[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

2-Aminopyridine 1-Oxides

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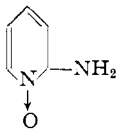
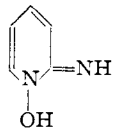
2-Acetamidopyridines are oxidized with peracetic acid to the corresponding 1-oxides. Upon hydrolysis 2-aminopyridine 1-oxides are formed.

2-Aminopyridine 1-oxide (I) has previously been prepared by the following steps: 2-picolinic acid, 2-picolinic acid 1-oxide, methyl 2-picolinate 1-oxide, 2-picolinic acid amide 1-oxide, 2-aminopyridine 1-oxide.[2]

During a study of pyridine oxides, it has been discovered that the 2-aminopyridine 1-oxides can be synthesized in a much simpler way. 2-Aminopyridines do not form the corresponding 1-oxides by the action of peracetic acid. In the case of 6-methyl-2-aminopyridine, an acetic acid salt was isolated from the reaction mixture. On the other hand, 2-acetamidopyridines are oxidized with the same reagent to the corresponding oxides in excellent yields. Saponification with aqueous alkali gives the 2-aminopyridine 1-oxides. In this way 2-aminopyridine 1-oxide (I), 2-amino-6-methylpyridine 1-oxide (III) and 2,6-diaminopyridine 1-oxide (IV) were prepared.


I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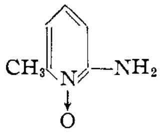
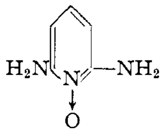
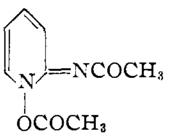

III


IV

These amine oxides may be represented by a tautomeric form as illustrated by structure II.[3] By the action of acetic anhydride on 2-aminopyridine 1-oxide[2] or on 2-acetamidopyridine 1-oxide, the same diacetyl derivative is formed. The infrared spectrum indicates this to have structure V.


V

Experimental

All melting points are corrected.

2-Acetamidopyridine 1-Oxide.—To a solution of 5.6 g. of 2-acetamidopyridine[4] in 7 ml. of glacial acetic acid, 6 ml. of 40% peracetic acid was added carefully. The resulting solution was heated for 3 hours at 50–60° and 4 hours at 65–70°. After removing the acetic acid by distillation under reduced pressure the residual oil crystallized; yield 5.6 g. (85%). Recrystallization from benzene-petroleum ether (b.p. 90–110°) gave colorless prisms, m.p. 130–131°. The product is readily sublimed at 120° (3 mm.).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.26; N, 18.42. Found: C, 54.90; H, 5.49; N, 18.15.

2-Aminopyridine 1-Oxide.—A solution of 2 g. of 2-acetamidopyridine 1-oxide in 25 ml. of 10% aqueous sodium hydroxide was refluxed for 4 hours. The reaction mixture was then acidified with dilute hydrochloric acid and extracted with three 30-ml. portions of chloroform. The chloroform solution was dried over anhydrous potassium carbonate and the solvent removed, yield 1.1 g. (76.4%). The residue solidified to a light-yellow crystalline mass which was purified by sublimation at 120° (3 mm.); colorless prisms, m.p. 164–165° (lit.[2] m.p. 161–163°).

Anal. Calcd. for $C_5H_6N_2O$: C, 54.44; H, 5.45; N, 25.46. Found: C, 54.63; H, 5.53; N, 25.57.

2-Acetamido-6-methylpyridine 1-Oxide.—By oxidation of 30 g. of 2-acetamido-6-methylpyridine[5] as described for the 2-acetamidopyridine 1-oxide 23.3 g. (75.8%) of product resulted. It was purified either by vacuum sublimation at 120° (3 mm.) or by recrystallization from benzene-petroleum ether (b.p. 90–110°); colorless prisms, m.p. 123–124°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.83; H, 6.02; N, 16.87. Found: C, 57.91; H, 6.14; N, 17.11.

2-Amino-6-methylpyridine 1-Oxide.—By hydrolysis of 1.1 g. of 2-acetamido-6-methylpyridine 1-oxide following the procedure previously described 0.79 g. (85.3%) of 2-amino-6-methylpyridine was obtained. By recrystallization from chloroform-petroleum ether (b.p. 30–60°) it formed colorless prisms, m.p. 153–154°. The compound gives a blue coloration with ferric chloride solution similar to that given by 2-aminopyridine 1-oxide.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.06; H, 6.45; N, 22.58. Found: C, 58.14; H, 6.69; N, 22.83.

2,6-Diacetamidopyridine 1-Oxide.—By oxidation of 9 g. of 2,6-diacetamidopyridine[6] with 40% peracetic acid, 7.7 g. (79%) of product resulted. After washing with water, it was recrystallized from water; colorless needles, m.p. 212–213°.

