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Syntheses of Heterocyclic Compounds. Part XIX.[1] Preparation and Nucleophilic Reactions of Polyhalogeno-substituted *N*-Oxides

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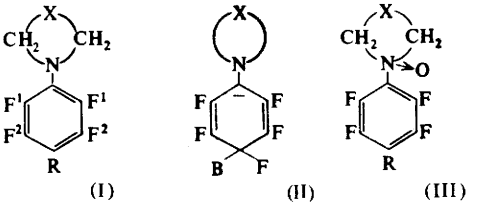
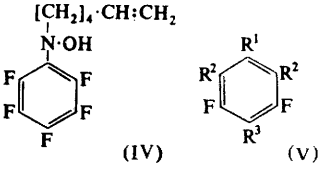
The preparation and reactions of various polyfluorophenyl-substituted *N*-oxides with secondary and primary amines are described. The former give predominantly di-*ortho*- and the latter mono-*o*-substituted products. *p*-Substitution prevails, however, with methanol or water as solvent. Structural assignment of the products was made on the basis of their ^{19}F nuclear magnetic resonance spectra and a mechanism to account for the orientation is discussed.

HEXAFLUOROBENZENE reacted smoothly with various heteroparaffinic amines (pyrrolidine, piperidine, hexamethylene imine, and morpholine) at water-bath temperature to give the corresponding pentafluorobenzenes (I; R = F, X = $[CH_2]_{2-4}$ and $CH_2{\cdot}O{\cdot}CH_2$) in good yield with only very small amounts of *p*-disubstituted products. The bromo-, the chloro-, and the iodo-pentafluorobenzene gave also high yields of the corresponding *p*-substituted tetrafluorobenzenes (I: R = Br, Cl, or I; X as before) and no further substitution occurred even on prolonging the reaction time. Treatment of the pentafluorobenzenes (I; R = F, X as before) with various nitrogen-containing heteroparaffins at reflux temperatures led predominantly to *p*-substituted products. Structures of all these tetrafluorobenzenes followed from their ^{19}F n.m.r. spectra which according to the nature of the substituents showed chemical-shift differences between the F^1 and F^2 fluorines [cf. (I)]. The outcome of further substitution in our *N*-pentafluorophenyl heterocycles (I; R = F) is analogous to that observed for pentafluoro-*N*-dimethylaniline [2] and can be rationally interpreted on the grounds that were used by Burdon [3] to explain the result of nucleophilic replacement in the latter compound: owing to interaction with the "*ortho*-fluorines" the heteroparaffinic substituent is twisted out of the ring plane. This reduces the otherwise strong electron-repulsion of nitrogen ($I\pi$) to below that of fluorine and consequently renders the *p*-quinonoid transition state (II; B = base, X = $[CH_2]_n$) which precedes *p*-substitution, more stable than any other in which the negative charge would be on a fluorine-substituted carbon atom. Hexamethylene imine gave the lowest yield of all the heteroparaffins unless the reaction time was considerably increased. Steric hindrance is probably responsible for the reduced nucleophilicity since morpholine, which is a weaker base, gave still satisfactory yields.





The *N*-oxides of several pentafluoro- (III; R = F) and tetrafluoro-phenyl (III; R = Br, Cl, or I) heterocycles were prepared using cold performic acid, usually in good yield (cf. Table 4). The pyrrolidine *N*-oxides (III; R = Cl or F, X = $[CH_2]_2$) were unstable and the hexamethyleneimine compound (I; R = F, X = $[CH_2]_4$) underwent ring-opening on oxidation even at low temperature and formed an unsaturated hydroxylamine (IV) by a Cope elimination.[4] Its infrared spectrum agreed with the assigned structure since it showed bands at 3572 (OH) and 3081 cm.$^{-1}$ (CH:CH_2). Its ^1H n.m.r. spectrum had a peak at τ 3·55 (OH, confirmed by deuteriation), a triplet at τ 6·65 (CH_2 next to nitrogen) and a quartet at τ 7·9 assignable to allylic CH_2. The different behaviour of this heterocycle towards oxidation

[1] Part XVIII, G. S. Puranik and H. Suschitzky, *J. Chem. Soc.* (*C*), 1967, 1006.
[2] J. G. Allen, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1965, 6329.
[3] J. Burdon, *Tetrahedron*, 1965, **21**, 3373.
[4] A. C. Cope and E. R. Trambuk, *Org. Reactions*, 1960, **11**, 317.

