374. *Syntheses of Heterocyclic Compounds. Part X.*[1] *Halogen Substituted* N*-Oxides*

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The chemical reactivity and spectroscopic properties of various halogen-substituted pyridine *N*-oxides, particularly those with a methyl group *ortho* to the N ⟶ O function have been investigated.

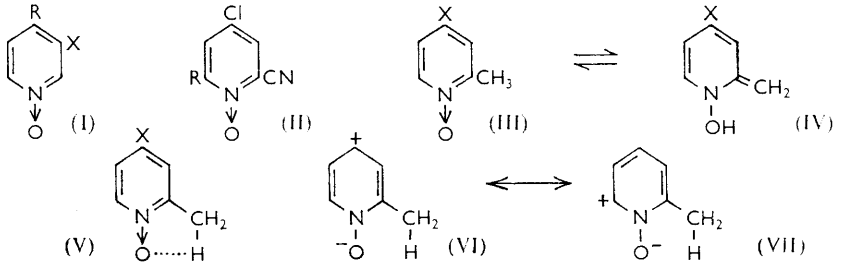
As a continuation of previous work,[2] 3-fluoropyridine *N*-oxide (I; R = H, X = F) was nitrated to give the 4-nitro-compound (I; R = NO_2, X = F), a result analogous to that of the 3-chloro-[3] and 3-bromo-analogue [4] (I; R = H, X = Cl or Br). The directing effect of the *N*-oxide group thus predominates even over that of fluorine, which is one of the strongest *para*-directing groups. The constitution of the nitration product follows from its reaction with piperidine which yields a piperidino-derivative (I; R = NO_2, X = $C_5H_{10}N$) identical with that obtained from the known 3-chloro-4-nitro-compound (I; R = NO_2, X = Cl). On treatment of the fluoro-compound (I; R = NO_2, X = F) with cold methanolic sodium methoxide both the fluorine and the nitro-group were replaced to give the dimethoxypyridine *N*-oxide (I; R = X = OMe). This result is in striking contrast to the behaviour of the corresponding chloro-compound (I; R = NO_2, X = Cl) which under the same reaction conditions [5] and also on prolonged refluxing suffers only nitro-group replacement to yield the monomethoxypyridine (I; R = OMe, X = Cl). The different reactivity shown by the two halogens (Cl and F) towards the strongly nucleophilic methoxide and not towards piperidine is unexpected. In the corresponding un-nitrated halogen

[1] Part IX, B. Hughes and H. Suschitzky, *J.*, 1965, 875.
[2] M. Bellas and H. Suschitzky, *J.*, 1963, 4007.
[3] T. Talik and Z. Talik, *Roczniki Chem.*, 1962, **36**, 539.
[4] H. J. den Hertog and J. Overhoff, *Rec. Trav. chim.*, 1950, **69**, 468.
[5] T. Talik, *Roczniki Chem.*, 1962, **36**, 1465.

compounds (I; R = H, X = Cl or F) this selective reactivity towards nucleophiles was not observed.[2]

It is well known that a halogen in the 4-position of pyridine or its *N*-oxide is readily replaced by nucleophiles. Because of this reactivity neither 4-fluoropyridine nor its *N*-oxide can be prepared since they are liable to self-condensation.[2,6] The introduction of an α-methyl group, however, reduces the lability of such a halogen atom in a striking manner. Thus, the preparation of 4-fluoro-α-picoline and its *N*-oxide, as well as that of the other halogeno-analogues, becomes possible.[7] Moreover, we found 4-fluoro-α-picoline *N*-oxide, which we made by oxidation of the requisite picoline with monoperphthalic acid, to be stable in boiling water and to be hydrolysed only slowly by 0·1N-aqueous sodium hydroxide. Ionic fluorine was produced rapidly with hot 2N-sodium hydroxide, and the 4-piperidino-*N*-oxide was obtained after prolonged refluxing with excess of the base in ethanol. The lability of the fluorine atom had in fact been reduced roughly to that of the halogen in the 3-fluoro-*N*-oxide [2] (I; R = H, X = F). The " blocking " effect of an α-methyl group against anionic replacement can also be inferred from the literature. For instance, 4-chloro-2,6-dimethyl- and 4-chloro-2-methyl-pyridine *N*-oxide are reported to react with sodium hydroxide only under pressure and at elevated temperature to give the corresponding hydroxy-compound in 17 and 80% yield, respectively.[8] By contrast, 4-chloro-3-methyl-pyridine *N*-oxide reacts under the same conditions with nucleophiles as its unmethylated parent compound.[9]

