762. *Heterocyclic Fluorine Compounds. Part V.*[1] *Fluoropyridine Oxides and Fluoroquinoline* N*-Oxides.*

By M. Bellas and H. Suschitzky.

3-Fluoropyridine and 3-, 5-, 6-, 7-, and 8-fluoroquinoline *N*-oxide have been prepared and the reactivity of the fluorine atom towards nucleophilic reagents has been studied.

It is known [2] that various substituents in certain positions of heteroaromatic *N*-oxides are prone to nucleophilic displacement. As this has not been demonstrated for fluorine we prepared a number of fluorine-substituted heterocyclic *N*-oxides, of which the only previously reported examples appear to be in the pyridine [3,4] and the phenazine [5] series. Our oxides were obtained by oxidation of the parent base with hydrogen peroxide in acetic acid, except 8-fluoroquinoline *N*-oxide which could only be made with monoperphthalic acid in ether. Attempts to introduce fluorine by a Balz–Schiemann reaction into the aminopyridine *N*-oxides failed, and treatment of 2-fluoropyridine with peracetic acid at 60° gave only 2-acetoxypyridine.

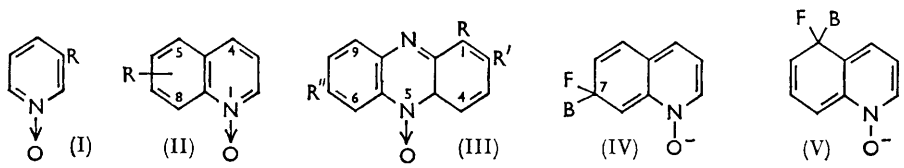
The fluorine atom in 3-fluoropyridine *N*-oxide (I; R = F) is readily replaced by nucleophilic reagents. Thus within minutes hot aqueous 0·1N-sodium hydroxide produces ionic fluorine and heating the compound with an excess of piperidine or in aqueous hydrazine affords 3-piperidino- (I; R = $C_5H_{10}N$) and the 3-hydrazino-pyridine *N*-oxide (I; R = $NH{\cdot}NH_2$), respectively. The ease of replacement is noteworthy considering that the rate of halogen displacement by piperidine in the corresponding chloro-compound (I; R = Cl) under similar conditions is too slow for kinetic assessment [6] and that the bromine atom

[1] Part IV, Barben and Suschitzky, *J.*, 1960, 672.
[2] Ochiai, *J. Org. Chem.*, 1953, **18**, 534; Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[3] Profft and Richter, *J. prakt. Chem.*, 1959, **9**, 164.
[4] Cava and Weinstein, *J. Org. Chem.*, 1958, **23**, 1616.
[5] Chernetsky, Yagupolsky, and Serebryany, *J. Gen. Chem.* (*U.S.S.R.*), 1955, **25**, 2161.
[6] Coppens, Declerck, Gillet, and Nasielski, *Bull. Soc. chim. belges*, 1961, **70**, 480.

in the *N*-oxide (I; R = Br) will only react with bases under forcing conditions.[7] This fluorine compound is in fact a feasible starting material for the preparation of 3-substituted pyridine *N*-oxides unobtainable by direct oxidation of the corresponding pyridine. The reactivity of the 3-fluorine atom shows the *N*-oxide group to be a stronger activating group than the nitro-group, in agreement with results obtained by rate studies of halogenopyridine *N*-oxides.[8]

The fluorine atom in 6- and 8-fluoroquinoline *N*-oxide (cf. II; R = F) is unaffected by nucleophilic reagents, but in the 3- and the 7-isomer it is about equally reactive towards aqueous sodium hydroxide, piperidine, and hydrazine. The 5-fluoro-isomer (cf. II) reacts only on prolonged boiling in aqueous sodium hydroxide or methanolic sodium methoxide and is almost inert towards the less nucleophilic piperidine.

