Dissociation Constants of 2-Substituted Pyridines

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Received June 5, 1959

As part of a research program on pyridine chemistry, the dissociation constants of several 2-substituted pyridines were measured.

EXPERIMENTAL

The half-neutralization method was used and all *p*H measurements were made at 25 ± 0.2°. At least 2 solutions of different concentrations, half neutralized with hydrochloric acid were made for each compound, and four *p*H measurements were made on each solution; this was repeated with a fresh sample of the same solution. All measurements were made on solutions freshly made up from the pyridines immediately after their purification.

All distillations were done on an all-glass column packed with Fenske rings. This column had twelve theoretical plates when tested at atmospheric pressure with benzene–carbon tetrachloride.

Since $BH^+ \rightleftarrows B + H^+$

$K_a = a_B \cdot a_{H^+}/a_{BH^+} = c_B \cdot \gamma_B \cdot a_{H^+}/c_{BH^+}\gamma_{BH^+}$

We assume $\gamma_B = 1.00$ and $c_B = c_{BH^+}$

then $pK_a = pH + \log \gamma_{BH^+}$

The Debye-Huckel limiting law was used in the form $\log \gamma = -0.509\sqrt{\mu}/(1 + \sqrt{\mu})$

No difference in results could be found using carbon dioxide–free water or ordinary distilled water. It was found that carbon dioxide in the air did not change the measured *p*H values even for the weakest acids.

The values in Table I indicate the expected trend in +I effect:

$$(CH_2)_x\,CH_3 > CH_3 > H > CH_2C_6H_5 > CH = CH_2 > Br > Cl$$

TABLE I

Compound	Fraction Used B.P., °C.	Fraction Used Pressure, mm. Hg	n_D^{30}	Conc. of Solutions mol./l.	pK_a at 25° (thermodynamic)
2-Amylpyridine	211	760	1.4848	0.00500, 0.00560	6.00 ± 0.02
2-Hexylpyridine	87	6	1.4850	0.0010	5.95 ± 0.02
2-Methylpyridine	128	760	1.4940	0.142, 0.101	5.94 ± 0.01 (lit. 5.96[a]; 6.02[b])
Pyridine[c]	115	760	1.5033	0.100, 0.005	5.25 ± 0.01 (lit. 5.23[a]; 5.25[b])
2-Benzylpyridine	123–126	5	1.5732	0.00580, 0.00184	5.13 ± 0.01
2-Vinylpyridine	42–44	10	1.5386	0.0220, 0.0128	4.98 ± 0.01
2-Bromopyridine[d]	66	10	1.5658	0.0928, 0.102	0.71 ± 0.01
2-Chloropyridine[d]	170.5	760	1.5262	0.109, 0.114	0.49 ± 0.02
					Standard deviations given

[a] A. Gero and J. Markham, *J. Org. Chem.* **16**, 1835 (1951). [b] R. Pearson and F. Williams, *J. Am. Chem. Soc.* **75**, 3073 (1953). [c] Prepared by several methods: (1) redistilled from reaction of sodium and pyridine; (2) redistilled from pyrolysis of pyridine at 700–800; (3) from zinc chloride addition compound. [d] Since this base is very weak the assumption of $C_B = C_{BH^+}$ is not valid. This pK_a was estimated from $C_{H^+} = a_{H^+}/\gamma_{H^+}$ (using $\gamma_{H^+} = \gamma_{BH^+}$ from Debye-Hückel), $C_{BH^+} = C_{HCl} - C_{H^+}$ and $C_B = C_B^0 - C_{BH^+}$ (where C_{HCl} is concentration of added hydrochloric acid and C_B^0 is initial concentration of the pyridine). Then $pK_a = pH + \log \gamma_{BH^+} + \log C_{BH^+}/C_B$.

The author is grateful to the Research Corporation for financial assistance. Thanks are due Mr. Alexander Kaczmarczyk for making the measurements.