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.26; N, 20.10. Found: C, 51.65; H, 5.35; N, 20.20.

2,6-Diaminopyridine 1-Oxide.—A solution of 2.5 g. of 2,6-bis-acetamidopyridine 1-oxide in 15 ml. of 10% aqueous sodium hydroxide was refluxed for 8 hours. After acidification with dilute hydrochloric acid the mixture was concentrated to a volume of about 5 ml. and was extracted with three 25-ml. portions of ether. After removal of the ether the residue solidified to a crystalline mass; 1 g. (66%). It was purified by recrystallization from ethanol by addition of ether, m.p. 206–207°. The compound gives a blue coloration with ferric chloride solution.

Anal. Calcd. for $C_5H_7N_3O$: C, 48.00; H, 5.60; N, 3.36. Found: C, 47.79; H, 5.32; N, 3.66.

Diacetyl 2-Aminopyridine 1-Oxide.—When 2-acetamidopyridine 1-oxide was refluxed with excess acetic anhydride and the excess anhydride and acetic acid removed, an oil resulted which gradually solidified over a period of two days. It was purified by sublimation at 120° (3 mm.), m.p. 159–160°. The product was identical with that formed by acetylation of 2-aminopyridine 1-oxide.[2]

The infrared spectrum showed absorption for the carbonyl of $C{=}NCOCH_3$ at 1675 cm.$^{-1}$, $C{=}N$ at 1590 cm.$^{-1}$ and ring $C{=}C$ at 1615 cm.$^{-1}$; for the $NOCOCH_3$, carbonyl at 1750 cm.$^{-1}$, N-O at 993 cm.$^{-1}$, C-O at 1192 cm.$^{-1}$ and no absorption for $N{\rightarrow}O$ or for a substituted pyridine.

Acetic Acid Salts of 2-Aminopyridine and 2-Amino-6-methylpyridine.—A solution of 10 g. of 2-amino-6-methylpyridine in 16 ml. of glacial acetic acid was added to 7 ml. of 40% peracetic acid and the resulting mixture was kept at 70–75° for 5 hours. Removal of the solvent and frac-

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[1] Rotary Foundation Fellow for advanced study, 1952–1953.

[2] G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, S. 133 (1949); in the abstract of papers presented before the Organic Division of the American Chemical Society in March 1952, it was reported by Robert W. Faessinger and E. V. Brown of Fordham University that α-dibenzoylaminopyridine was oxidized to the N-oxide which in turn upon hydrolysis yielded α-aminopyridine 1-oxide.

[3] K. H. Bauer, *Ber.*, **71**, 2226 (1938).

[4] R. Camps, *Arch. Pharm.*, **240**, 349 (1902).

[5] O. A. Seide, *J. Russ. Phys. Chem. Soc.*, **50**, 534 (1918).

[6] A. E. Chichibabin and O. A. Seide, *ibid.*, **50**, 522 (1918).

tionation under reduced pressure gave 5.2 g. (33.5%) of pale yellow liquid which solidified to colorless plates. It was purified by vacuum sublimation, m.p. 82–83°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.14; H, 7.14; N, 16.66. Found: C, 57.54; H, 7.28; N, 16.79.

This compound on decomposition with aqueous sodium hydroxide gave after extraction with chloroform 2-amino-6-methylpyridine identified as its picrate, m.p. 201–202°.

A similar treatment of 2-aminopyridine with peracetic acid resulted in an oil which did not solidify. On making this alkaline as described for the salt of the 2-amino-6-methylpyridine, 2-aminopyridine was obtained, picrate m.p. 216°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Reaction of Hydrazine with Mannich Bases

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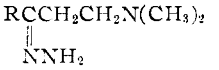
The following products have been obtained from the reaction of hydrazine and the Mannich base β-dimethylaminopropiophenone by varying the reaction conditions: the hydrazone II and azine IVa of β-dimethylaminopropiophenone, the pyrazolinoketone 1-(β-benzoylethyl)-3-phenyl-Δ²-pyrazoline (Va), and the azine of this ketone VI. Some reactions of β-dimethylamino-*p*-methoxypropiophenone and of β-dimethylamino-*p*-nitropropiophenone with hydrazine also have been investigated.

