O_8$: sap. value calcd., 637.5. Found: 640.

Hydrogenation of (V).—A mixture of 200 g. of (V) and 15 g. of Raney nickel was heated at 150° for five hours with hydrogen under pressure (1500 lb./sq. in.). The product was filtered and distilled. After the acetic acid had come off, a liquid fraction boiling at 80–90° at 1 mm. was collected. This material was saponified with aqueous sodium hydroxide solution by boiling for several hours and the clear solution acidified with hydrochloric acid. The crystalline product obtained was distilled at atmospheric pressure. It boiled at 215–220° and melted crude at 65°. Upon recrystallization from petroleum ether, the melting point rose to 69° which is the melting point of 2,4,6-trimethylphenol. Since an authentic sample of this material was not available for mixed melting points, the product was converted by the method described by Jacobsen[2] into the monobromo derivative melting at 80°, namely, 3-bromomesitol, thus establishing its identity with certainty.

(VI) 2,4,6-Tri-(acetoxymethyl)-*m*-cresyl Acetate.—To a mixture of 108 g. of *m*-cresol (1 mole) and 720 g. of 25% aqueous dimethylamine solution (4 moles) there was added dropwise while stirring and cooling to 20–5°, 350 g. of 30% formaldehyde solution (3.5 moles). The mixture was stirred for one hour at 25–30° and finally heated at 90–95° on the steam-bath for one and one-half hours with rapid stirring under a reflux condenser. The product was salted out from the hot solution with 200 g. of sodium chloride and the oil layer separated. The oil was then dried under reduced pressure on the steam-bath. The crude product

(2) Jacobsen, *Ann.*, **195**, 270 (1879).

thus obtained was a dark red oil consisting essentially of 2,4,6-tri-(dimethylaminomethyl)-*m*-cresol. It was soluble in cold water but only sparingly soluble in hot water. It can be distilled under a good vacuum; b. p. 200° (0.5 mm.). The crude oil was converted without distillation or purification to (VI) as follows:

A mixture of 84 g. of the above red oil and 153 g. of acetic anhydride was boiled under reflux for two and three-quarters hours and the reaction product fractionated under reduced pressure. The fraction boiling at 184–204° at 1–2 mm. was collected; yield 103 g. Upon redistillation the product came over at 194–204° (1 mm.) as a colorless oil. *Anal.* $C_{18}H_{22}O_8$: sap. value calcd., 612.8. Found: 608.

Summary

1. Phenol and *m*-cresol each react with excess formaldehyde and strongly basic non-aromatic secondary amines to take up three tertiary aminomethyl groups in the free ortho and para positions to the hydroxyl group. These free bases on acetylation with acetic anhydride split off the tertiary amino groups and form the tetra-acetates of the corresponding but hitherto unisolated trimethylolphenol or tri-methylol-*m*-cresol.

PHILADELPHIA, PA. RECEIVED OCTOBER 26, 1940

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY, HARVARD MEDICAL SCHOOL]

Studies of the Dielectric Properties of Protein Solutions. III. Lactoglobulin

BY JOHN D. FERRY AND J. L. ONCLEY

From measurements of the dielectric constant of a protein solution over a wide range of frequency, a description of the protein is obtained in terms of the dielectric increment and the form of the anomalous dispersion; and deductions may be drawn concerning the electrical symmetry and the size and shape of the molecule. Studies of solutions of hemoglobin[1] and of the water-soluble proteins of normal horse serum[2]—albumins and pseudoglobulin—have been reported previously from this Laboratory. Measurements upon egg albumin,[3] insulin[4] and edestin[5] have also been carried out and will be reported in detail later. The present paper is concerned with lactoglobulin.

The crystalline lactoglobulin of Palmer[6] can be prepared in a highly purified state, and its solubility in dilute salt solutions has been found to be nearly constant and independent of the amount of saturating body.[7] Furthermore, its salting-in in dilute salt is very large, suggesting a high value of the dipole moment of the molecule.[8] It seemed of particular interest, therefore, to investigate the dielectric properties of this protein.

Being a globulin, it has a very low solubility in water, and in aqueous solutions the increase in dielectric constant over that of water is too slight to permit its measurement with much accuracy. Although it is easily soluble in dilute salt (about 0.01 *M*), solutions with conductivities corresponding to over 5×10^{-4} *M* salt cannot be measured with our present apparatus. However, solutions of lactoglobulin in 0.25 and 0.50 *M* glycine can be studied easily.

The dielectric measurements here reported were made in conjunction with the solubility measurements of Cohn, Ferry and Blanchard.[9] Two preparations of crystalline lactoglobulin (I and II) were very kindly furnished by Dr. A. H. Palmer. Portions of these crystals, after being washed with conductivity water, were rotated in double glass-capped solubility bottles at 5 or 25° for periods of from two to seven days with successive portions of 0.25 or 0.50 *M* glycine. After filtration by the usual procedure of this Laboratory,[10] the filtrates were used for solubility and for dielectric constant measurements at 0 or 25°. For analysis, the protein was coagulated by heating to 100° in the presence of *M*/4 sodium chloride and was filtered on sintered glass, washed free of glycine, dried at 105°, and weighed.

Method.—The dielectric measurements on preparation I of lactoglobulin were made exactly as described in the first papers of this series[1,2] except that the use of a General Radio type 684A oscillator[11] permitted extending the frequency range down to 12,500 cycles.

Measurements on preparation II were made

(1) Oncley, THIS JOURNAL, **60**, 1115 (1938).
(2) Ferry and Oncley, *ibid.*, **60**, 1123 (1938).
(3) Oncley, Ferry and Shack, *Ann. N. Y. Acad. Sci.*, in press.
(4) Cohn, Ferry, Livingood and Blanchard, *Science*, **90**, 183 (1939).
(5) Oncley, *J. Phys. Chem.*, in press.
(6) Palmer, *J. Biol. Chem.*, **104**, 359 (1934).
(7) Sørensen and Palmer, *Compt. rend. trav. Carlsberg*, **21**, 283 (1938).
(8) Cohn, McMeekin, Ferry and Blanchard, *J. Phys. Chem.*, **43**, 169 (1939).
(9) Cohn, Ferry and Blanchard, to be published subsequently. Solubility measurements at two temperatures, 5 and 25°, indicated a heat of solution in 0.25 and 0.50 *M* glycine of approximately −2000 calories.
(10) Ferry, Cohn and Newman, THIS JOURNAL, **60**, 1480 (1938).
(11) General Radio Company, 30 State Street, Cambridge, Mass.