The transmission of the polar effect of the *N*-oxide to certain positions in an adjacent benzene ring has been noted for quinoline [9] and phenazine [5,10–12] compounds. For instance, 2,7-dichlorophenazine 5-oxide (III; R = H, R′ = R″ = Cl) has a reactive 7-chlorine and an unreactive 2-chlorine atom,[12] a situation analogous to the 7- and 6-fluoroquinoline *N*-oxides (cf. II; R = F). The halogen in 1-fluorophenazine 5-oxide (III; R = F, R′ = R″ = H) is less reactive than in the 7-isomer [5] (III; R″ = F, R = R′ = H) which corresponds to the fluorine reactivity in 5- and 7-fluoroquinoline *N*-oxide, respectively.



The enhanced reactivity of the 7- over the 5-position in quinoline *N*-oxide and of the analogous phenazine structures is not easily explained. Theoretical predictions of *N*-oxide reactivity [13] are often at variance with experimental observations.[6] Results have recently been adduced to support the view that a transition state involving predominantly a *para*-quinonoid resonance structure is more stable than one partaking of an "*ortho*"-resonance structure.[14] If this argument is applied to the nucleophilic substitution of the 7- and 5-halogenoquinoline *N*-oxides it accounts qualitatively for the differential reactivity of the fluorine atoms, because the 7-isomer can be assigned the more stable "*para*"-(IV; B = nucleophilic reagent) and the 5-halogeno-compound the less stable "*ortho*"-transition state (V; B = nucleophilic reagent). The structures (IV and V) are arrived at invariably when the electron surplus of the approaching nucleophile (B in IV and V) is transferred to the exocyclic oxygen atom.

Experimental

3-Fluoropyridine and 3-, 5-, and 8-fluoroquinoline were prepared as described by Roe and Hawkins; [15] 6- and 7-fluoroquinoline were made by a Skraup reaction [16] on *p*- and *m*-fluoroaniline, respectively.

3-Fluoropyridine N-Oxide and its Derivatives.—An acetic acid solution (22 ml.) of 3-fluoropyridine (2·56 g., 0·026 mol.) containing 30% aqueous hydrogen peroxide (7 ml.) was kept at

[7] Murrey and Hauser, *J. Org. Chem.*, 1954, **19**, 2008.
[8] Okamoto, Hayatsu, and Baba, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 892.
[9] Okamoto, *J. Pharm. Soc. Japan*, 1951, **71**, 297.
[10] Vivian, *J. Amer. Chem. Soc.*, 1949, **71**, 1139; 1951, **73**, 457.
[11] Landquist, *J.*, 1956, 2550.
[12] Pachter and Kloetzel, *J. Amer. Chem. Soc.*, 1952, **74**, 971.
[13] Barnes, *J. Amer. Chem. Soc.*, 1959, **81**, 1935.
[14] Chapman and Russell-Hill, *J.*, 1956, 1563.
[15] Roe and Hawkins, *J. Amer. Chem. Soc.*, 1947, **69**, 2443; 1949, **71**, 1785.
[16] Sweinbjornsson, Bradlow, Oae, and Vanderwerf, *J. Org. Chem.*, 1951, **16**, 1450; Mirek, *Roczniki Chem.*, 1960, **34**, 1599.

