TABLE IV

4-PHENYLPYRIDINES

2,6-Bis-4-phenylpyridine	Yield, %	Crystn. solvent	M.p., °C.	Mol. formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
(4-Methyl-2-pyridyl)-	18	Benzene	228–229	$C_{23}H_{19}N_3$	81.87	81.86	5.68	5.61
(4-Ethyl-2-pyridyl)-	16	Pet. ether	114–115	$C_{25}H_{23}N_3$	82.16	82.20	6.34	6.60
(6-Phenyl-2-pyridyl)-	17	Pet. ether	190–191	$C_{33}H_{23}N_3$	85.87	85.41	5.02	5.19
(4-Phenyl-2-pyridyl)-	21	Nitroethane	257–258	$C_{33}H_{23}N_3$	85.87	85.52	5.02	5.01
(2-Quinolyl)-	18	Benzene	295–296	$C_{29}H_{19}N_3$	85.06	85.49	4.68	4.78

Anal. Calcd. for $C_{14}H_{18}Cl_2N_2$: Cl, 24.86. Found: Cl, 24.53.

Preparation of Substituted Terpyridines (The general procedure of Frank and Seven[5] was used).—A mixture of 2.2 molar proportions (not over 5 g.) of substituted 2-acetylpyridine or quinoline, 1 mole of benzaldehyde, 0.3 mole of ammonium acetate and 9 moles of ammonia in 28% aqueous solution was heated in a sealed tube at 250° for five hours. The resulting mixture was extracted with hot benzene. Removal of the benzene yielded the crude terpyridine.

Acknowledgment.—The authors are indebted to the Rohm and Haas Company for a generous supply of 4-phenylpyridine.

PHILADELPHIA 22, PENNA.

[CONTRIBUTION FROM MULTIPLE FELLOWSHIP OF GULF RESEARCH & DEVELOPMENT COMPANY, MELLON INSTITUTE]

Synthesis and Properties of Porphyrin Vanadium Complexes[1]

BY J. GORDON ERDMAN, VIRGINIA G. RAMSEY, NORMAN W. KALENDA AND WILLIAM E. HANSON

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Procedures are described for the preparation and purification of several porphyrin vanadium complexes of the type which may occur in crude oils and other natural bitumens. Infrared and X-ray studies and elemental analyses are in agreement with the structure, porphyrin V=O. Spectral studies in the visible and ultraviolet indicate the formation of a weak addition complex with pyridine. A new method for the preparation of protoporphyrin IX from blood hemin is given.

Introduction

Metalloporphyrin complexes are widely distributed in nature. Those of iron and magnesium represent the principal photosynthetic pigments of plants and animals. The copper complex also occurs as an avian pigment.[2] In 1934, Treibs demonstrated the presence of porphyrin complexes of vanadium and nickel in a variety of natural bitumens[3] particularly in certain crude oils where the concentration of these metals may run as high as a thousand or more parts per million. Whether the vanadium and nickel complexes are chemical artifacts in the evolution of the photosynthetic and respiratory pigments or are formed by the replacement of the magnesium or iron of chlorophylls and hemins under earth conditions is not known.

Complexes of porphyrin with divalent metals are usually prepared by allowing the equivalent metal salt to react with the porphyrin in buffered acetic acid solution. The resulting molecules are planar, and the bonding between the porphyrin and the metal may be either ionic or coördinate covalent.[4]

Complexes of porphyrins with tri- or tetravalent metals are difficult to prepare directly. The ferric, cobaltic and manganic porphyrin complexes have been prepared only indirectly through oxidation of the ferrous, cobaltous or manganous complex.[5]

Treibs[6] published a preparation of the vanadium complexes of mesoporphyrin, mesoporphyrin dimethyl ester, etioporphyrin and protoporphyrin dimethyl ester using vanadium tetrachloride in a silver pressure vessel at 165° for 4 hr. The analytical results were indeterminate, falling between the values required for porphyrin VO (I), the hydrate porphyrin $V(OH)_2$ (II) and $(\text{porphyrin VOH})_2O$ (III), assuming the vanadium to be quadrivalent, or $(\text{porphyrin VO})_2O$ (IV), in which the vanadium is pentavalent. Structures II and IV were proposed by Treibs and accepted by Fischer and Orth.[7]

