The Structure of Löffler's Pyridonium Compounds

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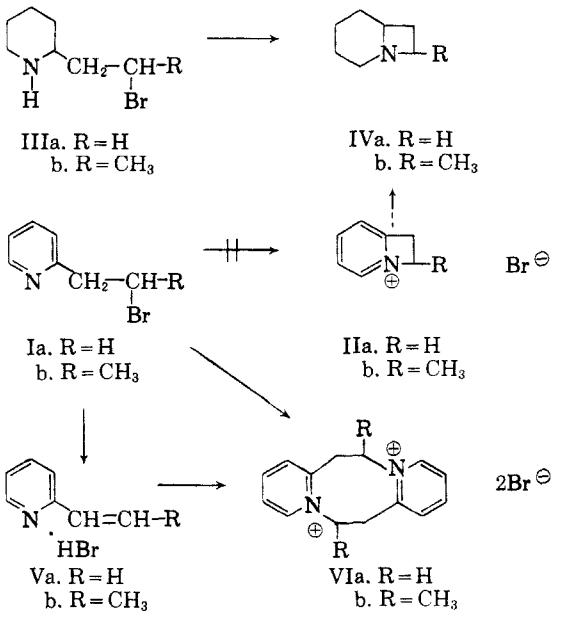
Löffler, *et al.* reported the facile cyclization of 2-(2-bromoethyl)pyridine (Ia) to the pyridonium compound (IIa)[2a] and of the propyl analog (Ib) to IIb.[2b] Price[3] and others have effected the analogous ring closure of 2-(2-haloethyl)piperidines (IIIa) to conidine (IVa) while IIIb has been cyclized to 2-methylconidine (IVb).[4] Strangely, however, there have been no reported attempts to convert the pyridonium compounds (II) into the corresponding conidines (IV). This fact, together with a suspicion that the conversion of I to II should be a rather difficult transformation,[5] led to our speculation that the structure II was incorrect. We therefore undertook to re-examine these compounds.



At this time Boekelheide and Feely,[6] in an examination of 2-(2-haloethyl)pyridines, showed that the substance represented as IIa by Löffler[1] should be assigned the dimeric structure (VIa). The dimer was hydrogenated to a hexahydro derivative (VII), b.p. 100° at 0.2 mm. By comparison the expected reduction product of a structure IIa, conidine (IVa), boils at 144°.[3] It was apparent that the structures of the various methyl analogs of IIa must be reconsidered. We have therefore examined the structure of the 2-methyl analog (IIb).

Treatment of 1-(2-pyridyl)-2-propanol (VIII) with hydrobromic acid afforded the pyridonium bromide, m.p. 164–165° as described by Löffler and Kirschner.[2] Hydrogenation resulted in the uptake of four equivalents of hydrogen and the formation of a *secondary* amine (IX). This amine and its crystalline derivatives were distinctly different from 2-methylconidine (IVb) and its derivatives, the expected reduction product of IIb. In addition, IX was much lower boiling than was expected for the reduction product of the dimeric structure (VIb).

Boekelheide and Feely[6] had prepared VIa by pyrolysis of 2-vinylpyridine hydrobromide (Va) as well as directly from Ia. In order to utilize the former method we prepared 2-propenylpyridine hydrobromide (Vb), m.p. 163–165°. Surprisingly, this material was identical in all respects to the pyridonium bromide prepared according to Löffler's conditions[2] (*via* Ib). Furthermore, pyrolysis of Vb under Boekelheide's conditions[6] led to its recovery unchanged. Hydrogenation of authentic Vb resulted in the uptake of four equivalents of hydrogen and the formation of 2-*n*-propylpiperidine (coniine) hydrobromide, identical in all respects to the hydrobromide of IX.

Therefore, Löffler's pyridonium bromide, m.p. 162°, is in fact 2-propenylpyridine hydrobromide (Vb). The iodide was reported to have m.p. 147°, which is very close to that of a synthetic sample of 2-propenylpyridine hydriodide, m.p. 150–151.5°.

It may be concluded that 2-(2-haloethyl)pyridines can be cyclized to the dimeric compounds (VIa) but 2-(2-halopropyl)pyridines (Ib) preferentially will eliminate hydrogen halide under the same conditions. No evidence has been obtained for the existence of compounds of structure II.

