[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

Utilization of the Basic Properties of Pyrrocolines for the Synthesis of 1,2-Dihydro-3*H*-pyrrocolinium Salts[1]

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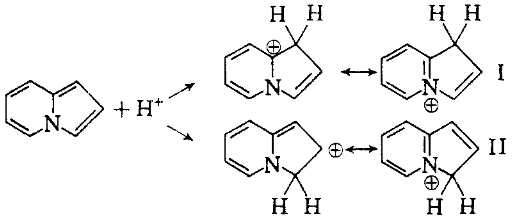
The basic properties of pyrrocolines are considered. An explanation of these properties suggested that hydrogenation in acidic solution in the presence of an appropriate catalyst offered a means for the synthesis of 1,2-dihydro-3*H*-pyrrocolinium salts. In accord with expectation, pyrrocoline was readily reduced to 1,2-dihydro-3*H*-pyrrocolinium bromide in hydrobromic acid solution.

In many respects pyrrocolines resemble pyrroles and indoles.[2] A notable difference is that they are weak but stable bases whereas pyrroles and indoles are only feebly basic or react so extensively in the presence of acids that their basicity has little meaning.[3] Indeed the moderate stability of pyrrocolines is such that Scholtz's[4] first synthesis of pyrrocoline from picolide (1,3-diacetylpyrrocoline) was accomplished by a hot hydrolysis with twenty-five per cent aqueous hydrochloric acid.

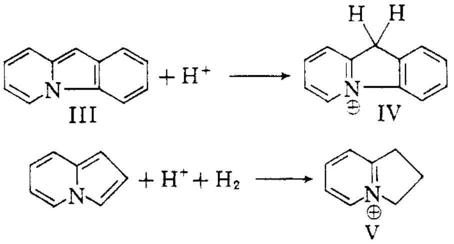
Another unusual aspect of the basic properties of pyrrocolines is that they do not dissolve readily in dilute acids.[4,5] This combination of properties—basicity, stability, and slowness to react—can be accounted for by neutralization occurring through a rate determining attack of a proton at carbon number one or three to give a carbonium ion which by a shift of electrons is seen to be a resonance-stabilized pyridinium ion conjugated with an olefinic double bond (I or II).[6]



This explanation for the basicity of pyrrocolines is very similar to that for other aromatic compounds. Thus, Brown and Brady[7] consider the reversible reaction of toluene with hydrogen chloride and aluminum chloride to give a resonance-stabilized carbonium ion. It was observed that this was not an instantaneous reaction but occurred, apparently, with an activation energy.

The interpretation of the basicity of azulene as presented by Plattner, Heilbronner, and Weber[8] also entails protonation in the five-membered ring with resultant aromatization in the adjoining ring and thus shows a marked analogy with the explanation given above.

Robinson and Saxton[9] have observed the basic properties of benzo[*b*]pyrrocolines (III) to be very similar to those of pyrrocolines. That basicity was due to the operation of a mechanism involving attack at a carbon was definitely established. Rossiter and Saxton[5,10] also would consider pyrocolinium ions to have pyridinoid structures.



The hydrogenation of a variety of pyrrocolines has been reported.[11] They appear to be preferentially hydrogenated in the six-membered ring with the aid of such catalysts as Raney nickel, copper chromite, and platinium oxide, though generally complete reduction is accomplished with the latter catalyst. The probability of the pyrrocolinium ion having structure I or II[12] suggested that in acid solution it would be possible to hydrogenate selectively the five-membered ring of pyrrocolines (V) by the use of catalyst that was sufficiently active to promote the reduction of an olefinic double bond and not active enough to promote the reduction of a pyridine ring. Such a catalyst, palladium-on-

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[1] Taken in part from the Ph.D. dissertation of O. G. L.

[2] E. T. Borrows and D. O. Holland, *Chem. Revs.*, **42**, 636 (1948).

[3] A. Treibs and H. G. Kolm, *Ann.*, **606**, 166 (1957).

[4] M. Scholtz, *Ber.*, **45**, 734 (1912).

[5] J. E. Saxton, *J. Chem. Soc.*, 3239 (1951).

[6] The carbonium ion would be one of the possible resonance structures and is indicated as such by the double-headed arrow.

[7] H. C. Brown and J. D. Brady, *J. Am. Chem. Soc.*, **74**, 3570 (1952).

[8] P. A. Plattner, E. Heilbronner, and S. Weber, *Helv. Chim. Acta*, **35**, 1036 (1952)

[9] R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 976 (1952).

[10] E. D. Rossiter and J. E. Saxton, *J. Chem. Soc.*, 3654 1953.

[11] E. T. Borrows and D. O. Holland, *Chem. Revs.*, **42**, 633 (1948).

[12] Appreciable amounts of both I and II may be present in equilibrium. Since substitution in pyrrocolines generally occurs at the three position,[2] II would be expected to predominate.

charcoal, was readily found. In the presence of this catalyst aqueous hydrobromic acid solutions of pyrrocoline smoothly took up one equivalent of hydrogen, and the expected product, 1,2-dihydro-3*H*-pyrrocolinium bromide, was obtained. The identity was established by comparison of the reaction product with authentic material synthesized from 2-(3-hydroxypropyl)-pyridine. In all respects these products and their derivatives were the same.

Pyrrocoline similarly took up one equivalent of hydrogen in hydrochloric acid solution; however, the product was not characterized. When hydrogenation over palladium-on-charcoal was attempted in seventy per cent aqueous ethanol, little hydrogen up-take occurred until an excess of hydrobromic acid was added. One equivalent of hydrogen was then absorbed in normal fashion.

This synthesis may have further application for the preparation of a variety of substituted dihydropyrrocolinium salts. The explanation of basicity has shown its utility in predicting a chemical reaction, but that hydrogenation occurs by a mechanism other than the reduction of the olefinic double bond of I or II is in no way precluded.

