S 29. *2-Aminopyridine 1-Oxide.*

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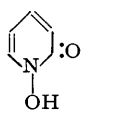
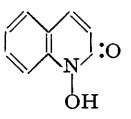
Picolinic acid has been converted into *picolinamide 1-oxide* and thence into *2-aminopyridine 1-oxide* (III). Some reactions of the latter are described.

We have recently described a synthesis of the simple cyclic hydroxamic acid, 1-hydroxy-2-pyridone (2-hydroxypyridine 1-oxide) (I) by the peroxidation of 2-ethoxypyridine followed by acid hydrolysis of the product, and a similar method was employed for the synthesis of 1-hydroxycarbostyril (2-hydroxyquinoline 1-oxide) (II) (Newbold and Spring, *J.*, 1948, 1864). This paper describes a synthesis of 2-aminopyridine 1-oxide (III) [2-imino-1-hydroxy-1 : 2-dihydropyridine (IV)] which was undertaken in the hope that it would offer an alternative route to the pyridine hydroxamic acid (I).

Although simple derivatives of 2-aminopyridine 1-oxide do not appear to have been previously described, Bauer (*Ber.*, 1938, **71**, 2226) has prepared 2-amino-3-phenylquinoline 1-oxide (VI, R = Ph) and ethyl 2-aminoquinoline-3-carboxylate 1-oxide (VI; R = CO_2Et) by partial reduction of *o*-nitro-α-phenylcinnamonitrile (V; R = Ph) and ethyl *o*-nitro-α-cyanocinnamate (V; R = CO_2Et) respectively, using hydrogen and a palladium catalyst; Bauer commented that these compounds could also be represented by the tautomeric ciphers (VI*a*). A relatively simple method has now been developed for the preparation of 2-aminopyridine 1-oxide starting from picolinic acid.

Picolinic acid 1-oxide (VII; R = OH) has been obtained by Diels and Alder (*Annalen*, 1932, **498**, 16; 1933, **505**, 103) by peroxidation of picolinic acid (cf. Diels and Meyer, *Annalen*, 1934, **513**, 129; Borrows, Holland, and Kenyon, *J.*, 1946, 1069). Esterification of picolinic acid 1-oxide by methanolic hydrogen chloride followed by treatment of the ester with ammonia gave *picolinamide 1-oxide* (VII; R = NH_2) in excellent yield. Direct oxidation of picolinamide with hydrogen peroxide gave the *ammonium* salt of picolinic acid 1-oxide and not picolinamide 1-oxide; it is noteworthy that picolinic acid 1-oxide, its amide, and its ammonium salt all melt at *ca.* 162°. Using the conditions under which picolinic acid is converted into the 1-oxide, methyl picolinate is unchanged after treatment with hydrogen peroxide.


(I.)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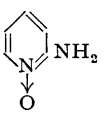
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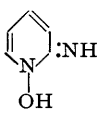
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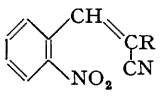
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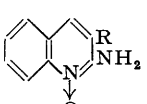
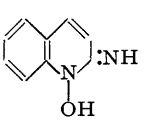
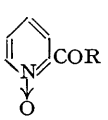

(VI.)


(VI*a*.)


(VII).

Treatment of picolinamide 1-oxide with alkaline hypobromite solution yielded *2-aminopyridine 1-oxide*. The possibility of an intramolecular rearrangement during this reaction resulting in the formation of *2-hydroxylaminopyridine* was excluded by the synthesis of the latter by the partial reduction of 2-nitropyridine (Kirpal and Bohm, *Ber.*, 1932, **65**, 680; 1931, **64**, 767) with hydrogen in the presence of a platinum catalyst. 2-Hydroxylaminopyridine is different from the product obtained from picolinamide 1-oxide.

2-Aminopyridine 1-oxide does not liberate iodine from acidified potassium iodide solution. It has been characterised by the preparation of a *monohydrochloride* and a *diacetate*. It forms an unstable picrate which decomposed on attempted recrystallisation. One of the most characteristic properties of 2-aminopyridine 1-oxide is the intense, pure blue coloration which it gives with ferric chloride solution. Attempts to convert 2-aminopyridine 1-oxide into 1-hydroxy-2-pyridone (I) by treatment with alkali under relatively drastic conditions were unsuccessful, the material being recovered unchanged. Reduction of 2-aminopyridine 1-oxide with tin and hydrochloric acid proceeds smoothly with the formation of 2-aminopyridine.

Experimental.

