870. *Heterocyclic Fluorine Compounds. Part VI.*[1] *Fluoroisoquinoline N-Oxides.*

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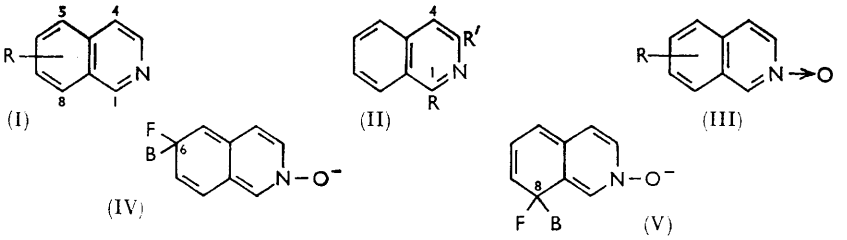
All monofluoroisoquinoline *N*-oxides, except the 1-isomer, have been prepared. The halogen reactivity towards nucleophilic reagents has been investigated.

In continuing the study of fluorine-substituted, heterocyclic *N*-oxides all monofluoroisoquinolines were prepared. The 1-isomer (I; R = F) could not be obtained by a Schiemann reaction on the 1-amino-compound, but was made in higher yield than reported [2] by replacement of the halogen in the 1-chloro-isomer with potassium fluoride in dimethyl sulphone, as described for 2-fluoroquinoline.[3] All other monofluoroisoquinolines were prepared by a Balz–Schiemann reaction on the appropriate amino-compound. For the preparation of the 8-amino-isomer (I; R = NH_2) catalytic dehalogenation of 8-amino-5-chloroisoquinoline according to Ahmad and Hey's method [4] worked best. Attempted removal of chlorine from the 5-chloro-8-nitro-isomer in presence of palladium and ammonium acetate [5] gave only the chloro-amine. Similarly other routes to the 8-fluoro-compound (I; R = F) such as selective dehalogenation of 5-chloro-8-fluoroisoquinoline in hydrazine [6] or a Pomeranz-Fritsch synthesis on *o*-fluorobenzylideneamino-acetal, failed. It is noteworthy that cyclisation of the *para*-isomer was also unsuccessful.[2] By a modification (cf. Experimental section) 4-isoquinolinediazonium borofluoride hitherto described as an unstable oil [2] was obtained as a stable salt.

The dihalogen compounds 1-bromo-3-fluoro- and 3-chloro-1-fluoro-isoquinolines were also made, the former by a Schiemann reaction on the 3-amino-1-bromoisoquinoline and the latter by replacement of the more reactive chlorine in the 1-position of 1,3-dichloroisoquinoline with anhydrous potassium fluoride.

Oxidation to *N*-oxides was carried out with hydrogen peroxide in acetic acid as previously described.[1] Neither 1,3-dichloro- nor 1-bromo-3-fluoro-isoquinoline could be oxidised even with trifluoroacetic acid as solvent which was successfully used in the case of 2,6-dibromopyridine.[7] Oxidation of 1-fluoro- and 1-fluoro-3-chloro-isoquinolines produced the corresponding isocarbostyril (II; R = OH, R′ = H or R = OH, R′ = Cl) as expected since the 1-fluoro-atom is readily displaced in warm water or dilute acid. For similar reasons the attempted conversion of 1-chloroisoquinoline into its *N*-oxide was unsuccessful.[8]



Apart from the 1-fluoro-isomer none of the fluoroisoquinolines had a replaceable halogen atom when treated with hot sodium hydroxide. Since 6-fluoroisoquinoline *N*-oxide

[1] Part V, Bellas and Suschitzky, *J.*, 1963, 4007.
[2] Roe and Teague, jun., *J. Amer. Chem. Soc.*, 1951, **73**, 687.
[3] Hamer, Link, Jurjevich, and Vigo, *Rec. Trav. chim.*, 1962, **81**, 1058.
[4] Ahmad and Hey, *J.*, 1961, 3882.
[5] Osborn and Schofield, *J.*, 1956, 4191.
[6] Mosley, *Chem. and Ind.*, 1959, **44**, 1348.
[7] Evans, van Ammers, and den Hertog, *Rec. Trav. chim.*, 1959, **78**, 408.
[8] Robison and Robison, *J. Org. Chem.*, 1958, **23**, 1071.

possesses a very labile fluorine atom (cf. below), it was thought that the halogen in 6-fluoroisoquinoline might be the most mobile of the stable isomers. Fluoride ions were in fact detected when an acetic acid solution of this compound was heated for several hours in the presence of sodium acetate and aniline. This weakly acidic buffer mixture helped to enhance the activating polar effect of the heterocyclic nitrogen on the halogen by quaternisation without impairing the nucleophilic power of aniline by protonation. A similar approach has recently been used to prepare 7-arylamino-compounds from 7-chloro-4-hydroxyquinaldine.[9]

