and for 3-carbomethoxy-1-methylpyridinium iodide from water to ethanol to chloroform,[10] these colors are due to a shift of the charge-transfer band toward longer wave lengths. A more complete study of this interesting and valuable phenomenon will appear in a future publication.[10]

Acknowledgments.—The authors are grateful to Dr. Sidney D. Ross for helpful correspondence and to the Research Corporation for a Frederick Gardner Cottrell grant which provided funds for some of the materials used in this research.

BETHLEHEM, PA.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Preparation of Some Substituted 2,6-Bis-(2-pyridyl)-pyridines

BY FRANCIS H. CASE AND THOMAS J. KASPER

RECEIVED MAY 24, 1956

The following substituted 4-phenylpyridines have been synthesized by a modified Tschitschibabin reaction: 2,6-bis-(4-methyl-2-pyridyl), 2,6-bis-(4-ethyl-2-pyridyl), 2,6-bis-(4-phenyl-2-pyridyl), 2,6-bis-(6-phenyl-2-pyridyl) and 2,6-bis-(2-quinolyl). The preparation of 4,4'-diethyl- and diphenyl-2,2'-bipyridines is also described.

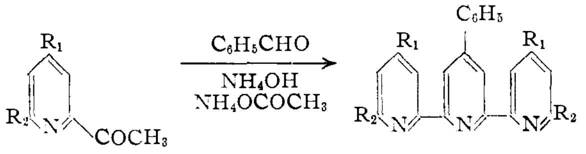
The extreme sensitiveness of the color given by the ferrous complex of 2,6-bis-(2-pyridyl)-pyridine (molecular extinction coefficient 12,500) and of 2,6-bis-(2-pyridyl)-4-phenylpyridine[1] (I), (*E* 22,000) have been pointed out by Wilkins and Smith.[2] It seemed to us, on the basis of experience in the 1,10-phenanthroline series, that the introduction of further alkyl or phenyl substituents, particularly in the 4-positions to nitrogen, should further enhance the sensitivity of the molecule. This has already been confirmed by the above authors in the case of 2,6-bis-(4-methyl-2-pyridyl)-4-phenylpyridine (II) (*E* 26,300) prepared by us.

The synthesis of II was effected in the following manner: 2-bromo-4-methylpyridine[3] was converted to the nitrile by the method of Craig[4] and this in turn to the acetyl derivative by a methyl Grignard. The 4-methyl-2-acetyl pyridine was then converted to II by reaction with benzaldehyde, ammonium acetate and ammonium hydroxide (method of Frank and Seven[5]). The synthesis of 2,6-bis-(4-ethyl-2-pyridyl)-4-phenylpyridine (III) was accomplished in a similar manner, starting from the hitherto unknown 2-amino-4-ethylpyridine.

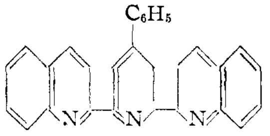
In the case of 2,6-bis-(4-phenyl-2-pyridyl)-4-phenylpyridine (IV), and 2,6-bis-(6-phenyl-2-pyridyl)-4-phenylpyridine (V), 4-phenylpyridine[6] and 2-phenylpyridine,[7] respectively, were converted to their 2-cyano derivatives through the 2-amino and 2-bromo compounds. In these cases conversion to the 2-acetyl derivatives by a methyl Grignard was found unsuccessful. The cyano compounds were therefore converted to the carbethoxy derivatives which were condensed with ethyl acetate to form the substituted ethyl acetoacetate derivatives. Hydrolysis then yielded the acetyl derivatives[8] which were condensed with benzaldehyde and ammonia as before.

For the preparation of 2,6-bis-(2-quinolyl)-4-phenylpyridine (VI), 2-acetylquinoline[9] was used in the above reaction. Compound VI has been found lacking in chelating properties.[2]

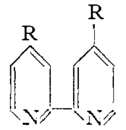
From 2-bromo-4-ethyl-and 2-bromo-4-phenylpyridine an Ullmann reaction yielded the corresponding 4,4'-diethyl-(VII) and 4,4'-diphenyl-(VIII)-2,2'-bipyridines. These will also be tested for metal-chelating properties.



I, R$_1$ = H; R$_2$ = H
II, R$_1$ = CH$_3$; R$_2$ = H
III, R$_1$ = C$_2$H$_5$; R$_2$ = H
IV, R$_1$ = C$_6$H$_5$; R$_2$ = H
V, R$_1$ = H; R$_2$ = C$_6$H$_5$



VI



VII, R = C$_2$H$_5$
VIII, R = C$_6$H$_5$

Experimental

Preparation of 2-Aminopyridines.—A mixture of one molar proportion of 2- or 4-substituted pyridine, 1.18 moles of sodamide and 2.2 moles of dimethylaniline was heated at 150–160° (130–140° in the case of 4-ethylpyridine) for 6 hr. The reaction mixture, after cooling, was poured into water, and the dimethylaniline layer separated and dried over anhydrous potassium carbonate. After removal of solvent *in vacuo* the residue was distilled *in vacuo* (except in the case of the 4-phenyl-2-aminopyridine, which solidified at once). The distillates then solidified and were purified by crystallization.

