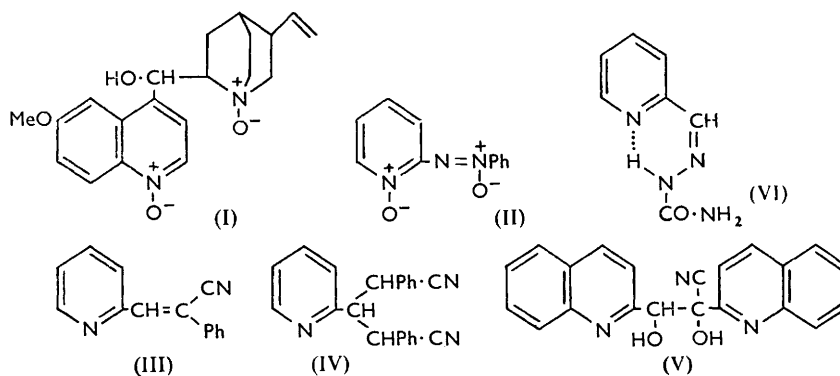


31. *N*-Oxides and Related Compounds. Part VII.¹ Per-acid Oxidation of Some Conjugated Pyridines.

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β -3- and -4-Pyridylacrylic acid and their ethyl esters and amides, 2- and 4-styrylpyridines, and pyridine-2-aldoxime and its semicarbazone gave 1-oxides with peracetic acid.

CONJUGATED pyridine 1-oxides, previously little known, were required for physical measurements. Previous work on the per-acid oxidation of pyridines containing sensitive groups showed that quinine gave successively the quinuclidine monoxide and the di-*N*-oxide (I) without affecting the isolated vinyl group,² but that 2-benzylthiopyridine and tri-2-pyridyl-phosphine and -arsine gave the sulphoxide,³ phosphine oxide, and arsine oxide⁴ and not *N*-oxides. 2-Phenylazopyridine gave the azoxy-oxide (II).⁵ We now show that oxidation of pyridines containing conjugated carbon-carbon and carbon-nitrogen double bonds gives the 1-oxides.



β -3- and -4-Pyridylacrylic acid and the corresponding ethyl esters and amides with peracetic acid all gave single products containing one extra oxygen atom, in good yield.

¹ Part VI, Hands and Katritzky, *J.*, 1957, 4385.

² Ochiai, *J. Org. Chem.*, 1953, **18**, 534.

³ Shaw, Bernstein, Losee, and Lott, *J. Amer. Chem. Soc.*, 1950, **72**, 4362.

⁴ Mann and Watson, *J. Org. Chem.*, 1948, **13**, 502.

⁵ Colonna and Risaliti, *Gazzetta*, 1955, **85**, 1148.

In each series the same position had been oxidised, for the esters gave the corresponding amides and acids. The products were shown to be *N*-oxides, and not epoxides, by infrared and ultraviolet spectra.⁶ 2- and 4-Styrylpyridine with peracetic acid gave the corresponding *N*-oxides in poor yield, identical with the products of reaction of 2- and 4-picoline 1-oxide with benzaldehyde. 3-Pyridylacetic acid (itself readily *N*-oxidised) with benzaldehyde gave β -phenyl- α -3-pyridylacrylic acid, which it is hoped to convert into 3-styrylpyridine.

Pyridine-2-aldehyde and benzyl cyanide in conflicting reports^{7,8} are stated to give compounds (III) and (IV): we obtained only the former; peracetic oxidation failed, as did that of the *O*-benzoyl derivative of pyridine-2-aldehyde cyanohydrin. Hydrogen peroxide is known to hydrolyse cyano-groups very readily⁹ although both 2-¹⁰ and 3-cyanopyridine¹¹ have given 1-oxides directly. In the attempted preparation of quinoline-2-aldehyde cyanohydrin, only the quinaldoin cyanohydrin (V) was obtained; a similar product in the pyridine series is known.¹²

Pyridine-1-aldehyde with peracetic acid gave successively 2-picolinic acid (oxidation to the acid has been reported in the 4-series¹³) and the corresponding 1-oxide, but pyridine-2-aldoxime and the related semicarbazone gave 1-oxides, each convertible into the dinitrophenylhydrazone oxide. A by-product, isomeric with the starting material, was isolated on oxidation of the semicarbazone. This was the *cis*-semicarbazone (VI) (known in other cases¹⁴) (which would be expected to be more difficult to oxidise than the predominating *trans*-isomer) for it gave pyridine-2-aldehyde 2 : 4-dinitrophenylhydrazone. Oxidation of the benzoyl derivative of the oxime gave only benzoic acid and pyridoin. 4-Acetylpyridine hydrazone and the azine were not *N*-oxidised smoothly. 3- and 4-Pyridylcarboxyhydrazide gave only the corresponding acids with peracetic acid, but the analogous *N'*-benzenesulphonylhydrazides gave 1-oxides. β -4-Pyridylpropionamide and *N*-benzylisonicotinamide were readily *N*-oxidised.