In order to study this deactivating effect on halogen we made a number of methyl-substituted halogeno-pyridine *N*-oxides. The 4-chloro-compounds were obtained essentially by treating the corresponding 4-nitro-compound with acetyl chloride.[9,10] With 2,6-dimethyl-4-nitropyridine *N*-oxide we obtained, apart from the 4-chloro-compound, the cyano-*N*-oxide (II; R = CH:NOH). 4-Nitro-α-picoline *N*-oxide under similar conditions yields the 2-cyano-compound (II; R = H) as a by-product. This is supposed to occur *via* intermediate oxime formation [11] through the action of acetyl nitrite, which is a feasible reaction product, followed by dehydration. Isolation of our cyano-oxime supports this suggestion. Acetic anhydride or acetyl chloride yielded the acetylated oxime (II; R = CH:NOAc) and not the dicyanide (II; R = CN).



Attempts to prepare 2-fluoro-3-, -4-, or -5-methylpyridine *N*-oxide from the appropriate fluoropicolines with peracetic or monoperphthalic acid led invariably to fluorine replacement, although success in the preparation of 2-fluoropyridine *N*-oxide by this method has been claimed,[12] contrary to our own experience.[2]

The reactivity of the halogen in the various halogeno-*N*-oxides was assessed by refluxing in methanolic sodium methoxide (cf. Experimental section) and results are set out in Table 1.

In the quinoline series the " damping " effect of an α-methyl group is less pronounced,

[6] A. Roe and G. F. Hawkins, *J. Amer. Chem. Soc.*, 1947, **69**, 2443.
[7] E. Profft and H. Richter, *J. prakt. Chem.*, 1959, **9**, 164.
[8] H. N. Bojarska-Dahlig, *Rec. Trav. chim.*, 1959, **78**, 982.
[9] A. R. Katritzky, *J.*, 1956, 2404.
[10] E. Ochiai, *J. Org. Chem.*, 1953, **18**, 534.
[11] T. Kato and H. Hayashi, *J. Pharm. Soc.* (*Japan*), 1963, **83**, 352.
[12] B.P. 847,701/1958.

TABLE 1

Halogen replacement (%) in hydrolysis of halogenopyridine *N*-oxides in boiling 0·1N-methanolic sodium methoxide for 4 hr.

Substituent.....	4-Cl	4-Cl-2-Me	4-Cl-2,6-Me_2	4-Cl-3-Me	3-F-2,6-Me_2 *	5-I-2-Me *
(%)	87	55	16	72	0	0

* No hydrolysis occurred even after 24 hr.

probably because of the much greater reactivity of the halogenoquinolines. While the existence of 4-fluoroquinoline is questionable,[13] we obtained 4-fluoroquinaldine as an unstable hydrate. Addition of ethanolic picric acid produced the picrate of 4-ethoxyquinaldine and ionic fluorine. Thus no attempt was made to prepare the *N*-oxide. By contrast 4-fluoro-α-picoline is unaffected by water and gives a stable picrate.[7] 4-Chloroquinaldine and its *N*-oxide both react with weak nucleophiles without difficulty.[14]

We examined various possible causes which might account for the " shielding " effect of an α-methyl group. The reason that 4-fluoro-α-picoline and 4-fluoroquinaldine exist while their unmethylated parent substances quaternise immediately on formation is probably steric. Although the introduction of a methyl group into the 2-position raises the pK_a of the base [15] by a polar effect and should, therefore, facilitate the nucleophilic self-condensation, it is well known that an α-methylated pyridine imposes steric requirements which can considerably curtail the chemical reactivity arising from its base strength.[16]

