464. *The Preparation of Some Substituted Pyridine 1-Oxides.*

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The preparation of a series of substituted pyridine 1-oxides is described; some inconsistencies in the literature are shown to have resulted from polymorphism. Picrolonates are convenient for the characterisation of this type of compound.

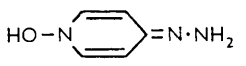
A SERIES of pyridine 1-oxides had to be prepared in connection with another investigation. New compounds and some other points of interest in the preparations are now briefly reported.

4-Nitropyridine 1-oxide with either acetyl chloride [1] or hydrochloric acid [2] gives 4-chloropyridine 1-oxide, but the melting points of the product were reported as 169·5° and 152·5—153·5° respectively. In our hands both methods gave the same product, m. p.

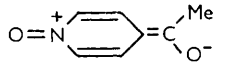
[1] Ochiai, *J. Org. Chem.*, 1953, **18**, 549.
[2] Den Hertog and Coombé, *Rec. Trav. chim.*, 1951, **70**, 581.

179·5—180° (decomp.). The melting point varied a little with the rate of heating, and the compound decomposes slowly on storage, but polymorphism is probably the cause of the discrepancy, because 4-ethoxypyridine 1-oxide, the melting point of which has been reported as 33° by Ochiai and Katada [3] and as 126·5—127·5° by den Hertog and Coombé [2] has now been shown to exist in three polymorphic forms, the melting points of two of which agree with the above figures.

4-Chloropyridine 1-oxide with dimethylamine and hydrazine afforded the corresponding 4-dimethylamino- and 4-hydrazino-derivative, but aniline gave, in low yield, 4-anilinopyridine by deoxygenation.[4] The possibility that 4-hydrazinopyridine 1-oxide exists partly or wholly in the tautomeric form (I) (compare the uncertainty with 4-aminopyridine 1-oxide [5]) is being investigated.



(I)



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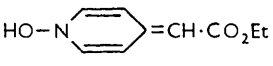

(III)

Ethyl pyridine-4-carboxylate 1-oxide and 4-acetylpyridine 1-oxide did not readily give picrates, perhaps because basicity is weakened by contribution of structures such as (II) to the resonance hybrid. However picrolonates were easily obtained; these derivatives were found generally useful for characterisation in this series; further examples are described in the Experimental section.

Attempts to convert methyl 4-pyridylacetate into its 1-oxide gave only pyridine-4-carboxylic acid 1-oxide; a similar result was reported [6] for ethyl 2-pyridylacetate. This is probably connected with tautomerism with the form (III), for ethyl 3-pyridylacetate 1-oxide was obtained in the usual way.

Sodium benzyloxide in benzyl alcohol and 3-methyl-4-nitropyridine 1-oxide gave an intensely green solution, but 4-benzyloxy-3-methylpyridine 1-oxide was not isolated (contrast 4-nitropyridine 1-oxide [1]) probably because of side reactions involving proton abstraction from the activated methyl group. However 3-methyl-4-nitropyridine 1-oxide was converted into the 4-hydroxy- and the 4-chloro-compound as expected.[1] The last, with sodium alkoxides, gave the 4-methoxy-, 4-ethoxy-, and 4-benzyloxy-derivative, and with morpholine and hydrazine respectively the 4-morpholino- and 4-hydrazino-oxide. 4-Chloro-3-methylpyridine 1-oxide and thiourea gave a thiuronium salt.

Meisenheimer [7] found that quaternary salts of aliphatic amine oxides with alkali gave the tertiary amine and aldehyde: $CH_2R'\cdot O\cdot NR_3^+ X^- \longrightarrow R_3N + R'\cdot CHO + HX$. Ochiai *et al.*[8] described a few quaternary salts of pyridine 1-oxides and their reaction with alkali, re-forming the pyridines, but no yields or experimental details are given in the available abstract. This reaction appeared of possible interest as a method of deoxygenating pyridine 1-oxides under non-reducing conditions. 2- and 4-Methylpyridine 1-oxide and pyridine-1-oxide readily gave crystalline methotoluene-*p*-sulphonates (methiodides could not be obtained) and with alkali these gave fair yields of the deoxygenated bases. (The yields of the deoxygenated bases were not improved by treating the methotoluene-*p*-sulphonates with alkaline sodium borohydride solution.) Preliminary attempts to extend the reaction to negatively substituted pyridines were not encouraging.