The reaction of hydrazine with a Mannich base, such as β-dimethylaminopropiophenone (Ia), could conceivably lead to the formation of a variety of products, the more obvious of which are the hydrazone II, the pyrazoline III and the azine IV. Recently, Beech and co-workers[2] reported the preparation of 3-phenyl-Δ²-pyrazoline (IIIa) in 81% from the reaction of excess hydrazine with Ia in refluxing ethanol. Earlier Jacob and Madinaveitia[3] observed that the hydrochloride of Ia, sodium acetate and an excess of hydrazine when heated at 100° in 70% acetic acid, gave a yellow crystalline compound, m.p. 141°, whose analyses corresponded to the formula $(C_6H_6N)_n$. To date the isolation of the hydrazone II or an azine IV of a Mannich base has not been reported.

The present paper is concerned with the products formed in the reaction of some representative Mannich bases (Ia, b, c) with hydrazine. At 100° in aqueous sodium bicarbonate solution one equivalent of hydrazine reacts with two equivalents of Ia to form 1-(β-benzoylethyl)-3-phenyl-Δ²-pyrazoline (Va) in 83% yield. This product was formed also from the reaction of Ia or its methiodide with 3-phenyl-Δ²-pyrazoline (III). The structure of Va was shown by the formation of an oxime, its oxidation to the corresponding pyrazole with lead dioxide[4] and by its absorption spectra.[5] When Va was treated with excess hydrazine in dilute hydrochloric acid, it was converted to the azine VI, which proved to be identical with the product obtained by the procedure of Jacob and Madinaveitia.[3]

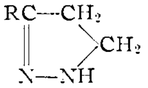
$RCOCH_2CH_2N(CH_3)_2$

Ia, R is C_6H_5
Ib, R is p-$CH_3OC_6H_5$
Ic, R is p-$NO_2C_6H_5$

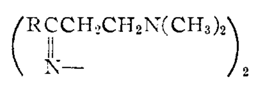


$R\underset{\underset{NNH_2}{\|}}{C}CH_2CH_2N(CH_3)_2$

II

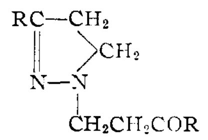


III, R is C_6H_5

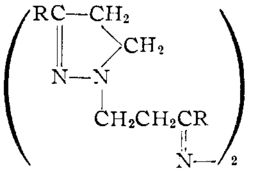


$\left(R\underset{\underset{N-}{\|}}{C}CH_2CH_2N(CH_3)_2\right)_2$

IVa, R is C_6H_5
IVb, R is p-$CH_3OC_6H_5$
IVc, R is p-$NO_2C_6H_5$



Va, R is C_6H_5
Vb, R is p-$CH_3OC_6H_5$



VI, R is C_6H_5

As the pyrazoline III is doubtless formed from an intermediate hydrazone II probably *via* the vinyl-hydrazone, so can the formation of the pyrazolinoketone V result from the addition of III to the phenyl vinyl ketone resulting from the elimination of dimethylamine from the Mannich base I. In the presence of an excess of hydrazine the secondary reaction of III with I is prevented by the complete conversion of I to III.

The Mannich base Ib was converted to Vb in 49% yield under the conditions used for the preparation of Va. Vb yielded an oxime and was converted by oxidation to the corresponding pyrazole.[4] In contrast to Ia and Ib, the nitro Mannich base Ic was converted with sodium bicarbonate solution at 100° into an acid-insoluble glass, which was doubtless a polymer of *p*-nitrophenyl vinyl ketone.

Under acidic conditions at 25° one equivalent of hydrazine reacts with two equivalents of the Mannich base Ia, b or c to yield the corresponding azines IV in a manner similar to the conversion of V (which is also a Mannich base) to the azine VI. It is apparent, therefore, that the nature of the reaction products from hydrazine and a Mannich base is dependent upon conditions of *p*H and temperature. The hydrazones II are probable intermediates in the formation of III, IV and V. It is well-

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[1] (a) Eli Lilly and Company, Indianapolis, Ind.; (b) Rohm and Haas Company, Philadelphia, Penna.

[2] S. G. Beech, J. H. Turnbull and W. Wilson, *J. Chem. Soc.*, 4686 (1952).

[3] A. Jacob and J. Madinaveitia, *ibid.*, 1929 (1937).

[4] *Cf.* K. v. Auwers and P. Heimke, *Ann.*, **458**, 199 (1927).

[5] The infrared spectrum of Va (solid in Stanolind oil) shows bands at 1670 cm.⁻¹ (ArCOR) and 1581 cm.⁻¹ (C=N in a ring). The first maximum in the ultraviolet spectrum occurs at 238 mμ, which lies between the 234 mμ maximum of acetophenone dimethylhydrazone and the 243 mμ maximum of acetophenone. A second maximum at 296 mμ falls between that of benzyl benzalhydrazone at 290 mμ and the 311 mμ maximum of acetophenone dimethylhydrazone.