EXPERIMENTAL

Oxidations with Peracetic Acid.—The pyridine (0.01 mole), aqueous 30% hydrogen peroxide (1.47 c.c.), and acetic acid (6 c.c.) were heated for 18 hr. at 70°, and volatile matter was removed at 100°/15 mm. The residue was either crystallised directly, or (if semi-solid) treated in hot chloroform (15 c.c.) with potassium carbonate (0.8 g.) and recovered from the chloroform by evaporation.

Pyridylacrylic Acid Derivatives.—The following 1-oxides were prepared: β -4-pyridylacrylic acid (50%), prisms (from pentyl alcohol), m. p. 237—240° (decomp.) (Found: C, 58.3; H, 4.5; N, 8.0. $C_8H_7O_3N$ requires C, 58.2; H, 4.3; N, 8.5%) [*hemiacetate*, plates, m. p. 237—240° (decomp.), from acetic acid (Found: C, 55.1; H, 4.8; N, 7.5. $C_8H_7O_3N, \frac{1}{2}C_2H_4O_2$ requires C, 55.4; H, 4.7; N, 7.2%); β -4-pyridylacrylamide (18%), prisms (from methanol or water), m. p. 246° (decomp.) (darkens above 235°) (Found: C, 58.7; H, 5.2. $C_8H_8O_2N_2$ requires C, 58.5; H, 4.9%); ethyl 2-4'-pyridylacrylate (51%), prisms [from benzene-light petroleum (b. p. 60—80°)], m. p. 145° (Found: C, 62.1; H, 5.5; N, 7.2. $C_{10}H_{11}O_3N$ requires C, 62.2; H, 5.7; N, 7.2%), which with 2*N*-aqueous sodium hydroxide during 12 hr. at 100° followed by acetic acid, gave the corresponding acid, m. p. and mixed m. p. 238—240° (decomp.), and with aqueous-methanolic ammonia in 5 days at 0° gave the amide (85%), m. p. and mixed m. p. 245° (decomp.); β -3-pyridylacrylic acid (95%), prisms (from acetic acid), m. p. 273—274° (decomp.,

⁶ Katritzky and co-workers, unpublished work.

⁷ Klosa, *Arch. Pharm.*, 1956, **289**, 177.

⁸ Profft, Schneider, and Beyer, *J. prakt. Chem.*, 1955, **2**, 147.

⁹ Radziszewski, *Ber.*, 1885, **18**, 355.

¹⁰ Leonard and Wajngurt, *J. Org. Chem.*, 1956, **21**, 1077.

¹¹ Jujo, *J. Pharm. Soc. Japan*, 1946, **66**, 21.

¹² Mathes and Sauermilch, *Chem. Ber.*, 1956, **89**, 1515.

¹³ Mathes and Sauermilch, *Chem. Zig.*, 1952, **76**, 519.

¹⁴ Wittig, "Stereochemie," Akademische Verlag, Leipzig, 1930, p. 200.

depends on rate of heating) (Found: C, 58.7; H, 4.5%); β -3-pyridylacrylamide (50%), needles [from ethanol-water (5 : 1)], m. p. 235° (decomp.) (Found: C, 59.0; H, 5.0%); ethyl β -3'-pyridylacrylate (96%), prisms (from ethyl acetate), m. p. 99–101°, also prepared (73%) by esterification with ethanol-sulphuric acid of the corresponding acid [converted (as in 4-series) into the acid (88%), m. p. and mixed m. p. 274–275° (decomp.), and the amide (71%), m. p. and mixed m. p. 235° (decomp.)] (Found: C, 61.9; H, 5.6%).

2- and 4-Styrylpyridine 1-Oxide.—(i) Oxidation gave the oxide (40%) of the 2-isomer as prisms (from benzene), m. p. 162° (Found: C, 78.9; H, 5.7; N, 7.1. $C_{13}H_{11}ON$ requires C, 79.2; H, 5.6; N, 7.1%); and the 4-isomer gave an oxide (28%), prisms (from ethyl methyl ketone), m. p. 169° (Found: C, 79.6; H, 5.8%).

(ii) Benzaldehyde (10.6 g.), 2-picoline 1-oxide (10.9 g.), and methanolic 5% potassium methoxide (50 c.c.) were refluxed for 3 hr. After 12 hr. more, excess of carbon dioxide was passed in, and the whole filtered and steam-distilled. 2-Styrylpyridine 1-oxide (4.3 g., 22%) crystallised from the residue and had m. p. and mixed m. p. 160°. 4-Picoline 1-oxide similarly gave 4-styrylpyridine 1-oxide (11%), m. p. and mixed m. p. 167–169°.