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1,3,5,7-Tetramethyl-2,4,6,8-tetracarbethoxyporphyrin[1]

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Received July 10, 1959

Corwin and Sydow[2] showed that it is possible to produce the copper complex of 1,3,5,7-tetramethyl-2,4,6,8-tetracarbethoxyporphyrin by the condensation of the appropriate bromomethene in the presence of cuprous chloride. Because of the importance of having a number of porphyrins with electron-attracting substituents available for study, we have attempted to improve upon the synthesis of this compound.

We have found that it is possible to prepare the free porphyrin directly without the necessity for an extra step to remove the metal. This is done by the substitution of silver powder for cuprous chloride in the condensation. The reaction is carried out in boiling terphenyl. Subsequent preparation of the silver complex has shown that silver is removed thermally under the reaction conditions, thus accounting for the occurrence of the free porphyrin under the conditions used. The mechanism of this unusual reaction is under investigation.

EXPERIMENTAL

1,3,5,7-Tetramethyl-2,4,6,8-tetracarbethoxyporphyrin. Ten grams of 3,5,4′-trimethyl-4,3′-dicarbethoxy-5′-bromodipyrrylmethene hydrobromide, 5 g. of silver powder and 15 g. of *p,p*′-terphenyl were mixed thoroughly. The mixture was heated in small amounts by a Bunsen burner flame until it started to give a thick smoky ring. This required approximately 10 seconds. After cooling, the material hardened together as a black mass. It was scraped off with a spatula,

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[1] Porphyrin Studies. XVI. Paper XV, A. H. Corwin and S. D. Bruck, *J. Am. Chem. Soc.*, **80**, 4736 (1958).

[2] A. H. Corwin and V. L. Sydow, *J. Am. Chem. Soc.*, **75**, 4484 (1953).

extracted with ethylene dichloride, and filtered. The filtrate was concentrated and chromatographed on a column of Fisher's alumina. It was developed with ethylene dichloride until it was washed free from yellow material. Later, the porphyrin was eluted with chloroform. After distilling the chloroform, the porphyrin was purified by extracting with 30% hydrochloric acid. Finally it was crystallized from a mixture of chloroform and methanol. Yield, 2.1% of analytically pure porphyrin.

Anal. Calcd. for $C_{36}H_{38}O_8N_4$: C, 66.06; H, 5.81. Found: C, 66.09; H, 6.35. Spectrum in chloroform: λ 653 mμ (log ε, 3.3377); λ 596 mμ (log ε, 3.7009); λ 557 mμ (log ε, 3.7467); λ 522 mμ (log ε, 4.1196).

Silver complex. Twenty milligrams of the porphyrin was dissolved in 1 ml. of pyridine and a concentrated solution of 50 mg. of silver acetate in pyridine was added. The mixture was heated on a steam bath until it gave a pure silver complex spectrum. (Two bands) The solvent was distilled nearly to dryness under reduced pressure. The residue was washed several times with hot water and dried in a desiccator. The dry material was crystallized from a mixture of benzene and methanol. Yield, 17 mg.

Anal. Calcd. for $C_{36}H_{36}O_8N_4Ag$: C, 56.84; H, 4.76. Found: C, 57.19; H, 4.77. Spectrum in chloroform: 592, 552. In pyridine, 595, 559.

Demetallation of the silver complex. In the presence of excess silver powder the following observations were made: (a) No demetallation in boiling benzene or naphthalene. (b) Heating the silver complex in terphenyl under the conditions used for the synthesis brought about complete demetallation as judged spectroscopically with the Hartridge reversion spectroscope. The demetallation can also be brought about in this solvent by heating in a Wood's metal bath for about 2 min., the time required for the test tube to reach the boiling temperature of the terphenyl. Experiments were performed in the presence and absence of added silver and demetallation took place equally well either way.

Acknowledgments. This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund. We also appreciate support received from the National Institutes of Health under Grant A-2877, B. B. C.