Preparation of 2-Bromopyridines.—(The method of Craig[4] was used).—To a solution of 0.3 mole of substituted 2-aminopyridine in 175 ml. of 48% hydrobromic acid was added 42 ml. of bromine. A solution of 52 g. of sodium nitrite in 74 ml. of water was then added gradually, keeping the temperature below 5° until near the end of the reaction, when it rose spontaneously to 12°. A solution of 112 g. of sodium hydroxide in 285 ml. of water was then added keeping the temperature below 20°. The reaction mixture was extracted with ether, the ether removed and the resulting oil distilled *in vacuo*. Except in the case of 2-bromo-4-

---

[1] R. L. Frank and E. F. Riener, THIS JOURNAL, **72**, 4183 (1950).

[2] D. H. Wilkins and G. F. Smith, *Anal. Chim. Acta*, **9**, 338 (1953).

[3] F. H. Case, THIS JOURNAL, **68**, 2574 (1946).

[4] L. C. Craig, *ibid.*, **56**, 232 (1934).

[5] R. L. Frank and R. P. Seven, *ibid.*, **71**, 2629 (1949).

[6] C. J. Schmidle and R. C. Mansfield, *ibid.*, **78**, 1702 (1956).

[7] J. C. W. Evans and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 517.

[8] H. Gilman, L. Tolman and S. P. Massie, THIS JOURNAL, **68**, 2399 (1946).

[9] K. N. Campbell, C. H. Helbing and J. F. Kerwin, *ibid.*, **68**, 1840 (1946).

TABLE I

2-AMINOPYRIDINES

2-Aminopyridine	Yield, %	M.p., °C.	Crystn. solvent	Mol. formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
4-Ethyl-	53	70–71	Pet. ether	$C_7H_{10}N_2$	68.81	68.89	8.25	8.21
4-Phenyl-	53	164–165	Benzene	$C_{11}H_{10}N_2$	77.62	77.33	5.92	6.05
6-Phenyl-	70	71–72	Pet. ether	$C_{11}H_{10}N_2$	77.62	77.49	5.92	5.96

TABLE II

2-BROMOPYRIDINES

2-Bromopyridine	Yield, %	M.p. or b.p., °C (mm.)	Mol. formula	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
4-Ethyl-	88	b.p. 103–105 (11)	C_7H_8BrN	45.18	45.24	4.33	4.37
4-Phenyl-	63	m.p. 65–66	$C_{11}H_8BrN$	56.43	56.58	3.44	3.67
6-Phenyl-	62	m.p. 51–52	$C_{11}H_8BrN$	56.43	56.52	3.44	3.60

TABLE III

2-CYANOPYRIDINES

2-Cyanopyridine	Yield, %	M.p. or b.p., °C. (mm.)	Mol. formula	Carbon, %		Hydrogen, %	
				Calcd.	Found	Calcd.	Found
4-Methyl-	28	m.p. 88–89	$C_7H_6N_2$	71.16	71.34	5.12	5.11
4-Phenyl-	60	m.p. 99–100	$C_{12}H_8N_2$	79.98	79.92	4.48	4.81
6-Phenyl-	67	m.p. 64–66	$C_{12}H_8N_2$	79.98	79.81	4.48	4.78
4-Ethyl-	61	b.p. 123–124 (11)	$C_8H_8N_2$	N, 21.20	21.54		

ethylpyridine the oil solidified and was crystallized from petroleum ether.

Preparation of 2-Cyanopyridines.—A mixture of one molar proportion of substituted 2-bromopyridine and 1.5 moles of cuprous cyanide (1.1 moles in the case of 2-bromo-4-methylpyridine) in a distillation flask with side arm and receiver was heated gently with a smoky flame until a reaction was seen to start. At this moment the system was evacuated as rapidly as possible to 5 mm. (40 mm. in the case of the methyl derivative) and the products of the reaction rapidly distilled. The solid distillate was crystallized from petroleum ether (except in the case of 2-cyano-4-ethylpyridine, which was a liquid).