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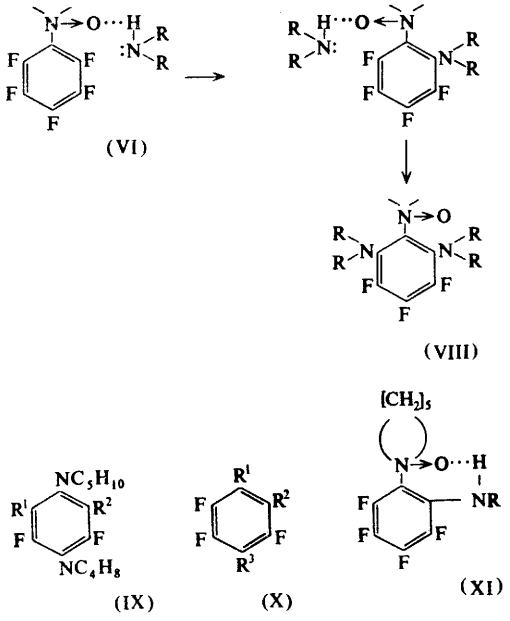
is undoubtedly due to greater steric interaction of the seven-membered ring with the *ortho*-fluorines than the smaller rings (as shown by Stuart–Briegleb models) combined with the favourable position of the hydrogens in the β-methylene group for a Cope elimination. The chloro-compound (I; R = Cl, X = $[CH_2]_4$) gave an analogous result. The *N*-oxides were readily deoxygenated with dilute sulphurous acid.

We have commented in a preliminary Communication [5] on the great facility with which these *N*-oxides undergo nucleophilic substitution reactions. With secondary amines, used neat or as a benzene solution, di-*o*-substitution occurred in an exothermic reaction which after deoxygenation gave the *vic*-trisubstituted benzenes (V; R^1 and R^2 = tertiary amino, R^3 = halogen) in excellent yield. Examples of these reactions are given in Table 5. The constitution of the products follows from their ^{19}F n.m.r. spectra in chloroform with C_6F_6 as internal standard: the trifluoro-compounds (V; R^1 and R^2 = tertiary amino, R^3 = F) show doublet and triplet bands of intensities 2 and 1 respectively with *J* (c./sec.) ~20 for *ortho*-fluorine coupling (cf. Table 6). We ascribe this unusual substitution pattern mainly to the operation of two factors. One is the strong nucleophilic activation of the *ortho*-fluorines by the inductive effect of the N ⟶ O group and the other is hydrogen-bonding between the secondary amine and the *N*-oxide group which "trues up" the oncoming reagent for *o*-substitution as set out (VI ⟶ VIII). To our know-



ledge these are the only reported examples of an almost exclusive di-*o*-substitution. Pentafluoronitrobenzene has recently been described as yielding a high proportion of mono-*o*-substituted product with ammonia or methylamine for similar reasons [6] but the bulkier dimethylamine gave a much reduced yield. Moreover, tetrafluoro-4-nitropyridine reacts with an ethereal solution of ammonia to give 3-aminotrifluoro-4-nitropyridine in almost 50% yield.[7]

However, in hydroxylic solvents (water or alcohol) the substitution pattern changed since *p*-replacement predominated. For instance, the piperidine *N*-oxide (III; R = F, X = $[CH_2]_3$) gave with a cold, aqueous solution of piperidine the 1,4-dipiperidinobenzene (I; R = $C_5H_{10}N$, X = $[CH_2]_3$) in over 80% yield, a trend which was also observed for other bases and morpholine *N*-oxide (cf. Table 7). It can reasonably be argued that the hydroxylic solvent competes successfully with the nucleophilic reagent for hydrogen bonding at the N ⟶ O group thereby preventing step (VI) and leading to *p*-substitution as is normally observed with $C_6F_5NR_2$ compounds.[3] It is noteworthy that sodium methoxide, which cannot form a hydrogen bond with the substrate (III; R = F, X = $[CH_2]_3$), substitutes predominantly in the *p*-position with methanol or benzene as solvent. This result is similar to that obtained in the reaction of methoxide with pentafluoronitrobenzene in ether.[8]