The synthesis of the vanadium complexes of the above porphyrins was reinvestigated. Vanadium tetrachloride was found to lead to chlorination on the methene bridge carbons as well as to complex formation, the vanadium complex of Neuman's dichloroetioporphyrin I[8] being isolated. Substitution of vanadyl salts yielded the desired vanadium complexes, the purely ionic vanadyl sulfate ($V_2O_2(SO_4)_2 \cdot 13H_2O$) proving much more reactive than vanadyl chloride. Increasing the solubility of the reactants and products by replacing the sodium acetate buffer with 25 to 33% by volume of pyridine also increased the reaction rate. In the present procedure the use of high temperatures for prolonged periods is eliminated, thus minimizing alteration of reactive side groups such as the vinyl groups of protoporphyrin.

The structures II and IV suggested by Treibs for the complex, and accepted by Fischer and Orth, must be ruled out on the basis of modern bond theory. The *p*-orbitals of oxygen used for bonding are directed at a 90° angle one to the other. To increase the angle to 180° would destroy almost

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[1] Presented at the General Session, Division of Petroleum Chemistry, of the American Chemical Society, Dallas, Texas, April 8-13, 1956.

[2] H. Fischer and J. Hilger, *Z. physiol. Chem.*, **138**, 49 (1924).

[3] A. Treibs, *Ann.*, **509**, 103 (1934).

[4] R. Lemberg and J. W. Legge, "Hematin Compounds and Bile Pigments," Interscience Publishers, Inc., New York, N. Y., 1949, p. 22 ff.

[5] J. F. Taylor, *J. Biol. Chem.*, **135**, 569 (1940).

[6] A. Treibs, *Ann.*, **517**, 192 (1935).

[7] H. Fischer and H. Orth, "Die Chemie des Pyrrols," Vol. II, Pyrrolfarbstoffe, Part 1, Leipzig, 1937, pp. 201, 445 and 450.

[8] H. Fischer and W. Neuman, *Ann.*, **494**, 225, 233 (1932).

completely the energy of the bonds. In addition, assuming normal covalent bond radii, the distance between the planes of the two porphyrin rings would be approximately 3.9 Å. In contrast to this, the van der Waals, or non-bonded radius of the methyl group, is approximately 2.0 Å., or a methyl–methyl distance of 4.0 Å. The rings, therefore, would have to remain essentially parallel one to another and any rocking motion would stretch and break the oxygen bridge.

Of the remaining two structures, elemental analyses of the present preparations of the vanadium complexes of etioporphyrin I, etioporphyrin III, mesoporphyrin IX dimethyl ester and protoporphyrin IX dimethyl ester support the vanadyl structure I, rather than that of the hydrate II. Similar results have been reported recently by Horeczy, *et al.*,[9] for the related tetraphenylporphyrin vanadium complex.

Direct evidence for the V=O bond was obtained by comparison of the infrared spectra of vanadium oxytrichloride with that of etioporphyrin I and its copper, nickel and vanadium complexes (Fig. 1). The curves of the three porphyrin complexes are similar except for a strong, sharp band for the vanadium complex at about 995 cm.$^{-1}$. This band corresponds closely to the extremely intense band in the spectrum of vanadium oxytrichloride at 1035 cm.$^{-1}$ which is assigned to the V=O stretching frequency.

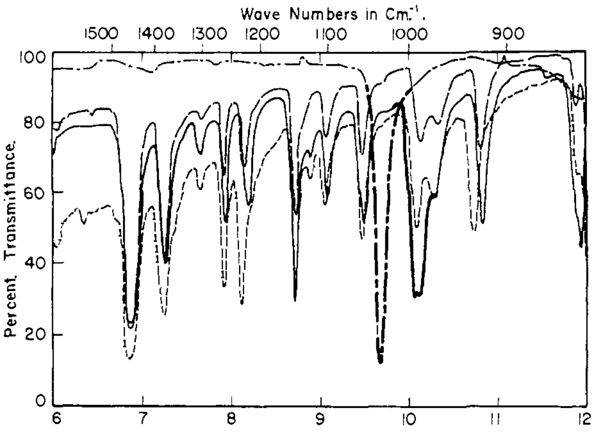

Fig. 1.—Infrared spectra of: etioporphyrin I copper complex, – – –; nickel complex, - - - -; vanadium complex,——; and vanadium oxytrichloride, - • • • -.