2-Acetyl-4-methylpyridine.—To an ice-cooled solution of 11.8 g. (0.1 mole) of 2-cyano-4-methylpyridine in a mixture of 125 ml. of dry benzene and 100 ml. of ether was added an ether solution of the Grignard reagent prepared from 35.5 g. of methyl iodide (0.25 mole) and 6 g. of magnesium. The reaction mixture was allowed to warm to room temperature and stirred for one hour. After decomposition with an ice-cold solution of ammonium chloride, the ether layer was separated, dried over anhydrous sodium sulfate, and the ether removed by distillation. The residue, on distillation *in vacuo*, yielded 8.0 g. (59%) of an oil, boiling at 95–97° (15 mm.). It solidified yielding a compound melting at 33–34° after crystallization from petroleum ether.

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71. Found: C, 70.76; H, 6.83.

2-Acetyl-4-ethylpyridine.—This was prepared from 2-cyano-4-ethylpyridine using the same molecular proportions of reagents as above. From 13.2 g. of cyano compound was obtained 7.0 g. (47%) of a colorless liquid, b.p. 100–101° (11 mm.).

Anal. Calcd. for $C_9H_{11}NO$: N, 9.44. Found: N, 9.64.

2-Carbethoxy-6-phenylpyridine.—Twenty grams of 2-cyano-4-phenylpyridine was refluxed with 220 ml. of saturated ethanolic hydrogen chloride for five hours. The precipitated ammonium chloride was removed by filtration from the cooled reaction mixture and the filtrate concentrated *in vacuo* on a steam-bath, cooled, poured into water, and neutralized with ammonium hydroxide. The resulting precipitate was separated, dried, and crystallized from petroleum ether. The yield of colorless solid melting at 56–57° was 79%.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 73.72; H, 5.88.

2-Carbethoxy-4-phenylpyridine.—This was prepared in the same manner as 2-carbethoxy-6-phenylpyridine. From 17.3 g. of 2-cyano-4-phenylpyridine was obtained 15.8 g. of product crystallized from petroleum ether, and melting at 60–61°; yield 73%.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 73.79; H, 5.78.

2-Acetyl-6-phenylpyridine.—To 9.2 g. (0.135 mole) of sodium ethoxide in 125 ml. of dry benzene was added with stirring a mixture of 20 g. (0.088 mole) of 2-carbethoxy-6-phenylpyridine and 14 g. (0.18 mole) of anhydrous ethyl acetate. The reaction mixture was then refluxed with stirring for 21 hours, cooled and poured into a cold solution of 4.4 g. of sodium hydroxide in 90 ml. of water. The further procedure followed the directions of Gilman, Tolman and Massie[8] for the preparation of methyl α-pyridyl ketone. Evaporation of the ether then yielded 9.3 g. (54%) of a solid melting at 75–76° after crystallization from petroleum ether.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 79.16; H, 6.00.

2-Acetyl-4-phenylpyridine.—This was prepared in the same way as 2-acetyl-6-phenylpyridine. From 14.5 g. of 2-carbethoxy-4-phenylpyridine was obtained 7.5 g. (60%) of product melting at 75–76° after crystallization from petroleum ether.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 79.28; H, 5.78.

4,4′-Diphenyl-2,2′-bipyridine.—A mixture of 6 g. of 2-bromo-4-phenylpyridine and 6 g. of copper powder in 12 g. of biphenyl was heated with stirring at 250° for 3 hours. The reaction mixture was then finely powdered and extracted several times with concentrated hydrochloric acid. The solution was made alkaline with a mixture of sodium hydroxide and ammonium hydroxide and extracted with ether. Evaporation of the ether and crystallization of the residue from benzene–petroleum ether yielded 0.7 g. (17.7%) of product melting at 187–188°.

Anal. Calcd. for $C_{22}H_{16}N_2$: C, 85.68; H, 5.23. Found: C, 85.58; H, 5.29.

4,4′-Diethyl-2,2′-bipyridine.—A mixture of 28 g. of 2-bromo-4-ethylpyridine and 43.5 g. of copper powder was heated to 200° and the temperature gradually raised to 220° during the course of one hour. The reaction mixture was then treated in the same way as for 4,4′-diphenyl-2,2′-bipyridine. The residue from the ether extract was distilled *in vacuo*, yielding 4.0 g. (25%) of a colorless liquid, b.p. 147–150° (0.3 mm.).

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60. Found: C, 79.14; H, 7.50.

The dihydrochloride of the above base was prepared by passing dry hydrogen chloride into an ether solution of it. The pure product melted at 193–195° after crystallization from ethanol–acetone.

TABLE IV

4-PHENYLPYRIDINES

2,6-Bis-4-phenylpyridine	Yield, %	Crystn. solvent	M.p., °C.	Mol. formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	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

RECEIVED MARCH 21, 1956

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 (porphyrin $VOH)_2O$ (III), assuming the vanadium to be quadrivalent, or (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

---

[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).