3-Pyridylacetic Acid.—Refluxing ethyl 3-pyridylacetate (20.4 g.) for 8 hr. with aqueous potassium hydroxide (11 g. in 11 c.c.) and ethanol (28 c.c.), followed by addition of aqueous 12N-hydrochloric acid (14.6 c.c.), filtration, evaporation, and extraction of the residue with methanol, gave the acid (12.5 g., 75%), m. p. 141–143° (lit.,¹⁵ m. p. 144°) [1-oxide (67%), prisms (from ethyl acetate-ethanol), m. p. 142–144° (decomp.) (Found: 54.9; H, 4.7. $C_7H_7O_3N$ requires C, 54.9, H, 4.6%)].

The acid (1.27 g.), benzaldehyde (1.5 c.c.), piperidine (0.2 c.c.), and pyridine (10 c.c.), when heated for 2 days at 115° and poured into water, gave β -phenyl- α -3-pyridylacrylic acid (0.85 g., 40%), needles (from ethanol), m. p. 234–235° (slight decomp.) (Found: C, 74.8; H, 5.3; N, 6.3. $C_{14}H_{11}O_2N$ requires C, 74.7; H, 4.9; N, 6.2%).

α -Phenyl- β -2-pyridylacrylonitrile.—Aqueous 10% sodium hydroxide (0.5 c.c.) was added slowly at 0° to pyridine-2-aldehyde (1.07 g.) and benzyl cyanide (1.17 g.) in ethanol (2.0 c.c.). After 18 hr., the nitrile (1.53 g., 74%) was collected; it formed prisms, m. p. 63–66° (lit.,⁷ m. p. 61–63°), from ethanol (Found: C, 81.2; H, 5.0; N, 13.3%; *M*, 185. Calc. for $C_{14}H_{10}N_2$: C, 81.5; H, 4.9; N, 13.6%; *M*, 206).

O-Benzoyl(pyridine-2-aldehyde Cyanohydrin).—This compound (26%) (prepared as for the oxime benzoate below), formed prisms, m. p. 102° from ethanol (Found: C, 70.1; H, 4.3; N, 11.7. $C_{14}H_{10}O_2N_2$ requires C, 70.6; H, 4.2; N, 11.8%). Pyridoin (12%), orange needles, m. p. 156° (lit.,¹² m. p. 156°), separated later from the aqueous mother-liquors (Found: C, 66.8; H, 4.5. Calc. for $C_{12}H_{10}O_2N_2$: C, 67.3; H, 4.7%).

1-Cyano-1 : 2-di-2'-quinolyethane-1 : 2-diol.—Aqueous sodium cyanide (0.94 g. in 2 c.c.) was slowly added at –10° to quinoline-2-aldehyde (3.14 g.) in aqueous 2N-hydrochloric acid (10 c.c.). Precipitated solid was recrystallised from benzene and from ethyl acetate, to give the diol (2.1 g., 62%) as brown plates, m. p. 133° (decomp.) (Found: C, 74.2; H, 4.6; N, 12.2. $C_{21}H_{15}O_2N_3$ requires C, 73.9; H, 4.4; N, 12.3%).

Pyridine-2-aldoxime Oxide and the Semicarbazone Oxide.—Oxidation gave the aldoxime oxide (62%), pale yellow needles (from ethanol), m. p. 222° (decomp.) (Found: C, 52.6; H, 4.5. $C_6H_6O_2N_2$ requires C, 52.2; H, 4.4%), and semicarbazone oxide (65%), insoluble in chloroform (chloroform-soluble by-product isolated, see below), needles (from acetic acid-ethyl acetate), m. p. 233° (decomp.) (Found: C, 46.5; H, 4.6. $C_7H_8O_2N_4$ requires C, 46.7; H, 4.5%).

Both compounds with 2 : 4-dinitrophenylhydrazine in ethanolic hydrochloric acid gave the corresponding 2 : 4-dinitrophenylhydrazone 1-oxide (55% and 35%), orange needles (from acetic acid), m. p. 285–290° (decomp.) (Found: C, 47.7; H, 2.7. $C_{12}H_8O_6N_6$ requires C, 47.7; H, 3.0%).

Extraction of crude pyridine-2-aldehyde semicarbazone 1-oxide with chloroform gave (from the chloroform) the cis-semicarbazone (3%), prisms (from ethanol), m. p. 158° (Found: C, 51.0; H, 4.8. $C_7H_8ON_4$ requires C, 51.2; H, 4.9%).