There is no direct evidence in the literature to show that α- or ε-conicein, dehydration products of the Hemlock alkaloid, conhydrine, are in fact 2-methylconidines (IVb) and not dimers.[7] A comparison of the boiling points of IVa(144°),[6] IVb (153°), and VII(100° at 0.2 mm.)[6] indicates that the coniceins (b.p. 150–153°) are monomeric.

EXPERIMENTAL[8]

Löffler's pyridonium bromide. The bromide was prepared from 1-(2-pyridyl)-2-propanol[9] according to Löffler's pro-

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(2a) K. Löffler, *Ber.*, **37**, 161 (1904).

(2b) K. Löffler and M. Kirschner, *Ber.*, **38**, 3329 (1905). The reported melting points were the bromide, m.p. 162° and the iodide, m.p. 147°.

(3) M. S. Toy and C. C. Price, Abstracts, American Chemical Society, 135th meeting, Boston, Mass., p. 31-O, April, 1959.

(4) K. Löffler, *Ber.*, **42**, 948 (1909).

(5) The four-membered ring of benzocyclobutenes, the hydrocarbon analogs of II, is formed only with difficulty and is readily opened, see M. P. Cava and K. Muth, *J. Am. Chem. Soc.*, **82**, 652 (1960).

(6) V. Boekelheide and W. Feely, *J. Am. Chem. Soc.*, **80**, 2217 (1958).

(7) L. Marion in *The Alkaloids*, ed. by R. H. F. Manske and H. L. Holmes, Academic Press, Inc., N. Y., 1950, Vol. I, p. 224.

(8) Melting points and boiling points are uncorrected. Analyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

cedure,[2] m.p. 164–165°, λ_{max} 6.06 μ. It discolored bromine solutions and gave a precipitate with silver nitrate. It did not depress the melting point of synthetic Vb (see below) and the infrared spectra of the two were identical.

Anal. Calcd. for $(C_8H_{10}NBr)_x$: C, 48.01; 5.04; N, 7.00; Br, 39.94. Found: C, 47.75; H, 5.25; N, 6.84; Br, 39.73.

Reduction of 0.2159 g. of the bromide with hydrogen over platinum in aqueous solution resulted in the uptake of 4.25 mmoles of hydrogen, 98% of theoretical for a molecular weight of 200. Evaporation of the supernatant and recrystallization of the residue from ethanol–ethyl acetate gave colorless needles, m.p. 199.5–201°, undepressed on admixture with an authentic sample of 2-*n*-propylpiperidine hydrobromide (see below). The free amine with *p*-toluenesulfonyl chloride gave a product which was insoluble in acid or base (*i.e.*, sulfonamide of a secondary amine).

2-Propenylpyridine. To 15.6 g. (0.114 mole) of 1-(2-pyridyl)-2-propanol[9] at −10° was added 31.0 g. (0.114 mole) of phosphorus tribromide portionwise with rapid stirring. The orange viscous oil was then stirred for 1 hr. at room temperature after which it was decomposed at ice temperatures by cautious addition of water. The solution was made basic with aqueous sodium hydroxide and extracted with chloroform. Evaporation of the solvent and distillation gave 4.9 g. (43%) of 2-propenylpyridine as a colorless liquid, b.p. 80–82° at 16 mm., n_D^{25} 1.5510, λ_{max} 6.06 μ, (lit.[10] b.p. 70–74° at 15 mm.) and 3.5 g. (16%) of crude 2-propenylpyridine hydrobromide (Vb) which crystallized from benzene-ethanol as colorless needles, m.p. 164–165°. It was identical with a sample prepared by bubbling anhydrous hydrogen bromide through a cold ethereal solution of 2-propenylpyridine.

Anal. Calcd. for $C_8H_{10}NBr$: C, 48.01; H, 5.04; N, 7.00; Br, 39.94. Found: C, 48.22; H, 5.12; N, 7.00; Br, 40.10.

A hot ethanolic solution of 2-propenylpyridine was treated with a saturated ethanolic solution of picric acid. Cooling gave the picrate as yellow plates, m.p. 144–146° (lit.,[10] m.p. 165–166°).

Anal. Calcd. for $C_{14}H_{12}O_7N_4$: C, 48.27; H, 3.47; N, 16.09. Found: C, 48.27; H, 3.37; N, 16.37.

Treatment of an acetone solution of 2-propenylpyridine with a few drops of 48% hydriodic acid solution followed by evaporation to dryness *in vacuo* and recrystallization of the tan solid from ethanol–ethyl acetate gave 2-propenylpyridine hydriodide as pale yellow needles, m.p. 150–151.5°.