Finally, a single-crystal X-ray study of the etioporphyrin I vanadium complex was carried out. The crystal proved to be triclinic and to contain two porphyrin rings per unit cell. Assuming structure I and with a knowledge of the cell dimensions, a density of 1.325 was calculated, which agrees well with the value 1.334 as determined by free flotation.

Porphyrin metallo complexes in many instances form addition complexes with nitrogen bases, where the bonding is either ionic or covalent depending upon the electronic configuration of the metal. It was of interest, therefore, to ascertain whether the porphyrin vanadium complex would form addition complexes with nitrogen bases, either utilizing the open face of the ring or by displacing the oxygen in somewhat analogous fashion to the assumed displacement of the OH of hematins to form (porphyrin-Fe-pyridine)$^{+}$OH^{-}.[10]

In Figs. 2 and 3 are shown the curves for the vanadium complexes of the four porphyrins studied, in dioxane and in moist pyridine. The typical covalent hemochromogen-like spectra[11] of the complexes in dioxane are altered in pyridine through the development of a new peak located about 15 mμ to the long wave length side of the Soret, or Great Peak, in the violet region of the spectrum. In the visible there has been a broadening of the two peaks. Decreasing the concentration of pyridine by replacement with dioxane decreased the spectral effect, indicating weak complex formation.

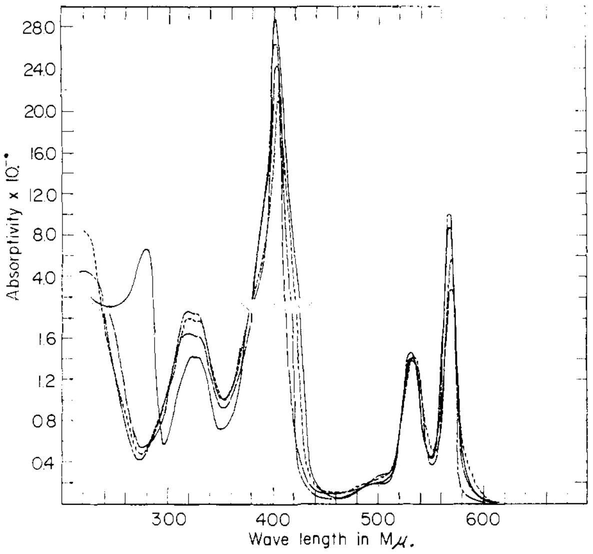

Fig. 2.—Visible and ultraviolet spectra in dioxane of the vanadium complexes of: etioporphyrin I, ——; etioporphyrin III, - • • • -: mesoporphyrin IX dimethyl ester, - - - -. and protoporphyrin IX dimethyl ester, – – –.

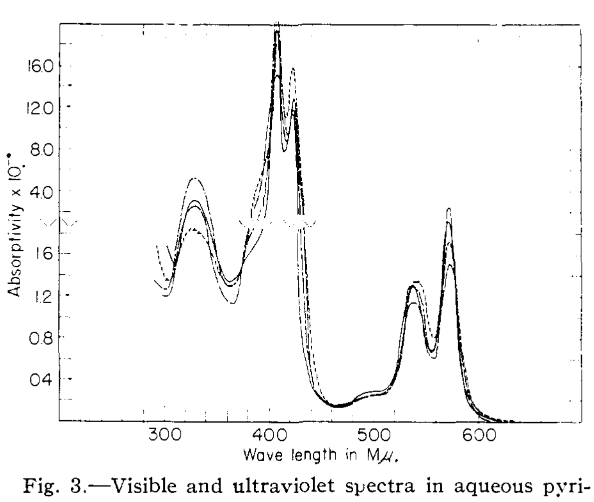

Fig. 3.—Visible and ultraviolet spectra in aqueous pyridine of the vanadium complexes of: etioporphyrin I, ——; etioporphyrin III, - • • • -; mesoporphyrin IX dimethyl ester, - - - -; and protoporphyrin IX dimethyl ester, – – –.