On treatment with ethanolic hydrochloric acid and 2 : 4-dinitrophenylhydrazine, both cis- and normal (*i.e.*, mainly *trans*-)pyridine-2-aldehyde semicarbazone gave the 2 : 4-dinitrophenylhydrazone (84% and 60%), m. p. 226–228°, identical with an authentic specimen (lit.,¹⁶ m. p. 229°).

¹⁵ Hartmann and Bosshard, *Helv. Chim. Acta*, 1941, **24**, 28E.

¹⁶ Grammaticakis, *Bull. Soc. chim. France*, 1956, 109.

O-Benzoyl(pyridine-2-aldoxime).—Benzoyl chloride (0.32 c.c.) was added slowly to pyridine-2-aldoxime (0.31 g.) in pyridine (1 c.c.) at 0°, the whole kept for 18 hr., and water added. The *benzoyl derivative* (0.45 g. 80%) formed prisms, m. p. 112.5°, from ethanol [mixed m. p. with the oxime (m. p. 112°), 85—90°] (Found: C, 69.2; H, 4.8; N, 12.0. $C_{13}H_{10}O_2N_2$ requires C, 69.0; H, 4.5; N, 12.4%).

Treatment with peracetic acid gave benzoic acid (18%) and pyridoin (40%), m. p. 152°, as the only products isolated.

4-Acetylpyridine Derivatives.—This ketone gave ¹⁷ the *azine* (68%), pale yellow plates [from light petroleum (b. p. 80—100°)], m. p. 125.5—127° (Found: C, 70.5; H, 5.8. $C_{14}H_{14}N_4$ requires C, 70.6; H, 5.9%). and, when heated for 1 min. with two parts of hydrazine hydrate (100%), gave the *hydrazone* (83%), plates (from benzene), m. p. 121—122° (Found: C, 62.1; H, 6.8. $C_7H_9N_3$ requires C, 62.2; H, 6.7%).

2-, 3-, and 4-(*N'*-Benzenesulphonylhydrazinocarbonyl)pyridine 1-Oxide.—Oxidation of the corresponding pyridine gave the 4-substituted *pyridine 1-oxide* (40%), needles (from water), m. p. 238—239° (decomp.; depends on heating rate) (Found: C, 49.3; H, 3.9; N, 14.0. $C_{12}H_{11}O_4N_3S$ requires C, 49.1; H, 3.8; N, 14.3%), the 3-*analogue* (44%), needles (from water or ethanol), m. p. 222—224° (decomp.) (Found: C, 48.7; H, 3.8; N, 14.1%), and the 2-*analogue* (48%), needles (from acetic acid, m. p. 209—212° (decomp.) (Found: C, 49.1; H, 4.0; N, 14.1%)).

Preparation and Oxidation of Amides.—Ethyl isonicotinate (5.5 g.) was refluxed for 4 hr. with benzylamine (12 c.c.). Removal of excess of amine at 100°/14 mm. then gave *N*-benzylisonicotinamide (71%), needles (from ethyl acetate–light petroleum), m. p. 90—92° (lit.,¹⁸ m. p. 84.5—85°); the *methotoluene-p-sulphonate* formed plates (from ethanol), m. p. 194.5—196.5° (Found: C, 63.1; H, 5.7. $C_{21}H_{22}O_4N_2S$ requires C, 63.3; H, 5.6%). *N*-2-(3-*Indolyl*)-ethylisonicotinamide was similarly prepared (73%) by heating the amine and ester for 10 hr. at 140° and separated from ethanol–benzene, having m. p. 165.5—167° (Found: C, 72.6; H, 5.8. $C_{16}H_{15}ON_3$ requires C, 72.4; H, 5.7%) [*methotoluene-p-sulphonate*, plates (from ethyl acetate–ethanol), m. p. 174—175.5° (Found: C, 63.4; H, 5.4; N, 9.3. $C_{24}H_{25}O_4N_3S$ requires C, 63.8; H, 5.6; N, 9.3%)].

Oxidation gave β -4-*pyridylpropion-* (42%), rods, m. p. 227°, from ethanol (Found: C, 57.9; H, 6.0; N, 16.6. $C_8H_{10}O_2N_2$ requires C, 57.8; H, 6.1; N, 16.9%), and *N*-benzylisonicotinamide 1-*oxide* (66%), prisms (from ethanol), m. p. 184° (Found: C, 68.4; H, 5.0. $C_{13}H_{12}O_2N_2$ requires C, 68.4; H, 5.3%).

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¹⁷ Horning, Horning, and Platt, *J. Amer. Chem. Soc.*, 1948, **70**, 288.

¹⁸ Billman and Rendall, *ibid.*, 1944, **66**, 540.