Experimental

Picrates and picrolonates were prepared in ethanol and recrystallised from that solvent.

4-Chloropyridine 1-Oxide.—Prepared by Ochiai's method [1] the oxide had m. p. 178—180° (decomp.) raised by recrystallisation from acetone to 179·5—180° (decomp.) (Found: C, 46·7; H, 3·3; N, 10·4; Cl, 26·9. Calc. for C_5H_4ONCl: C, 46·3; H, 3·1; N, 10·8; Cl, 27·4%). A

[3] Ochiai and Katada, *J. Pharm. Soc. Japan*, 1943, **63**, 265 (*Chem. Abs.*, 1951, **45**, 5152).
[4] Cf. Pachter and Kloetzel, *J. Amer. Chem. Soc.*, 1952, **74**, 971.
[5] Jaffé, *ibid.*, 1955, **77**, 4445.
[6] Adams and Miyano, *ibid.*, 1954, **76**, 3168.
[7] Meisenheimer, *Annalen*, 1913, **397**, 273.
[8] Ochiai, Katada, and Naito, *J. Pharm. Soc. Japan*, 1944, **64**, 210 (*Chem. Abs.*, 1951, **45**, 5154).

specimen prepared by den Hertog and Coombé's [2] method had identical m. p., mixed m. p., and infrared spectrum. The picrate formed yellow needles, m. p. 147·5—149° (satisfactory analytical figures were not obtained). The *picrolonate* formed yellow needles, m. p. 167—168° (decomp.) (Found : C, 46·3; H, 3·2; N, 17·9. $C_{15}H_{12}O_6N_5Cl$ requires C, 45·8; H, 3·1; N, 17·8%). Ochiai [1] gives m. p. 169·5° (decomp.) for the base; den Hertog and Coombé [2] give 152·5—153·5° (decomp.) for the base and m. p. 147—148° for the picrate (no analysis).

4-*Ethoxypyridine* 1-*Oxide*.—4-Chloropyridine 1-oxide (1·23 g.) was refluxed for 2 hr. with ethanolic sodium ethoxide (from 0·23 g. of sodium and 25 c.c. of ethanol). The mixture was evaporated to dryness and the residue crystallised from ethyl acetate, to give the oxide (0·92 g., 70%) as plates, m. p. 30—31°, unchanged by a further crystallisation (Found : C, 60·6; H, 6·7. Calc. for $C_7H_9O_2N$: C, 60·4; H, 6·5%). On other occasions this compound crystallised in deliquescent laths, m. p. 124·5—126·5°, and in fine needles, m. p. *ca.* 85—95°. The two modifications of lower m. p., on slow heating, sometimes gave a m. p. corresponding to that of highest m. p. The picrate formed needles, m. p. 124—125·5° (Found : C, 42·7; H, 3·3; N, 15·0. Calc. for $C_{13}H_{12}O_9N_4$: C, 42·4; H, 3·3; N, 15·2%). The *picrolonate* formed yellow needles, m. p. 190—192° (Found : C, 51·0; H, 4·3; N, 17·5. $C_{17}H_{17}O_7N_5$ requires C, 50·6; H, 4·2; N, 17·4%). Ochiai and Katada [3] give m. p. 33° for the base, and m. p. 125—126° for the picrate. Den Hertog and Coombé [2] give m. p. 126·5—127·5° for the base and m. p. 126·5—127·5° for the picrate).

4-*Dimethylaminopyridine* 1-*Oxide*.—4-Chloropyridine 1-oxide (2 g.) was heated with 30% aqueous dimethylamine (6 c.c.) for 15 hr. at 140°. The resulting dark solution was diluted with water (20 c.c.) and twice boiled with charcoal. The solution was evaporated to dryness and the residue was extracted with ethanol. These extracts were evaporated to dryness; the residue crystallised from ethyl acetate to give the *oxide* (0·42 g., 20%), needles, m. p. 95—96·5° (Found : C, 61·1; H, 7·4. $C_7H_{10}ON_2$ requires C, 60·9; H, 7·2%). The *picrate* formed yellow needles, m. p. 182—184° (decomp.) (Found : C, 42·7; H, 3·6; N, 18·7. $C_{13}H_{13}O_8N_5$ requires C, 42·5; H, 3·5; N, 19·1%); the *picrolonate* formed buff laths, decomp. 213—218° (Found : C, 51·0; H, 4·5; N, 20·6. $C_{17}H_{18}O_6N_6$ requires C, 50·8; H, 4·5; N, 20·9%).