70—80° for 20 hr. The solvent was removed under reduced pressure, and the residue neutralised with solid sodium carbonate and extracted with chloroform. After drying, evaporation of the extract left the *N*-oxide (1 g.) as hygroscopic white needles (from ethyl acetate–light petroleum), m. p. 64° (lit.,[4] 62—63°) (Found: C, 52·7; H, 4·0; N, 12·2. Calc. for C_5H_4FNO: C, 53·1; H, 3·6; N, 12·1%). The *N*-oxide (1 g.) was refluxed with piperidine (8 ml.) for 4 hr. Removing the excess of piperidine and recrystallising the residue from ethylacetate–light petroleum gave 3-*piperidinopyridine* N-*oxide* as needles, m. p. 86—87° (Found: N, 15·4. $C_{10}H_{14}N_2O$ requires N, 15·7%). Its *picrate*, from ethanol, had m. p. 193° (Found: C, 47·6; H, 4·2. $C_{16}H_{17}N_5O_8$ requires C, 47·2; H, 4·2%). Refluxing the oxide (0·5 g.) with hydrazine hydrate (1 ml.) in water (4 ml.) for 4 hr. gave, on evaporation, pale brown needles (from ethyl acetate–ethanol) of 3-*hydrazinopyridine* N-*oxide*, m. p. 148° (Found: C, 48·1; H, 5·4; N, 33·3. $C_5H_7N_3O$ requires C, 48·6; H, 5·6; N, 33·6%).

Fluoroquinoline N-*Oxides and their Derivatives*.—The 3-, 5-, 6-, and 7-isomer were made by oxidation of the parent fluoro-compound in acetic acid with hydrogen peroxide essentially as described for 3-fluoropyridine *N*-oxide. Purification was by sublimation *in vacuo*. 8-*Fluoroquinoline* N-*oxide* was obtained by adding 8-fluoroquinoline (1·75 g.) to ethereal monoperphthalic acid (6 g. in 30 ml.) at 0° and keeping the mixture at this temperature for one week. Isolation and purification were as for the other isomers. Details of the *oxides* are as tabulated.

Fluoroquinoline *N*-oxides and their picrates.

	Oxide			Oxide picrates §		
					Found (%)	
Posn. of F	M. p.	Found: * N (%)	Yield (%)	M. p.	C	H
3	118°	8·5	94	130°	45·8	2·4
5	176	8·4	60	136	46·3	2·4
6	100	8·6	30	130	46·3	2·0
7	67	7·1 †	63	Unstable	—	—
8	64 ‡	8·4	10·5	128	46·3	2·3

* C_9H_6FNO requires N, 8·6%; all contained fluorine. † Hydrated (Found: C, 56·8; H, 4·8. $C_9H_6FNO_3,1{\cdot}5H_2O$ requires C, 56·8; H, 4·8; N, 7·4%. ‡ Hygroscopic; the *hydrochloride* has m. p. 142° (Found: N, 7·0. C_9H_7ClFNO requires N, 7·3%). § $C_{15}H_9FN_4O_8$ requires C, 45·9; H, 2·3%; all were prepared in ethanol.

The following derivatives were obtained by treating the *N*-oxides possessing a reactive fluorine atom with a nucleophilic reagent as described for pyridine *N*-oxide above: 3-*Piperidinoquinoline* N-*oxide*, yellow prisms, m. p. 142° (Found: C, 73·8; H, 7·1. $C_{14}H_{16}N_2O$ requires C, 73·4; H, 7·2%) [*picrate*, needles, m. p. 182° (Found: C, 52·3; H, 4·3. $C_{20}H_{19}N_5O_8$ requires C, 52·5; H, 4·2%)]. 5-*Methoxyquinoline* N-*oxide*, m. p. 94° (from the oxide, sodium, and boiling methanol) (Found: C, 65·5; H, 5·6; N, 7·8. Calc. for $C_{10}H_9NO_2,0{\cdot}5H_2O$: C, 65·1; H, 5·5; N, 7·6%) (Okamoto [9] gives m. p. 105—106° for the anhydrous compound). 7-*Piperidinoquinoline* N-*oxide*, m. p. 142° (Found: C, 73·9; H, 6·9. $C_{14}H_{16}N_2O$ requires C, 73·8; H, 7·1%) [*picrate*, plates, m. p. 157° (Found: C, 52·1; H, 4·0. $C_{20}H_{19}N_5O_8$ requires C, 52·5; H, 4·2%)].

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ROYAL COLLEGE OF ADVANCED TECHNOLOGY,
SALFORD, LANCS.

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