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[9] J. T. Horeczy, *et al.*, *Anal. Chem.*, **27**, 1899 (1955).

[10] W. M. Clark and M. E. Perkins, *J. Biol. Chem.*, **135**, 643 (1940).

[11] H. Theorell, *Arkiv Kemi*, **16A**, No. 2 (42).

The spectra of etioporphyrin I vanadium complex in solutions of pyridine in dioxane were studied as a function of the pyridine concentration and the equilibrium constant for complex formation calculated by the procedure of Miller and Dorough[12] and also by the more general method of Clark, *et al.*[13] A weak complex ($K = 1.99 \times 10^{-2}$, 25°) involving a single molecule of pyridine is indicated. There is no evidence for oxygen displacement.

With the ferric porphyrin complexes, strong acid is capable of converting the hematin to the positive ion.[9,14] A similar reaction with the porphyrin vanadium complexes, *i.e.*, porphyrin VOH^+ and porphyrin V^{++} is indicated.

All of the studies performed on the porphyrin vanadium complex confirm the stability of the metal porphyrin binding and of the vanadium oxygen bond. Sterically the oxygen must project out from the center of the planar porphyrin ring. With the etioporphyrin I complex there is an axis of symmetry through the vanadium–oxygen bond. In the case of unsymmetrically substituted porphyrins such as etioporphyrin III and mesoporphyrin IX, the complex possesses an asymmetric center. Racemization could occur only through hydration, breaking of the vanadium–oxygen bond or dissociation of the complex.

Experimental

Etioporphyrin I.—The compound was prepared in 35% yield by condensation of two molecules of 3,4'-dimethyl-3',4-diethyl-5-bromomethyl-5'-bromodipyrrylmethene hydrobromide and the corresponding perbromide at 190° for 30 minutes in a maleic anhydride melt. The method is a modification of the procedure of Fischer and Stangler.[15]

To avoid contamination with des-ethylporphyrins, the ethyl oximinoacetoacetate used in the pyrrole ring synthesis was isolated and recrystallized. As an additional precaution, the 2,4-dimethyl-3-ethylpyrrole used for the preparation of the dipyrrylmethenes was fractionally distilled through a 100 × 1.5 cm. vacuum jacketed Vigreux column.

The porphyrin was chromatographed over activated alumina and crystallized from pyridine–methanol.

Anal. Calcd. for $C_{32}H_{38}N_4$: C, 80.29; H, 8.00; N, 11.70. Found: C, 80.2; H, 7.9; N, 11.5.

Reaction of Etioporphyrin I and Vanadium Tetrachloride. Part 1.—The procedure of Treibs[6] for the synthesis of etioporphyrin vanadium complex was followed except that a glass ampoule was used instead of a silver pressure vessel. For 500 mg. of etioporphyrin I, 400 mg. of sodium acetate and 10 ml. of acetic acid containing 500 mg. of vanadium tetrachloride was used.

The suspension was centrifuged while still in the ampoule, the ampoule was then opened and the supernatant liquid discarded. The residue was washed with methanol, dissolved in freshly boiled chloroform and filtered. Crystallization was induced by the addition of methanol, yielding glistening purple plates. The product contained chlorine and is believed to be the vanadium complex of the dichloroetioporphyrin I described by Fischer and Neuman.[8] The yield was essentially quantitative.

Anal. Calcd. for $C_{32}H_{36}N_4Cl_2VO$: C, 62.74; H, 5.60; N, 9.15; Cl, 11.59; V, 8.32. Found: C, 61.7; H, 5.5; N, 9.0; Cl, 11.3; V, 8.7.

Part 2.—To test the effect of the one variation in the procedure, the preparation was repeated adding granulated, pure (copper-free) silver to the reaction mixture in the glass ampoule. The concentration of chlorine in the resulting porphyrin vanadium complex was reduced to approximately 0.5%, *i.e.*, about 0.1 atom of chlorine per molecule.

Etioporphyrin I Vanadium Complex.—Since it appears likely that vanadium tetrachloride in glacial acetic acid is converted rapidly to vanadyl chloride, $V_2O_2Cl_4$, preparation of the complex was attempted using this reagent directly. Complex formation was found to proceed under the same conditions as with vanadium tetrachloride.