4-*Hydrazinopyridine* 1-*Oxide*.—4-Chloropyridine 1-oxide (5 g.) and hydrazine hydrate (18 c.c.) were heated cautiously to 105°. When the exceedingly vigorous reaction abated more 4-chloropyridine 1-oxide (3 g.) was added gradually so that the liquid boiled gently. Finally the whole was heated at 105° for 30 min. more. On cooling, the *product* (4·5—6·6 g., 58—85%) separated; it crystallised from ethanol in plates, changing to prisms, m. p. 183—185° (explosive decomp.) (immersion at 175°) (Found : C, 48·3; H, 5·5. $C_5H_7ON_3$ requires C, 48·0; H, 5·6%). The *picrate* formed yellow needles, m. p. 192—193° (decomp.) (immersion at 170°) (Found : C, 37·3; H, 3·0. $C_{11}H_{10}O_8N_6$ requires C, 37·3; H, 2·8%); the *picrolonate* formed orange-yellow needles, m. p. 208—210° (decomp.) (Found : C, 46·2; H, 4·0. $C_{15}H_{15}O_6N_7$ requires C, 46·3; H, 3·9%).

The hydrazine combined with acetophenone in acetic acid to give a *hydrazone*, plates (from ethanol), m. p. 243—245° (decomp.) (Found : C, 68·4; H, 5·6. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·7%).

4-*Anilinopyridine*.—Aniline (12 c.c.) and 4-chloropyridine 1-oxide (2·6 g.) were heated at 115° for 18 hr. The deep violet product was steam-distilled, then filtered from tar, and the aqueous solution was treated with charcoal and evaporated almost to dryness. Excess of potassium carbonate was added, and the whole extracted with chloroform. The dried ($MgSO_4$) extracts were evaporated to dryness and the residue was recrystallised from dioxan and twice from ethanol–water (1 : 3) to give the pyridine (0·21 g., 6%) in plates, m. p. 173·5—175° (Found : C, 77·5; H, 6·1; N, 16·7. Calc. for $C_{11}H_{10}N_2$: C, 77·6; H, 5·9; N, 16·5%) (lit.,[11] m. p. 175—176°).

1-*Oxides of* 3- *and* 4-*Acetyl- and -Carboxy-pyridine*.—Ethyl *iso*nicotinate (6·6 g.), acetic acid (40 c.c.), and 30% hydrogen peroxide (7 c.c.) were heated at 70° overnight, then solvent was removed at 100°/12 mm., water (15 c.c.) was added, and volatile compounds were again removed at 100°/12 mm.; ethyl pyridine-4-carboxylate 1-oxide (6·0 g., 82%) crystallised from light petroleum in needles, m. p. 63·5—65° (Found : C, 57·8; H, 5·7. Calc. for $C_8H_9O_3N$: C, 57·5; H, 5·4%) (Shimizu *et al.*[9] give only a b. p. for this compound). The *picrolonate* formed yellow laths, m. p. 121—122° (decomp.) (Found : C, 49·9; H, 4·0; N, 16·2. $C_{18}H_{17}O_8N_5$ requires C, 50·1; H, 3·9; N, 16·2%).

[9] Shimizu, Naito, Ohta, Yoshikawa and Dohmori, *J. Pharm. Soc. Japan*, 1952, **72**, 1474 (*Chem. Abs.*, 1953, **47**, 8077).