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Antihypertensive Agents. III. Dialkylaminoalkoxypiperidines and Related Compounds

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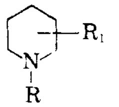
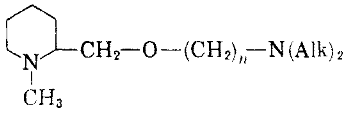
Received June 25, 1959

In a previous paper[1] selective effectiveness as hypotensive agents with bistertiary amines of the type I, R = CH_3, R_1 = 2—$CH_2O(CH_2)_nN(Alk)_2$, n = 2 and 3, *i.e.* (Ia), had been noted. In this report the effectiveness of 3- and 4-position analogs of Ia was evaluated. The structure (I), R_1 = 3—$O(CH_2)_nN(Alk)_2$ which retains the two-carbon chain between the piperidine nitrogen and the ether oxygen, characteristic of Ia, was also studied. In addition, replacement of R = CH_3 in Ia by R = $C_6H_5CH_2CH_2$— was investigated. This type of group replacement has been particularly effective in enhancing analgesic properties.[2] The compounds prepared are described in Table I.



I



Ia

The only compound showing even moderate hypotensive activity as the bistertiary amine was compound 7, which is related to Phillips[3] 1-methyl-3-(4′-dimethylaminobutyl)piperidine.

EXPERIMENTAL[4]

N-Alkyl-3-piperidinols. Reductive alkylation of *N*-alkyl-3-piperidinols[5] using formaldehyde and acetaldehyde, respectively, gave *N*-methyl-3-piperidinol (73%), b.p. 103–104° (40 mm.),[6] and *N*-ethyl-3-piperidinol (51%), b.p. 126–128° (40 mm.).[7]

3-(Hydroxymethyl)-1-methylpyridinium bromide. A solution of 56.8 g. (0.52 mol.) of 3-pyridinemethanol in 500 ml. of acetonitrile was cooled to −5° during the addition of 95 g. (1.0 mol.) of methyl bromide. After storage at 20° for 20 hr., 101 g. of product was separated and recrystallized (isopropanol–isopropyl ether) to give 89 g. (84%), m.p. 92–94°.

Anal. Calcd. for $C_7H_{10}BrNO$: C, 41.2; H, 4.9; N, 6.9. Found: C, 40.7; H, 5.2; N, 6.9.

1-Methanol-3-piperidinemethanol hydrobromide was prepared in 70% yield (using the method previously described[1] for the 2-hydroxymethyl analog), m.p. 113–115° (ethanol–methyl ethyl ketone).

Anal. Calcd. for $C_7H_{16}BrNO$: C, 40.0; H, 7.7; N, 6.7. Found: C, 40.3; H, 7.9; N, 6.6.

1-Ethyl-4-piperidinemethanol. A solution of 89.1 g. (0.82 mol.) of 4-pyridinemethanol and 133 g. (1.2 mol.) of ethyl bromide in 800 ml. of acetonitrile was heated under reflux for 24 hr. Removal of the solvent and seeding gave a solid which after trituration with ether yielded 170 g. of crude 4-(hydroxymethyl)-1-ethylpyridinium bromide.

The crude quaternary salt was hydrogenated directly by the method described above[1] and converted to the piperidine base with 40% sodium hydroxide. The reaction mixture was salted with potassium carbonate, extracted with ether, dried (anhydrous magnesium sulfate) and distilled to yield 4-hydroxymethyl-1-ethylpiperidine (31%) b.p. 90–92° (0.15 mm.).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.1; H, 12.0; N, 9.8. Found: C, 66.7; H, 12.0; N, 9.5.

2-Hydroxymethyl-1-phenethylpyridinium bromide. 2-Pyridinemethanol (22 g., 0.2 mol.) and 40.7 g. (0.22 mol.) of phenethyl bromide were dissolved in 250 ml. of acetonitrile

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(1) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

(2) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).

(3) A. P. Phillips, *J. Am. Chem. Soc.*, **76**, 2211 (1954).

(4) Descriptive data shown in the table are not reproduced in the Experimental section.

(5) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc.*, (*Sci. Ed.*), **46**, 333 (1957).

(6) S. Tchelitcheff, U. S. Patent **2,489,546** (Nov. 29, 1949), reports b.p. 79° (15 mm.).

(7) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Am. Chem. Soc.*, **74**, 1485 (1952), report b.p. 93-95° (15 mm.).