The procedure was also repeated using the purely ionic vanadyl sulfate, $V_2O_2(SO_4)_2 \cdot 13H_2O$. Where attempts to bring about a reaction with vanadyl chloride in open vessels at the boiling point of the acetic acid, *i.e.*, 118°, had resulted in very little complex formation, almost complete conversion was achieved under the same conditions with vanadyl sulfate.

Synthesis (Method 1).—In a round-bottomed flask fitted with a ground glass joint to a reflux condenser was placed 18.8 ml. of glacial acetic acid, 587 mg. of sodium acetate, 297 mg. of vanadyl sulfate and 200 mg. of etioporphyrin I. The mixture was refluxed until a sample withdrawn with a pipet indicated spectrally that no more complex was being formed, *i.e.*, 95% or better conversion. The mixture was cooled and diluted with approximately 15 ml. of water and let stand overnight for crystal growth. The crystals were collected on a fritted glass filter and washed with water until the filtrate was colorless, *i.e.*, until the blue color of vanadyl salt had disappeared. The product was air-dried to give a dark purple crystalline powder. The yield was essentially quantitative.

Synthesis (Method 2).—The reaction was carried out as before except that the charge consisted of 13.5 ml. of glacial acetic acid, 6.5 ml. of pyridine, 297 mg. of vanadyl sulfate and 200 mg. of etioporphyrin I. The mixture was refluxed until the reaction was essentially complete, usually 2 to 3 hr. The cooled reaction mixture was worked up as before. The yield also was essentially quantitative.

Purification.—The complex was dissolved in benzene, using 1 ml. of benzene per milligram of complex. The solution was twice chromatographed over 60–200 mesh Davison silica gel using 1.8 ml. of silica gel per milligram of crude complex. The chromatograms were developed with a 1:1 mixture of benzene and *n*-propyl alcohol. Continued washings eluted the complex, the unreacted porphyrin remaining on the column. The porphyrin was recovered by elution with benzene–methanol.

The benzene–*n*-propyl alcohol solution of the complex was evaporated to dryness in a stream of nitrogen. The residue was dissolved in hot benzene and crystallization induced by the addition of methanol. The product consisted of glistening purple platelets.

Anal. Calcd. for $C_{32}H_{36}N_4VO$: C, 70.70; H, 6.68; N, 10.31; O. 2.94; V, 9.38. Found: C, 70.9; H, 6.8; N, 10.8; O, 3.3; V, 8.9.

Etioporphyrin III.—The compound was prepared in 17% yield by condensation of 3,4'-dimethyl-3'.4-diethyl-5.5'-dibromomethyldipyrrylmethene hydrobromide and 3.3'-diethyl-4,4'-dimethyl-5,5'-dibromodipyrrylmethene hydrobromide in maleic anhydride melt for 1 hr. at 190°. The method is a modification of the procedure of Fischer and Stangler.[16]

To ensure maximum purity of the product, the 3,3'-diethyl-4,4'-dimethyl-5,5'-dibromodipyrrylmethene hydrobromide was purified chromatographically as the free base.

Etioporphyrin III Vanadium Complex.—The preparation of the crude complex was carried out according to method 1 for etioporphyrin I. The crude material was purified by mixing with 10 ml. of glacial formic acid, heating at 65–75° for 1 hr., adding a little Celite and filtering through a bed of Celite. The filter cake was washed with 2 ml. of formic acid, dispersed in 15 ml. of acid and heated to boiling for 5 minutes. The mixture was cooled at 0° for 15 minutes and filtered. The cake was then further washed with water and dried.

The porphyrin complex was extracted from the Celite with 60 ml. of hot benzene and chromatographed over a column of silica gel. The complex formed a brilliant purple band which was eluted with a 1:1 mixture of benzene and *n*-propyl alcohol. The eluate was filtered through Whatman No. 42 paper and concentrated to 50 ml. Just enough benzene was then added to the hot solution to effect complete solution and the mixture cooled. The sparkling

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(12) J. R. Miller and G. C. Dorough, THIS JOURNAL, **74**, 3977 (1952).