Picolinamide 1-Oxide.—(*a*) Dry hydrogen chloride was passed through a refluxing solution of picolinic acid 1-oxide (2·5 g.) in dry methanol (40 c.c.) for 2½ hours. The solution was concentrated under reduced pressure, and diluted with iced water (30 c.c.). The mixture was made alkaline by the addition of solid sodium hydrogen carbonate and extracted with chloroform (6 × 30 c.c.). The dried (Na_2SO_4) extract was evaporated and the oil treated with aqueous ammonia (*d* 0·88; 40 c.c.). After standing overnight, the crystalline solid was collected and recrystallised from methanol to yield *picolinamide 1-oxide* as prismatic needles, m. p. 161—162°. A second crop was obtained by concentration of the ammoniacal mother liquor (yield, 2·02 g.) (Found: C, 52·2, 52·5; H, 4·5, 4·3. $C_6H_6O_2N_2$ requires C, 52·2; H, 4·3%).

(*b*) An ice-cooled suspension of picolinic acid 1-oxide in methanol, obtained by rapidly chilling a boiling solution of the acid (2·0 g.) in methanol (15 c.c.), was treated with an ethereal solution of diazomethane prepared from nitrosomethylurea (12 g.), potassium hydroxide solution (50%, 40 c.c.), and ether (80 c.c.). The diazomethane solution was added dropwise with shaking. The slightly yellow solution was filtered from unchanged acid (100 mg.), and the filtrate evaporated under reduced pressure. The oily residue was dissolved in chloroform, and the solution washed with aqueous sodium hydrogen carbonate and again evaporated. The amber-coloured oil was treated with aqueous ammonia (*d* 0·88; 30 c.c.) and kept overnight. The crystalline solid was collected and recrystallised from methanol (charcoal) to give picolinamide 1-oxide (300 mg.) as needles, m. p. 161—162°, undepressed when mixed with the specimen described above.

(*c*) A solution of picolinic acid 1-oxide (2·0 g.) in aqueous ammonia (*d* 0·88; 20 c.c.) was evaporated under reduced pressure at 35°. The solid residue was crystallised from methanol–ether from which the ammonium salt of picolinic acid 1-oxide separated as felted needles, m. p. 160—161° (decomp.). A solution of the ammonium salt (1·0 g.) in warm water (20 c.c.) was treated with a solution of silver nitrate (1·2 g.) in water (10 c.c.). The crystalline silver salt (1·23 g.) was washed with distilled water and dried at 110° (Found: Ag, 43·3. $C_6H_4O_3NAg$ requires Ag, 43·9%). The dry, powdered, silver salt was refluxed for 30 minutes with methyl iodide (5 c.c.), the mixture diluted with chloroform and filtered, and the filtrate evaporated. Treatment of the residual oil with ammonia as described above gave picolinamide 1-oxide (170 mg.) as prismatic needles from methanol, m. p. 160—161° either alone or when mixed with the two specimens described above.

Ammonium Picolinate 1-Oxide.—A solution of picolinamide (1·0 g.) (Engler, *Ber.*, 1894, **27**, 1784) in glacial acetic acid (4 c.c.) was treated with hydrogen peroxide (100 vol., 8 c.c.) and kept at 100° for 1 hour. The solution was evaporated under reduced pressure and the viscous oil dried in a vacuum over phosphoric oxide. Crystallisation from methanol–ether gave the ammonium salt as felted needles, m. p. 160—161° (decomp.) undepressed when mixed with the specimen obtained directly from picolinic acid 1-oxide. Treatment of the salt with cold 2N-sodium hydroxide liberates ammonia, and when this solution is boiled and acidified with hydrochloric acid it yields picolinic acid 1-oxide, m. p. and mixed m. p. 161° (decomp.). When heated for 2 hours at 56°/1 mm. the ammonium salt loses ammonia and gives picolinic acid 1-oxide, m. p. and mixed m. p. 161° (decomp.) (Found: C, 52·2; H, 3·8. Calc. for $C_6H_5O_3N$: C, 51·8; H, 3·6%).