In the *N*-oxides the fluorine atom in the 5- and 7-positions (cf. III; R = F) was unaffected by nucleophilic reagents, a situation which is analogous to the unreactive 6- and 8-fluoroquinoline *N*-oxides.[1] The polar effect of the *N*-oxide group is, however, transmitted to the 6- and 8-positions of the isoquinoline structure. Thus the 6-fluoro-isomer (cf. III; R = F) readily gave a piperidino-derivative (III; R = $C_5H_{10}N$·) on reflux with the base. The 8-fluoro- and the 5-chloro-8-fluoro-isoquinoline *N*-oxides remained unaffected in boiling piperidine or dilute sodium hydroxide, but could be made to react with boiling methanolic sodium methoxide to give the corresponding methoxide. The difference in the reactivity of the two isomers can be compared with the situation observed in the *N*-oxides of 7- and 5-fluoroquinoline,[1] respectively. It can also be explained similarly,[1] because replacement of the more reactive 6-fluoro-atom involves the more stable "*para*"- (IV; B = nucleophilic reagent), and replacement of the 8-fluoro-atom involves the less stable "*ortho*"-transition state (V; B = nucleophilic reagent).

The halogen in both the 3- and the 4-fluoroisoquinoline *N*-oxides (III; R = F) was readily replaced by warm N/10-sodium hydroxide, and piperidine slowly reacted with the 3-fluoro-isomer even at room temperature. It is of interest to note that 3-fluoroquinoline *N*-oxide,[1] which can be regarded as positional analogue to the 4-fluoroisoquinoline *N*-oxide, is unaffected by N/10-sodium hydroxide. Moreover, 3-chloro- and 4-bromo-isoquinoline *N*-oxides were hydrolysed only by 2N-sodium hydroxide or other nucleophiles (cf. Experimental section) at reflux temperatures. The high reactivity of the fluorine in the 3- and 4-positions make these *N*-oxides potential starting materials for the preparation of correspondingly substituted isoquinolines by nucleophilic displacement.

The inductive effect of the *N*-oxide group on the adjacent 3-position clearly accounts for the lability of the 3-fluoro-isomer. The high mobility in the 4-position is, however, difficult to explain on the basis of the inductive effect alone and could be partly due to extra resonance stability of the transition state involved in nucleophilic displacement because of the adjacent benzene ring.[10]

Two predictions [11,12] of nucleophilic reactivity based on recent calculations of electron densities in isoquinoline *N*-oxide are at variance with each other and not in full agreement with our observations of fluorine reactivity. Kubota [12] recognises the 4-position as a nucleophilic centre equal to that of the 1-position, but ascribes similar anionic reactivity to positions 5 and 8, while Tsoucaris [11] asserts equal reactivity for positions 6 and 8, but does not consider a reactive position 4. By contrast the positional order of nucleophilic reactivity in isoquinoline *N*-oxide based on experimental fluorine mobility is $1 \gg 3 > 4 > 6 > 8$.

Experimental

Fluoroisoquinolines.—(*a*) The 3- and the 5-fluoroisoquinolines were prepared as described by Roe and Teague.[2]

(*b*) 5-Chloro-8-fluoroisoquinoline and 4-, 6-, and 7-fluoroisoquinolines were made by a modification of the above procedure as exemplified by the following preparation of the 7-fluoro-isomer. A solution of pure, sublimed 7-aminoisoquinoline [4] (7 g.) in hydroborofluoric acid

[9] Buchmann and Grimm, *J. prakt. Chem.*, 1962, [4], **17**, 135.
[10] Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, 1949, p. 174.
[11] Tsoucaris, *J. Chim. phys.*, 1961, **58**, 613.
[12] Kubota, *Bull. Chem. Soc. Japan*, 1962, **35**, 946.

(30 ml., 40%) was diazotised at −10° with vigorous stirring by addition of finely powdered sodium nitrite (3·5 g.). When diazotisation was complete the diazonium borofluoride did not separate. The reaction mixture was washed with small portions of ether (3 × 10 ml.) and then agitated with a mixture of ethanol and ether (20 ml., equal volumes). This procedure precipitated the diazonium borofluoride (15 g.) m. p. 133° (decomp.). It was washed on the filter with a little dry ether, dried *in vacuo*, and then made to decompose in boiling cumene. The reaction mixture was acidified with hydrochloric acid and the solvent removed by steam-distillation. The residue was made alkaline with sodium hydroxide and steam-distilled yielding by extraction of the distillate (ether) *7-fluoroisoquinoline* (1 g.), b. p. 256—258°, $n_D^{20} = 1{\cdot}6057$ (cf. Table 1 for analysis). *5-Chloro-8-fluoroisoquinoline* was obtained in 21% yield, m. p. 93° (Found: C, 60·0; H, 2·9; N, 7·9. C_9H_5ClFN requires C, 59·5; H, 2·8; N, 7·7%). Its *picrate* had m. p. 203° (Found: C, 43·9; H, 2·0. $C_{15}H_8ClFN_4O_7$ requires C, 43·9; H, 2·0%). 4-Isoquinolinediazonium borofluoride had decomp. temp. 82° and yield of the 4-fluoro-isomer was 45%. Details of other preparations are given in Table 1.