(13) W. M. Clark, *et al.*, *J. Biol. Chem.*, **135**, 561 (1940).

(14) C. S. Vestling, *ibid.*, **135**, 623 (1940).

(15) H. Fischer and G. Stangler, *Ann.*, **459**, 91 (1927).

(16) H. Fischer and G. Stangler, *Ibid.*, **462**, 265 (1928).

purple platelets were filtered off and washed with *n*-propyl alcohol.

Anal. Calcd. for $C_{32}H_{36}N_4VO$: C, 70.70; H, 6.68; N, 10.31; O, 2.94; V, 9.38. Found: C, 70.9; H, 6.8; N, 10.5; O, 2.9; V, 9.4.

Mesoporphyrin IX.—The compound was prepared and purified according to the procedure of Corwin and Erdman.[17]

Mesoporphyrin IX Dimethyl Ester Vanadium Complex.—Crude mesoporphyrin IX vanadium complex was prepared according to method 1 for etioporphyrin I and then esterified by refluxing with a methanolic solution of dry hydrogen chloride.

The crude material was purified by repeated extraction with a total of 11 ml. of glacial formic acid followed by repeated extraction with a total of 25 ml. of 50% aqueous formic acid, which removed most of the uncomplexed porphyrin.

The complex, dissolved in benzene, was chromatographed over calcium carbonate. Development and elution was accomplished with benzene. The solution corresponding to the brilliant purple band was filtered through Whatman No. 42 paper, concentrated to 20 ml. and hot methanol added to incipient precipitation. The complex crystallized on cooling and was washed with cold methanol.

Anal. Calcd. for $C_{36}H_{40}O_4N_4VO$: C, 65.54; H, 6.11; N, 8.49; O, 12.13; V, 7.72. Found: C, 65.6; H, 6.3; N, 8.9; O, 11.7; V, 7.6.

Protoporphyrin IX Dimethyl Ester.—Protoporphyrin IX was prepared from protohemin IX and purified by the same procedure used for mesoporphyrin IX except that platinum oxide was used in place of palladium oxide. Platinum in formic acid reduces the iron to the ferrous state which is readily separated from the porphyrin by the acid but, unlike palladium, does not reduce the vinyl groups. Esterification was performed by refluxing the porphyrin diacid with a solution of methanolic HCl for 15 minutes.

Protoporphyrin IX Dimethyl Ester Vanadium Complex.—An attempt to prepare this complex using vanadyl chloride in a pressure tube resulted in a large amount of gray, insoluble material. Only about 15% of the porphyrin was recovered as complex.

The crude complex was prepared in good yield according to method 1, except that the quantity of acetic acid and sodium acetate was increased by 60%.

The product of the reaction was washed with 65% formic acid at room temperature until the washings were no longer colored. The residue was then washed with water and dried. Extraction with benzene left a small amount of dark amorphous material which was discarded. The solution in benzene then was chromatographed over calcium carbonate and crystallized according to the procedure used for the mesoporphyrin IX dimethyl ester complex.

Anal. Calcd. for $C_{36}H_{36}O_4N_4VO$: C, 65.92; H, 5.53; N, 8.55; O, 12.20; V, 7.77. Found: C, 65.8; H, 5.8; N, 8.6; O, 11.7; V, 7.6.

Spectrophotometric Measurements.—The infrared data were obtained using a Baird double beam spectrophotometer. The porphyrin metallo complexes were prepared as Nujol oil mulls. Vanadium oxytrichloride, which is a liquid, was studied in the pure state.

The visible and ultraviolet data were obtained by first scanning with the Beckman DK-1 automatic recording spectrophotometer. Wave length positions and intensities of absorption peaks were then determined precisely with a calibrated Beckman DU spectrophotometer with controlled slit width.

X-Ray Crystallographic Measurements.—The single-crystal study was carried out in the Department of Chemical Physics at Mellon Institute by Drs. S. Ohlberg and L. E. Alexander. Details of the work will be published in *Acta Crystallographica*.

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PITTSBURGH 13, PENNA.

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[17] A. H. Corwin and J. G. Erdman, THIS JOURNAL, 68, 2473 (1946).