2-Aminopyridine 1-Oxide.—Picolinamide 1-oxide (0·55 g.) was added with vigorous shaking to an ice-cold solution of potassium hypobromite (10 c.c.). The hypobromite solution was prepared by the addition of bromine (2·05 c.c.) to 10% potassium hydroxide solution (100 c.c.) at 0°. The solid dissolved rapidly; after being kept at room-temperature for 20 minutes, the solution was heated at 80° for 15 minutes. The solution was neutralised by the careful addition of acetic acid and evaporated to dryness under reduced pressure. The residual solid was dried at 100°/10 mm. and extracted with hot ethanol, and the filtered extract evaporated to dryness. The solid was extracted with boiling chloroform (5 × 10 c.c.), and the extract evaporated to dryness. The crystalline residue (210 mg.) sublimed at 110—120°/10^{-3} mm., and the crystalline sublimate recrystallised from light petroleum (b. p. 40—60°)–chloroform from which *2-aminopyridine 1-oxide* separated as blades, m. p. 161—163°. It is readily soluble in water and ethanol, moderately soluble in chloroform, and sparingly soluble in benzene and light petroleum. It crystallises readily from pyridine, from which it separates as needles. An aqueous solution of 2-aminopyridine 1-oxide gives with aqueous ferric chloride a deep, pure blue coloration which does not fade but is discharged by dilute hydrochloric acid. 2-Aminopyridine 1-oxide was recovered unchanged (175 mg. from 200 mg.) after being heated with 10% potassium hydroxide solution at 130—140° for 7 hours and then at 190° for 1 hour (Found: C, 55·0; H, 5·3; N, 25·35. $C_5H_6ON_2$

requires C, 54·5; H, 5·45; N, 25·45%). Light absorption in alcohol: Maxima at 2260 A., $\varepsilon = 21{,}000$; 2480 A. (inflection), $\varepsilon = 4000$, and 3190 A., $\varepsilon = 5000$.

2-*Aminopyridine* 1-*oxide hydrochloride* was prepared by passing dry hydrogen chloride into a solution of the base in methanol–ether; it separates from methanol–ether as fine needles, m. p. 153—156° (Found: Cl, 24·6. $C_5H_7ON_2Cl$ requires Cl, 24·2%).

2-*Aminopyridine* 1-*Oxide Diacetate*.—2-Aminopyridine 1-oxide (100 mg.) was refluxed with acetic anhydride (2 c.c.) for 5 minutes. The solution was evaporated under reduced pressure, and the solid crystallised from methanol (from which it separated as needles) and sublimed at 120°/3 mm. The *diacetate* separates from benzene–light petroleum (b. p. 40—60°) as leaflets, m. p. 158—160° (with some sintering at 150°). It does not give a colouration with aqueous ferric chloride (Found: N, 14·3. $C_9H_{10}O_3N_2$ requires, N, 14·4%).

2-*Aminopyridine*.—2-Aminopyridine 1-oxide (150 mg.) in hydrochloric acid (*d* 1·19; 3 c.c.) was heated under reflux with granulated tin (2·0 g.) for 4 hours, further portions of acid (3 c.c.) being added during this period. The solution was decanted from tin and evaporated to dryness. The residue was made alkaline with 5N-sodium hydroxide and extracted with ether (3 × 15 c.c.). The dried (Na_2SO_4) extract was evaporated, and the oily residue treated with ethanolic picric acid, whereupon a picrate, m. p. 218—220° (260 mg.), immediately separated. Recrystallised from ethanol, it formed small felted needles, m. p. 224—226°, not depressed when mixed with 2-aminopyridine picrate, m. p. 224—226° (Marckwald, *Ber.*, 1894, **27**, 1327, gives m. p. 216—217° for 2 aminopyridine picrate).

2-*Hydroxylaminopyridine*.—A solution of 2-nitropyridine (1·24 g.) in dry ethanol (50 c.c.) was shaken with hydrogen at room temperature in the presence of platinum from platinum oxide (120 mg.) for 15 minutes, by which time the rate of hydrogen absorption had markedly decreased (hydrogen absorbed = 460 c.c. at N.T.P.). The mixture was filtered, and the filtrate evaporated under reduced pressure. The oil partly crystallised after being kept at room temperature for 1 day. The solid was washed with a little benzene and recrystallised from benzene–light petroleum (b. p. 60—80°), from which 2-*hydroxylaminopyridine* (250 mg.) separated as blades, m. p. 80—82°. After sublimation at 70—80°/10^{-3} mm. the m. p. was 83—85°. The compound gives a blue colouration with a little ferric chloride solution; on addition of excess of ferric chloride, the colouration changes to light green. 2-Hydroxylaminopyridine is not stable in air; after 3 months, a sample had completely decomposed to give a dark brown resin (Found: C, 54·6; H, 5·4. $C_5H_6ON_2$ requires C, 54·5; H, 5·45%).

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