EXPERIMENTAL[13]

Pyrrocoline. Picolide was prepared as described by Scholtz[4] at the temperature recommended by Chichibabin and Stepanow.[14] The picolide was hydrolyzed under the conditions used by Scholtz. Pyrrocoline was steam-distilled from the reaction mixture and purified by sublimation at 60° (2 mm.), m.p. 74°. Reported m.p. 74°.[4]

Hydrogenation of pyrrocoline in hydrobromic acid solution. A solution of 1 g. of pyrrocoline in 45 ml. of 2*N* hydrobromic acid was hydrogenated at room temperature and pressure in the presence of 0.15 g. of 10% palladium-on-charcoal. During 55 min. 227 ml. of hydrogen were taken up, then hydrogenation slowed down abruptly.[15] Catalyst was filtered from the hydrogenated mixture and the solution evaporated to dryness under vacuum. The resulting oil was dissolved in absolute ethanol and ether added to the point of cloudiness. On cooling to acetone–Dry Ice temperatures, crystals formed. There was thus obtained 1.45 g. (85%) of *1,2-dihydro-3H-pyrrocolinium bromide,* m.p. 173–178°. Crystallization from ethanol-ether gave colorless prisms, m.p. 176–179°. This compound was very deliquescent.

The *picrate* of the product was obtained as yellow prisms, m.p. 109–110°, by crystallization from ethanol.

Anal. Calcd. for $C_{14}H_{12}N_4O_7$: C, 48.28; H, 3.47; N, 16.09. Found: C, 48.32; H, 3.62; N, 15.67.

The *iodide* derivative was prepared by treating an aqueous solution of the hydrogenation product with freshly prepared silver oxide and neutralizing with hydroiodic acid after removal of insoluble material. The solution was evaporated and the residue crystallized from ethanol-ether to give slightly colored plates, m.p. 112–114°. This compound was not so markedly deliquescent as the bromide.

Anal. Calcd. for $C_8H_{10}NI$: C, 38.88; H, 4.08; N, 5.67. Found: C, 38.87; H, 3.82; N, 5.93.

The *p-toluene sulfonate* was prepared in a manner similar to the preparation of iodide. Crystallization from ethanol-ether gave colorless, deliquescent prisms, m.p. 120–122°.

Anal. Calcd. for $C_{15}H_{17}NO_3S$: C, 61.82; H, 5.88; N, 4.81. Found: C, 62.76, 62.70; H, 5.87, 5.92; N, 4.67, 4.76.

2-(3-Hydroxypropyl)pyridine. This compound was prepared from 2-picolyl lithium and ethylene oxide as described by Walter.[16] The product was obtained in 50% yield as a colorless oil, b.p. 100–102° at 2 mm. and n_D^{25} 1.5280. Reported b.p. 111–115° at 3 mm.[17] and 116–118° at 4 mm.[16]

1,2-Dihydro-3H-pyrrocolinium bromide. A mixture of 13.7 g. (0.10 mole) of 2-(3-hydroxypropyl)pyridine, 46 ml. (0.40 mole) of 48% hydrobromic acid, and 10.6 ml. (0.20 mole) of concentrated sulfuric acid was heated at reflux for 6 hr. The dark reaction mixture was cooled in an ice bath and neutralized with sodium hydroxide solution. The oil which separated was extracted with ether. The ether extract became cloudy on standing, and after evaporation 0.60 g. of ether-insoluble solid, m.p. about 150° was obtained. The neutralized aqueous phase was concentrated until considerable inorganic salt had separated. The salt was removed and the concentration and removal of salt repeated. Additional crops of salt were then removed by crystallization from water-ethanol. The resulting solution was evaporated and the residue thoroughly dried under vacuum. On extracting the residue with hot chloroform and cooling the extract with acetone–Dry Ice, a crystalline product was obtained. This was collected, washed with ether, and a second crop taken. The 12.4 g. of this product, m.p. 174–178°, was combined with the 0.60 g. of product obtained earlier (total yield 65%) and crystallized from ethanol-ethyl acetate with charcoal decolorization. Tan prisms, m.p. 177–179°, were obtained. Further crystallization from the same solvent gave very deliquescent, colorless prisms, m.p. 178–180°. Reported m.p. 140°.[17] Mixed m.p. with the bromide obtained by hydrogenation of pyrrocoline was 176–180°.

Anal. Calcd. for $C_8H_{10}NBr$: C, 48.02; H, 5.04; N, 7.00. Found: C, 47.57; H, 5.14; N, 6.29.

The *picrate* of the product was obtained as yellow prisms, m.p. 109–111°. Mixed m.p. with the picrate obtained from the hydrogenation product of pyrrocoline was 109–111°.

The *iodide* derivative was prepared in the same manner as the iodide derived from the hydrogenation product of pyrrocoline. Crystallization from ethanol-ether gave pale yellow plates, m.p. 113–116°. Mixed m.p. with the previous iodide was 112–115°.

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(13) All melting points were taken on a Fisher-Johns block. Analyses are by H. Beck, J. Sorensen, and C. White.

(14) A. E. Chichibabin and F. N. Stepanow, *Ber.*, **62**, 1068 (1929) and **63**, 470 (1930).

(15) The hydrogenation was observed to be autocatalytic, that is, the reaction rate rose to a maximum before dropping off close to the absorption of one equivalent of hydrogen. The equivalents of hydrogen absorbed varied from 0.96 to 1.10.

(16) L. A. Walter, *Org. Syntheses,* **23**, 85, Note 7 (1943).

(17) K. Winterfeld and E. Müller, *Arch. Pharm.*, **284**, 269 (1951).