The following were similarly prepared : 4-acetylpyridine 1-oxide (84%), needles (from ethyl acetate), m. p. 132·5—135° (lit.,[10] m. p. 132°) [*dinitrophenylhydrazone*, red prisms (from acetic acid), m. p. 255—259° (decomp.) (Found : C, 49·2; H, 3·7; N, 22·1. $C_{13}H_{11}O_5N_5$ requires C, 49·2; H, 3·5; N, 22·1%); *picrolonate*, buff needles, m. p. 138—139° (decomp.) (Found : C, 50·6; H, 3·9; N, 17·5. $C_{17}H_{15}O_7N_5$ requires C, 50·9; H, 3·7; N, 17·5%)]; ethyl pyridine-3-carboxylate 1-oxide (85%), prisms (from ethyl acetate), m. p. 100·5—102·5° (lit.,[9] m. p. 101—102°) [*picrolonate*, fawn needles, m. p. 131—131·5° (decomp.) (Found : C, 50·1; H, 4·0; N, 15·9%)]; 3-acetylpyridine 1-oxide, prisms (from ethyl acetate or methanol), m. p. 145—147° (lit.,[10] m. p. 142°) {*dinitrophenylhydrazone*, orange prisms (from acetic acid), m. p. 252—256° (decomp.) (Found : C, 49·2; H, 3·5%); *picrate*, yellow needles, m. p. 122—123·5° (Found : C, 42·9; H, 2·9. $C_{13}H_{10}O_9N_4$ requires C, 42·6; H, 2·7%); *methotoluene*-p-*sulphonate*, needles [from ethyl acetate–ethanol (6 : 1)], m. p. 115—117° (Found : C, 55·4; H, 5·4; N, 4·5. $C_{15}H_{17}O_5N_3$ requires C, 55·7; H, 5·3; N, 4·3%)}.

Picrolonates.—The following were also prepared : 2-, yellow needles changing to buff rods, m. p. 150—151° (decomp.) (Found : C, 51·6; H, 4·1; N, 18·6. $C_{16}H_{15}O_6N_5$ requires C, 51·5; H, 4·0; N, 18·8%), and 4-*methylpyridine* 1-*oxide picrolonate*, yellow needles, m. p. 180—181° (Found : C, 51·7; H, 4·5%), and *pyridine* 1-*oxide picrolonate*, yellow needles, m. p. 182—184° (Found : C, 50·5; H, 3·7; N, 19·4. $C_{15}H_{13}O_6N_5$ requires C, 50·2; H, 3·6; N, 19·5%).

Oxidation of Esters of 3- *and* 4-*Pyridylacetic Acid.*—Ethyl 3-pyridylacetate (4·7 g.), acetic acid (30 c.c.) and 30% aqueous hydrogen peroxide (10 c.c.; half added only after 12 hr.) were heated at 60° for 36 hr. Working up in the usual way gave the corresponding 1-*oxide* (2·4 g., 47%), needles (from ethyl acetate), m. p. 100·5—102° (Found : C, 59·5; H, 6·3. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1%). The *picrolonate* separated from ethanol in yellow needles, m. p. 154—154·5° (decomp.) (Found : C, 51·2; H, 4·6. $C_{19}H_{19}O_8N_5$ requires C, 51·2; H, 4·3%).

The action of peracetic acid on methyl 4-pyridylacetate gave no product when potassium carbonate was used to dry the chloroform extracts, but use of magnesium sulphate gave a little pyridine-4-carboxylic acid 1-oxide, m. p. 263—265° (Found : C, 51·3; H, 3·9; N, 10·1. Calc. for $C_6H_5O_3N$: C, 51·8; H, 3·6; N, 10·1%) (lit.,[12] m. p. 266°).

4-*Hydroxy*-3-*methylpyridine* 1-*Oxide.*—This *compound*, prepared by heating 3-methyl-4-nitropyridine 1-oxide with acetic anhydride and dimethylaniline, as for the non-methylated analogue,[1] formed prisms (from ethanol), m. p. 224—226° (decomp.) (Found : C, 57·6; H, 5·4. $C_6H_7O_2N$ requires C, 57·6; H, 5·6%).

4-*Chloro*-3-*methylpyridine* 1-*Oxide.*—Prepared by using acetyl chloride as with 4-chloropyridine 1-oxide above, the *oxide* (93%) formed stout needles or prisms, m. p. 122—123°, from ethyl acetate (Found : C, 50·1; H, 4·2; N, 9·5; Cl, 24·8. C_6H_6ONCl requires C, 50·2; H, 4·2; N, 9·8; Cl, 24·7%). The *picrolonate* formed fine yellow needles, m. p. 173—175° (decomp.) (Found : C, 47·3; H, 3·7. $C_{16}H_{14}O_6N_5Cl$ requires C, 47·1; H, 3·4%).