In the *N*-oxides steric interference between the 2-methyl and the *N*-oxide group which could lead to reduced halogen reactivity, was ruled out on the basis of molecular models. We also considered the tautomeric equilibrium (III ⇌ IV), which has so far not been reported for heterocyclic *N*-oxides but is known to occur in the structurally related aliphatic nitrones.[17] Predominance of the hydroxy-form (IV) may account for a less reactive halogen. In fact methyl-hydrogen mobility in α-picoline *N*-oxide has recently been demonstrated by deuterium exchange particularly in presence of bases such as piperidine.[18] An analysis of the infrared spectra of 4-chloropyridine *N*-oxides in chloroform, however, did not support the tautomerism (III ⇌ IV) since the C–CH_3 bond (*ca.* 1380 $cm.^{-1}$) was normal, as was also the stretching vibration of the methyl group (*ca.* 2960 $cm.^{-1}$).[19] A strong OH absorption near 3300 $cm.^{-1}$ is attributable to hydrogen bonding of the N ⟶ O group with the hydrogen in chloroform, since bands at 2915 and 2460 $cm.^{-1}$ in the spectrum of 4-chloropyridine *N*-oxide were not compensated and are characteristic of hydrogen-bonded chloroform.[20] The influence of the 4-chloro-atom on the N ⟶ O frequency is small and completely suppressed in presence of a 2-methyl group (Table 2).

The ultraviolet spectra (Table 2) confirm that introduction of a 2-methyl group into a pyridine *N*-oxide causes a shift to lower wavelength [21] which is partly offset by the " weighting " of the nucleus with halogen. This effect of a 2-methyl group has been interpreted [21] as being due to an intramolecular hydrogen bond between the methyl-hydrogen and the oxygen atom (V). As a feasible consequence the importance of canonical structures such as (VI) and (VII) may be diminished which would explain the reduced activity of a 4-positioned halogen in 2-methyl-*N*-oxides. Further evidence of intramolecular hydrogen bonding is provided by the steam-volatility of 4-chloro-2-methyl- and 4-chloro-2,6-dimethyl-pyridine *N*-oxide as well as of 3-fluoro-2,6-dimethylpyridine *N*-oxide. By contrast 4-chloro-3-methyl- and 4-chloro-pyridine *N*-oxide are not steam-volatile.

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TABLE 2

Spectra of substituted pyridine *N*-oxides

Substituent	N → O stretching in CCl_4 ($cm.^{-1}$)	Ultraviolet spectrum (95% ethanol) $\lambda_{max.}$ (mμ)	$\varepsilon_{max.}$
None	1264	263	12,440
4-Cl	1267	274	19,460
3-F	1290	266	12,610
2-Me	1260	—	—
4-Cl-2-Me	1260	270	15,590
2,6-Me_2	1255	—	—
4-Cl-2,6-Me_2	1257	268	15,260
3-Me	1283	—	—
4-Cl-3-Me	1257	274	18,230
3-F-2,6-Me_2	1245	260	12,060
5-I-2-Me	—	269	11,790

EXPERIMENTAL

Spectra.—Infrared spectra were measured on a Unicam S.P. 200 and ultraviolet spectra on a Unicam S.P. 800 instrument.

3-*Fluoro*-4-*nitropyridine* N-*Oxide.*—To a stirred solution of 3-fluoropyridine *N*-oxide [2] (2 g.) in concentrated sulphuric acid (10 ml.) kept at 120—130° was added fuming nitric acid (4 ml.) during 1 hr. The mixture, after having been heated for another 3 hr., was poured on ice, neutralised with sodium hydrogen carbonate, and thoroughly extracted with chloroform. Removal of the solvent gave 3-*fluoro*-4-*nitropyridine* N-*oxide* (0·6 g.) which recrystallised from light petroleum (b. p. 100—120°) as pale yellow plates, m. p. 122° (Found: C, 38·4; H, 1·9; N, 17·3. $C_5H_3FN_2O_3$ requires C, 38·0; H, 1·9; N, 17·7%). When treated with excess of piperidine, the mixture became hot and yielded 4-*nitro*-3-*piperidinopyridine* N-*oxide* as red needles (from light petroleum, b. p. 100—120°), m. p. 171° (Found: C, 53·9; H, 6·1; N, 19·0. $C_{10}H_{13}N_3O_3$ requires C, 53·8; H, 5·9; N, 18·8%). The same compound was obtained from 3-chloro-4-nitropyridine *N*-oxide [3] and piperidine.