TABLE 1.

Fluoroisoquinolines and their picrates.

Posn. of F	M. p. (b. p.)	Found: * N (%)	Yield † (%)	Decomp. temp. of ArN_2BF_4	Picrates § M. p.	Picrates § Found (%) C	Picrates § Found (%) H
6	52°	9·2	54	125°	204	48·3	2·4
7	27	9·1 ‡	15	133	219	47·8	2·4
8	30 ¶ (233)	9·5	89	158	196	47·8	2·6

* C_9H_6FN requires N, 9·5%. † Based on amine. ‡ Hydrated (Found: C, 69·1; H, 4·0. $C_9H_6NF,0{\cdot}5H_2O$ requires C, 69·2; H, 4·5%). § $C_{15}H_9FN_4O_7$ requires C, 47·9; H, 2·4%; all were made in ethanol. ¶ Dyke [16] reports b. p. 87—88°/4 mm. and m. p. of picrate as 200—201°.

8-Fluoroisoquinoline was made by heating its diazonium borofluoride on an oil-bath at 150°. The required amine was obtained from 8-amino-5-chloroisoquinoline by catalytic dehalogenation.[4] Reductive dehalogenation of 5-chloro-8-nitroisoquinoline gave only a 5% yield of the 8-amino-compound.

In another attempt to prepare the 8-fluoro-compound *o*-fluorobenzaldehyde (20 g.) made as described for the *meta*-isomer [13] was condensed with amino-acetal (20 g.) for 2 hr. at 60°. Ether extraction followed by distillation of the extract gave *o-fluorobenzylidineaminoacetal* as pale yellow oil (22 g.), b. p. 160°/15 mm. (Found: C, 64·8; H, 8·2; N, 6·3. $C_{13}H_{18}FNO_2$ requires C, 65·2; H, 7·6; N, 5·9%). Cyclisation under Pomeranz–Fritsch conditions failed.

(*c*) 1-Bromo-3-fluoroisoquinoline was made in the following way. By cooling a warm solution of 3-amino-1-bromoisoquinoline [14] (1·75 g.) in borofluoric acid (6 ml.) a yellow fluoroborate was produced. A suspension of the dried salt in benzene was diazotised at room temperature with finely powdered sodium nitrite (0·8 g.). The solvent was driven off and the reaction mixture after neutralisation (aqueous sodium hydroxide) steam-distilled to give *1-bromo-3-fluoroisoquinoline* (0·5 g.), m. p. 60° purified by sublimation *in vacuo* (Found: C, 48·0; H, 2·2; N, 6·0. C_9H_5BrFN requires C, 47·8; H, 2·2; N, 6·2%).

(*d*) 1-Fluoro- and 3-chloro-1-fluoro-isoquinolines were made by chlorine replacement as illustrated by the preparation of the latter compound. A mixture of 1,3-dichloroisoquinoline (4·3 g.) prepared by Gabriel's method,[15] dimethyl sulphone (28 g.), and potassium fluoride (8 g.) was kept on an oil-bath at 180—190°. After 15 hr. more potassium fluoride was added (2 g.) and the total heating time was 40 hr. *3-Chloro-1-fluoroisoquinoline* (1·07 g., 23%), m. p. 67° was obtained by steam-distilling the reaction mixture (Found: C, 59·9; H, 3·2; N, 7·5. C_9H_5ClFN requires C, 59·5; H, 2·8; N, 7·7%). After 15 hr. reflux the yield was only 17%. It gave 3-chloro-1-hydroxyisoquinoline, m. p. 218° (lit.,[15] m. p. 219—220°) on being refluxed for 10 min. with aqueous hydrochloric acid (10%).

1-Fluoroisoquinoline (1·34 g., 73·6%) was obtained from 1-chloroisoquinoline (2 g.) by this method when refluxed for 90 hr., b. p. 235° (Found: C, 72·8; H, 4·4; N, 9·6. Calc. for C_9H_6FN:

[13] Pelchowicz, Kaluszyner, and Bentov, *J.*, 1961, 5418.
[14] Johnson and Nasutavicus, *J. Org. Chem.*, 1962, **27**, 3953.
[15] Gabriel, *Ber.*, 1886, **19**, 2354.
[16] Belsten and Dyke, *J.*, 1964, 22.