The following were prepared from 4-chloro-3-methylpyridine 1-oxide essentially as given above or in the literature [1] for their non-methylated analogues : 4-*methoxy*-3-*methyl*-, needles (from ethyl acetate), m. p. 80·5—82·5° (Found : C, 60·7; H, 6·8. $C_7H_9O_2N$ requires C, 60·4; H, 6·5%); 4-*ethoxy*-3-*methyl*-, needles (from benzene), m. p. 134—135° (Found : C, 62·3; H, 7·4. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2%); 4-*benzyloxy*-3-*methyl*-, laths (from benzene), m. p. 64—65° with resolidification and remelting at 128—130° (Found : C, 72·3; H, 6·2. $C_{13}H_{13}O_2N$ requires C, 72·6; H, 6·0%); 3-*methyl*-4-*morpholino*-, needles (from ethyl acetate or acetone), m. p. 107—109·5° (Found : C, 61·8; H, 7·3. $C_{10}H_{14}O_2N_2$ requires C, 61·9; H, 7·2%); and 4-*hydrazino*-3-*methyl-pyridine* 1-*oxide*, prisms (from ethanol), m. p. 187—188° (decomp.) (Found : C, 51·4; H, 6·5. $C_6H_9ON_3$ requires C, 51·8; H, 6·5%) [*picrate*, yellow needles, m. p. 185—186° (decomp.) (Found : C, 39·4; H, 3·6. $C_{12}H_{12}O_8N_6$ requires C, 39·1; H, 3·3%); *picrolonate*, yellow needles, m. p. 187—188° (decomp.) (Found : C, 47·9; H, 4·5. $C_{16}H_{17}O_6N_7$ requires C, 47·6; H, 4·2%)]; (3-*methylpyridine* 1-*oxide*)-4-*thiuronium chloride*, rods (from ethanol), m. p. 130—131·5° (Found : N, 19·2. $C_7H_{10}ON_3SCl$ requires N, 19·1%).

Methotoluene-p-*sulphonates of Pyridine* 1-*Oxides.*—Pyridine 1-oxide (4·75 g.) and methyl toluene-*p*-sulphonate (9·3 g.) were heated at 110° for 5 hr.; the product crystallised from ethanol–ethyl acetate to give 1-*methoxypyridinium toluene*-p-*sulphonate* (10·45 g., 74%) in deliquescent plates, m. p. 86—90° (Found : C, 55·4; H, 5·2. $C_{13}H_{15}O_4NS$ requires C, 55·5; H, 5·3%).

Similarly were prepared : 1-*methoxy*-2-*methylpyridinium* (68%), deliquescent needles, m. p.

[10] Kanno, *J. Pharm. Soc. Japan*, 1953, **73**, 120 (*Chem. Abs.*, 1953, **47**, 11154).
[11] Petrow, *J.*, 1945, 927.
[12] Ghigi, *Ber.*, 1942, **75**, 1318.

109—112°, from ethanol–ethyl acetate (Found : C, 56·7; H, 6·0. $C_{14}H_{17}O_4NS$ requires C, 56·9; H, 5·8%), and 1-*methoxy*-4-*methylpyridinium toluene*-p-*sulphonate* (86%), needles m. p. 154·5—155·5°, from ethanol–ethyl acetate (Found : C, 56·9; H, 5·6%).

Decomposition of Metho-salts of Pyridine 1-*Oxides by Alkali.*—1-Methoxypyridinium toluene-*p*-sulphonate (1·40 g., 5 millimoles) was treated with water (10 c.c.) and 2·5N-sodium hydroxide (3 c.c.), and the mixture was distilled almost to dryness; more water (5 c.c.) was added and the whole again distilled. From the combined distillates were isolated in separate experiments pyridinium picrate (0·86 g., 56%), m. p. and mixed m. p. 165·5—167·5°, and pyridinium picrolonate (0·97 g., 57%), m. p. and mixed m. p. 232—233° (decomp.). Authentic *pyridinium picrolonate* formed fine yellow needles, m. p. 232—233° (decomp.) (Found : C, 52·6; H, 4·2; N, 20·2. $C_{15}H_{13}O_5N_5$ requires C, 52·5; H, 3·8; N, 20·4%).

Similarly the 1-methoxy-2-methyl and 1-methoxy-4-methyl analogues gave respectively 2-picoline as picrate (64%), m. p. and mixed m. p. 164—166·5°, or picrolonate (67%), m. p. 212—214° (decomp.) (lit.,[13] m. p. 214—215°), and 4-picoline as picrate (85%), m. p. and mixed m. p. 164—166·5°.

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[13] Hackmann and Wibaut, *Rec. Trav. chim.*, 1943, **62**, 229.