The fluoro-compound (0·1 g.) in methanol (10 ml.) containing sodi 0·1 g.) after 1 hr. at room temperature gave 3,4-*dimethoxypyridine* N-*oxide monohydrate*, m. p. 102° (from light petroleum–ethyl acetate) (Found: C, 48·8; H, 6·5. $C_7H_9NO_3,H_2O$ requires C, 48·6; H, 6·4%). Its picrate (ethanol) had m. p. 146° (Found: C, 40·2; H, 3·4. $C_{13}H_{12}N_4O_{10}$ requires C, 40·6; H, 3·2%). Under similar conditions and also after refluxing (2 hr.) the 3-chloro-4-nitro-compound gave 3-chloro-4-methoxypyridine *N*-oxide monohydrate, m. p. 115° (lit.,[5] m. p. 99—100°) (Found: C, 40·8; H, 4·9; N, 8·1. Calc. for $C_6H_6ClNO_2,H_2O$: C, 40·6; H, 4·5; N, 7·9%). Its picrate had m. p. 142° (lit.,[5] m. p. 152°) (Found: C, 37·2; H, 2·6. Calc. for $C_{12}H_9ClN_4O_9$: C, 37·1; H, 2·3%).

Fluoropicoline N-*Oxides.*—(*a*) 4-*Fluoro*-α-*picoline* N-*oxide.* A solution of 4-amino-α-picoline (10 g.) in hydroborofluoric acid (40%; 30 ml.) kept at −10° was diazotised by gradual addition of sodium nitrite (6·4 g.) with rapid stirring. The solution was washed repeatedly with ether, precipitating the diazonium borofluoride which decomposed spontaneously on standing. The mixture after complete decomposition was made alkaline (sodium hydroxide) and steam-distilled. Extraction of the distillate with ether gave 4-fluoro-α-picoline (3·15 g., 30·7%), b. p. 125—127° (lit.,[7] b. p. 128—132°). Profft and Richter's method [7] gave only a 9% yield. The picoline (3·3 g.) was oxidised with monoperphthalic acid (20 g.) in ether (200 ml.) at 0° for 1 week. Neutralisation with aqueous ammonia followed by chloroform extraction gave, on driving off the chloroform, 4-fluoro-α-picoline *N*-oxide (0·5 g., 13%) as a red oil, b. p. 126—130°/12 mm. (Found: fluorine present; N, 11·0%. Calc. for C_6H_6FNO: N, 11·0%). On reflux with excess of piperidine for 3 hr. and vacuum distillation of the residue after removal of solvent, 4-*piperidino*-α-*picoline* N-*oxide* was obtained as an oil. Its *picrate* had m. p. 110° (Found: C, 48·7; H, 4·5. $C_{17}H_{19}N_5O_8$ requires C, 48·6; H, 4·5%).

(*b*) 2-*Fluoropicolines.* Oxidation of 2-fluoro-4-methyl- and 2-fluoro-6-methylpyridine [22] with peracetic led to fluorine replacement and with monoperphthalic acid gave starting material.

3-*Fluoro*-2,6-*lutidine* N-*Oxide.*—A solution of 3-amino-2,6-lutidine (3 g.) in hydroborofluoric acid (40%; 10 ml.) was diazotised as described for 4-aminopicoline. The yellow diazonium

[22] A. Roe, P. H. Cheek, and G. F. Hawkins, *J. Amer. Chem. Soc.*, 1949, **71**, 4152.

borofluoride, m. p. 40° (decomp.), was filtered off, washed with dry ether and allowed to decompose in light petroleum (b. p. 60—80°). The petrol was evaporated and the residue made alkaline and steam-distilled to yield on ether extraction of the distillate 3-*fluoro*-2,6-*dimethylpyridine*, b. p. 140°/76 mm. (Found: C, 67·3; H, 6·8; N, 10·8. C_7H_8FN requires C, 67·2; H, 6·4; N, 11·2%). Its *picrate* had plates, m. p. 177° (Found: C, 44·4; H, 3·4. $C_{13}H_{11}FN_4O_7$ requires C, 44·1; H, 3·1%). The N-*oxide*, obtained as a hemihydrate by oxidation of an acetic acid solution of the fluoro-compound containing 30% aqueous hydrogen peroxide at 70—80° for 20 hr., had m. p. 53° (Found: C, 56·4; H, 6·05; N, 9·3. $C_7H_8FNO,0{\cdot}5H_2O$ requires C, 56·0; H, 6·0; N, 9·3%).