C, 73·4; H, 4·1; N, 9·5%), n_D^{20} 1·5853. It gave isocarbostyryl m. p. 207° when kept for 0·5 hr. in warm water.

Fluoroisoquinoline N-*Oxides and their Derivatives*.—Oxidation of the parent fluoro-compound was carried out in acetic acid with hydrogen peroxide as described previously.[1] Purification was by sublimation *in vacuo*. Details of the fluorine-substituted *oxides* are given in Table 2. 3-Chloro- and 4-bromo-isoquinoline *N*-oxides had m. p.s as given in the literature.[17,18] The former gave a *picrate*, m. p. 159° (Found: C, 44·2; H, 2·3. $C_{15}H_9ClN_4O_8$ requires C, 44·1; H, 2·2%) and the latter a *picrate*, m. p. 134° (Found: C, 39·9; H, 2·2. $C_{15}H_9BrN_4O_8$ requires C, 39·8; H, 2·0%).

5-*Chloro*-8-*fluoroisoquinoline* N-*oxide* (46%) had m. p. 195° (Found: N, 7·1. C_9H_5ClFNO requires N, 7·1%). Its *picrate* had m. p. 152° (Found: C, 42·3; H, 2·1. $C_{15}H_8ClFN_4O_8$ requires C, 42·2; H, 1·9%).

TABLE 2.

Fluoroisoquinoline *N*-oxides and their picrates.

	Oxide			Oxide picrates †		
					Found (%)	
Posn. of F	M. p.	Found * N (%)	Yield (%)	M. p.	C	H
3	163°	8·4	23	153°	46·2	2·3
4	173	8·3	72	162	45·7	2·5
5	145	8·7	78	157	46·0	2·5
6	222	8·4	45	172	45·7	2·0
7	184	8·3	82	138	45·6	2·8
8	175	8·3	63	158	45·9	2·7

* C_9H_6FNO requires N, 8·6%; all contained fluorine. † $C_{15}H_9FN_4O_8$ requires C, 45·9; H, 2·3%; all were made in ethanol.

TABLE 3.

Derivatives of isoquinoline *N*-oxides.

		Found (%)			Reqd. (%)	
Substituent	M. p.	C	H	Formula	C	H
3-$C_5H_{10}N$	136° *	73·7	7·2	$C_{14}H_{16}N_2O$	73·6	7·1
4-$C_5H_{10}N$.....	136 †	73·5	7·1	,,	,,	,,
6-$C_5H_{10}N$	—‡	—	—	—	—	—
3-NH_2·NH	148 §	—	—	—	—	—
4-NH_2·NH	200	58·7	5·6	$C_9H_9N_3O,0·5H_2O$	58·4	5·4
3-OH	194	67·1	4·4	$C_9H_7NO_2$	67·0	4·4
4-OH	233	60·1	4·9	$C_9H_7NO_2,H_2O$	60·3	5·1
5-Cl-8-MeO	240	57·2	3·9	$C_{10}H_8ClNO_2$	57·3	3·9
8-MeO	127	65·0	5·5	$C_{10}H_9NO_2,0·5H_2O$	65·1	5·5

* Its *picrate* had m. p. 164° (Found: C, 52·4; H, 4·3. $C_{20}H_{19}N_5O_8$ requires C, 52·5; H, 4·2%). † Its *picrate* had m. p. 167° (Found: C, 52·6; H, 4·4%). ‡ Unstable oil. Its *picrate* had m. p. 194° (Found: C, 52·0; H, 4·5%) and its *dihydrochloride* had m. p. 170° (Found: N, 9·2. $C_{14}H_{18}Cl_2N_2O$ requires N, 9·3%). § Unsuitable for analysis. Its *acetone* derivative has m. p. 95° (Found: N, 19·5. $C_{12}H_{13}N_3O$ requires N, 19·5%).

The *N*-oxides with a reactive fluorine atom as well as 3-chloro- and 4-bromo-isoquinoline *N*-oxide were treated with various nucleophilic reagents (piperidine, ethanolic solution of hydrazine hydrate, aqueous sodium hydroxide and methanolic sodium methoxide) to yield the derivatives given in Table 3.

We thank the Governors of the Royal College of Advanced Technology for a studentship (to M. B.) and Dr. S. F. Dyke for the communication of work before publication.

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[*Received, January 29th*, 1964.]

[17] Robison and Robison, *J. Amer. Chem. Soc.*, 1958, **80**, 3443.
[18] Ochiai and Ikehara, *Pharm. Bull.* (*Japan*), 1954, **2**, 72.