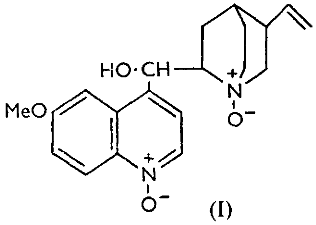
## 31. N-*Oxides and Related Compounds. Part VII.*[1] *Per-acid Oxidation of Some Conjugated Pyridines.*

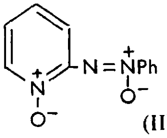
By A. R. Katritzky and A. M. Monro.

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 oxide [4] 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.



(I)



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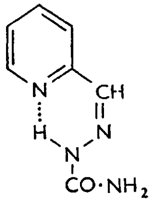

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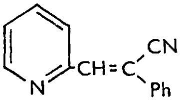

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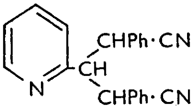
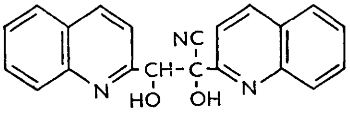


(IV)



(V)

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.

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[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 readily [9] although both 2- [10] and 3-cyanopyridine [11] 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-series [13]) 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 cases [14]) (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*-benzyl*iso*nicotinamide 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 2N-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.,

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[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. Ztg.*, 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; 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′-*quinolylethane*-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. $C_{12}H_9O_5N_5$ 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°).

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[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 *iso*nicotinate (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*-benzyl-*iso*nicotinamide (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*)-*ethyl*iso*nicotinamide* 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-*benzyl*iso*nicotin-amide* 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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The Dyson Perrins Laboratory, Oxford University. [*Received, July 25th*, 1957.]

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

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