Anal. Calcd. for $C_8H_{10}NI$: C, 38.89; H, 4.08; N, 5.67. Found: C, 38.72; H, 4.18; N, 5.86.

A 1.0-g. sample of Vb was heated for 3 hr. at 170–180° in a sealed tube. The residual black solid was recrystallized from benzene-ethanol in 95% yield as colorless needles, m.p. 162.5–164.5°, undepressed on admixture with Vb. The infrared spectra of the two samples were identical.

2-n-Propylpiperidine(coniine). To a slurry of prereduced platinum oxide in water was added 0.3419 g. (1.71 mmoles) of Vb. After 4.5 hr. 7.1 mmoles of hydrogen had been absorbed and the uptake ceased (104% of 4 equivalents). Evaporation of the supernatant and recrystallization of the resulting solid from ethanol-ethyl acetate gave 2-*n*-propylpiperidine hydrobromide as colorless fine needles, m.p. 199–200° (lit.,[11] m.p. 211°).

Anal. Calcd. for $C_8H_{18}NBr$: C, 46.16; H, 8.72; N, 6.73; Br, 38.39. Found: C, 46.24; H, 8.46; N, 6.84; Br, 38.46.

The free base liberated from its salt with sodium carbonate solution, boiled at 164°. It formed a picrate which crystallized from ethanol as yellow needles, m.p. 157.5–159°.

2-Methylconidine (IVb). *A.* A solution of 10 g. (0.073 mole) of 1-(2-pyridyl)-2-propanol[9] in 80 ml. of water containing 10 ml. of 6*N* hydrochloric acid and 0.9 g. of platinum dioxide was shaken under 45 lbs. of hydrogen pressure. After 2.5 hr. 107% of 3 equivalents of hydrogen had been absorbed. The catalyst was removed, the solution made basic with 10% sodium hydroxide solution and the amino alcohol extracted with chloroform. Removal of the solvent left 8.5 g. (82%) of 1-(2-piperidyl)-2-propanol as a colorless solid, m.p. 50–52°. It crystallized from hexane as colorless plates, m.p. 56–59° (lit.,[12] m.p. 45–47°).

Anal. Calcd. for $C_8H_{15}NO$: C, 67.10; H, 11.96; N, 9.78. Found: C, 67.36; H, 12.12; N, 10.05.

Heating a solution of 8.0 g. (0.056 mole) of the amino alcohol with 40 ml. of 48% hydrobromic acid for 6 hr. at 160° in a sealed tube followed by addition of base, extraction with chloroform and distillation of the amines gave 1.0 g. (15%) of 2-methylconidine (IVb) as a colorless liquid which darkened on standing, b.p. 67–69° at 51 mm., n_D^{21} 1.4600. It formed a picrate which crystallized from ethanol as yellow needles, m.p. 216–217° (lit.,[4] b.p. 150–153°; picrate m.p. 220–221°).

Anal. Calcd. for $C_{14}H_{16}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.65; H, 5.27; N, 15.70.

B. A solution of 2.0 g. (0.014 mole) of the amino alcohol in 30 ml. of 48% hydrobromic acid was heated under reflux for 17 hr. after which the solvent was removed *in vacuo*, leaving a crystalline mass. Recrystallization from ether-ethanol gave 1-(2-piperidyl)-2-bromopropane hydrobromide as colorless fine needles, m.p. 168–169°, in 55% yield (lit.,[13] m.p. 171°).

Heating a heterogeneous solution of 1.85 g. (6.5 mmoles) of the above hydrobromide in 25 ml. of 10% sodium hydroxide solution for 3 hr. under reflux followed by extraction with chloroform afforded 0.50 g. (63%) of crude 2-methylconidine, characterized as its picrate which crystallized from ethanol as yellow needles, m.p. 216.5–217.5° undepressed on admixture with a sample prepared *via* method A above.

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The Metalation of 7H-Benzo[c]phenothiazine with *n*-Butyllithium

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As a part of a continuing investigation on the chemistry of benzophenothiazines,[2,3] we have studied the metalation of 7H-benzo[c]phenothiazine (I). Phenothiazine metalates in the 1-position (adjacent to nitrogen)[4] and 12H-benzo[a]phenothiazine metalates in the unusually high yield of 94% in the 1-position (*peri* to nitrogen).[5] However, the majority of heterocyclic ring systems containing

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