5-*Iodo*-α-*picoline* N-*Oxide*.—The iodopicoline was prepared by a literature method [23] and had m. p. 48° (lit.,[23] 48—49°) (Found: C, 32·7; H, 2·7. Calc. for C_6H_6IN: C, 32·9; H, 2·8%). Oxidation as above gave the N-*oxide* as needles, m. p. 192° (Found: C, 31·2; H, 2·7; N, 6·1. C_6H_6INO requires C, 30·7; H, 2·6; N, 6·0%).

Chloropyridine N-*Oxides*.—(*a*) 4-Chloro- and 4-chloro-3-methylpyridine *N*-oxide were prepared as described elsewhere.[9,10]

(*b*) 4-*Chloro*-α-*picoline* N-*oxide*. 4-Nitro-α-picoline *N*-oxide (30 g.) was dissolved in acetyl chloride (150 ml.) and the solution kept at 20—25° for 7 hr. The mixture was then poured into water (150 ml.) with cooling, and the resulting solution made alkaline (sodium hydrogen carbonate) and allowed to stand for 3 hr. Solids were filtered off and the filtrate was continuously extracted with hot chloroform. Evaporation of the solvent gave a red oil which on fractionation yielded 4-chloro-α-picoline *N*-oxide (7·0 g., 21%), m. p. 30°, b. p. 118—122°/2·3 mm. (lit.,[24] m. p. 37°).

(*c*) 4-*Chloro*-2,6-*dimethylpyridine* N-*oxide*. A solution of 2,6-dimethyl-4-nitropyridine *N*-oxide (17 g.) in acetyl chloride (110 ml.) was heated on a water-bath (5 hr.). Cooling followed by filtration gave the *N*-oxide hydrochloride as needles (from ethanol), m. p. 228° (decomp.) (lit.,[8] 185°) (Found: C, 43·1; H, 4·7. Calc. for $C_7H_9Cl_2NO$: C, 43·3; H, 4·7%). Treatment of the salt with aqueous sodium hydrogen carbonate gave the N-*oxide* as prisms, m. p. 101° from light petroleum (b. p. 80—100°) on quick cooling, or as needles, m. p. 87°, on slow cooling (Found: C, 53·4; H, 5·1; N, 8·8. C_7H_8ClNO requires C, 53·3; H, 5·1; N, 8·9%). The picrate had m. p. 147° (lit.,[8] 226° and lit.,[25] 147°).

The filtrate was evaporated and the residue triturated with a little acetone which on decantation left insoluble starting material (0·6 g.). From the acetone was obtained 4-*chloro*-2-*cyano*-6-*hydroxyiminomethylpyridine* N-*oxide* (II; R = CH:N·OH) (0·67 g.) as needles (from dioxan), m. p. 264° (Found: C, 42·9; H, 2·1; N, 20·9. $C_7H_4ClN_3O_2$ requires C, 42·6; H, 2·0; N, 21·3%). When heated with acetyl chloride or acetic anhydride (2 hr.) it gave the *acetyl derivative* as plates (light petroleum–ethyl acetate), m. p. 168° (Found: C, 45·2; H, 2·7. $C_9H_6ClN_3O_3$ requires C, 45·1; H, 2·5%).

4-*Fluoroquinaldine*.—A solution of 4-aminoquinaldine (5 g.) in fluoroboric acid (30 ml.) was treated as described for 4-fluoropicoline *N*-oxide to produce a diazonium borofluoride (decomp. 52°). The salt was decomposed in boiling light petroleum (b. p. 60—80°) and the mixture, after addition of sodium hydroxide, was steam-distilled to give an unstable hydrate of 4-fluoroquinaldine (1·76 g.), m. p. 40°. Treatment with ethanolic picric acid gave the *picrate* of 4-ethoxyquinaldine as plates, m. p. 228° (Found: C, 52·0; H, 3·9. $C_{18}H_{16}N_4O_8$ requires C, 51·9; H, 3·9%).

Hydrolysis of Halogeno-N-*oxides*.—A weighed amount of the *N*-oxide was refluxed for 4 hr. in 0·1N-methanolic sodium methoxide. The mixture was then treated with a known volume of 0·1N-hydrochloric acid and the excess of acid found by back-titration with standard sodium hydroxide. Results are given in Table 1.

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