We attempted to introduce more than two substituents into the *N*-oxides (III) by raising the reaction temperature which led, however, to an inseparable mixture of products. Extension of the reaction time was more successful and gave the tetrasubstituted difluorobenzene (V; $R^1 = R^2 = R^3 = C_5H_{10}N$) from the piperidine *N*-oxide (III; R = F, X = $[CH_2]_3$) and piperidine. By carrying out the substitution on the *N*-oxide (III; R = F, X = $[CH_2]_3$) stepwise with different bases the difluoro-compound (IX; $R^1 = R^2$ = morpholino) was produced. Its ^{19}F n.m.r. spectrum was consistent with the symmetrical structure as it gave only one signal at −30·2 p.p.m. The alternative structure in which the two fluorines are adjacent would be expected to show doublets for the *ortho*-fluorines (cf. below). In another experiment the piperidine *N*-oxide (III; R = F, X = $[CH_2]_3$) was made to react with pyrrolidine in methanol and the isolated *p*-substituted *N*-oxide (III; R = C_4H_8N, X = $[CH_2]_3$) treated with morpholine to give the trifluoro-compound (IX; R^1 = F, R^2 = morpholino). Its structure was confirmed by analysis and its ^{19}F n.m.r. spectrum which showed the *ortho*-fluorines (cf. IX; R^1 = F) as two doublets at −9·19 and −10·6 p.p.m. with *J* (c./sec.) = 18 for *ortho*-fluorine coupling. Thus introduction of an electron-releasing substituent *para* to the *N*-oxide group (III; R = C_4H_8N) appears to reduce the (−*I*) effect of the *N*-oxide sufficiently to give a mono-*o*-substituted product only.

We also studied reactions of the piperidine *N*-oxide (III; R = F, X = $[CH_2]_3$) with primary amines under various conditions. Without a solvent, or in benzene

[5] M. Bellas and H. Suschitzky, *Chem. Comm.*, 1965, 367.
[6] G. M. Brooke, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1961, 802; J. G. Allen, J. Burdon, and J. C. Tatlow, *ibid.*, 1965, 1045.
[7] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1966, 220.
[8] J. Burdon, D. Fisher, D. King, and J. C. Tatlow, *Chem. Comm.*, 1965, 65.

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at room temperature, benzylamine gave (after sulphur dioxide was passed through the reaction mixture) the mono-*o*-substituted tetrafluorobenzene (X; $R^1 = C_5H_{10}N$, $R^2 = Ph{\cdot}CH_2{\cdot}NH$, $R^3 = F$). In water *para*-substitution was again prevalent yielding the symmetrical tetrafluorobenzene (I; $R = Ph{\cdot}CH_2{\cdot}NH$, $X = [CH_2]_3$). Analogous results were observed with butylamine and cyclohexylamine in benzene. We attribute the non-occurrence of di-*ortho*-replacement when primary amines are used partly to hydrogen bonding between the N ⟶ O group and the substituent [cf. (XI)] This prevents the *N*-oxide group from "guiding" another amine molecule into the vacant *o*-position as in the reaction with secondary amines [(VI) ⟶ (VIII)]. The infrared spectrum of the *N*-oxide (XI; $R = Ph{\cdot}CH_2{\cdot}NH$) supports the existence of an intramolecular hydrogen bridge as the usual NH absorption is not visible in the 3300—3450 $cm.^{-1}$ region. Hydrogen bonding has undoubtedly shifted the N–H stretching band which had thus become buried among the C–H stretching vibrations of the piperidine ring (3100—2700 $cm.^{-1}$). On deoxygenation, however, the N–H bond reappeared at *ca.* 3300 $cm.^{-1}$. The benzylamine-substituted *N*-oxide (XI; $R = Ph{\cdot}CH_2{\cdot}NH$) proved resistant to further substitution even when heated with piperidine on the water-bath. This loss of *N*-oxide reactivity is due to the presence of the secondary amine moiety. Unlike a tertiary amine substituent it deviates little from the plane of the fluorobenzene ring and its mesomeric electron-release is thus more effective in reducing the reactivity of the ring towards nucleophiles.

Reaction of the *N*-oxide (III; $R = F$, $X = [CH_2]_3$) with aqueous or liquid ammonia was slow and gave a complex mixture of products. However, on passing the dry gas for several days through a benzene solution of the *N*-oxide, practicable yields of the *N*-oxide (XI; $R = H$) were obtained which gave the 2-amino-compound (X; $R^1 = C_5H_{10}N$, $R^2 = NH_2$, $R^3 = F$) after deoxygenation.

EXPERIMENTAL

Fluorine n.m.r. spectra were measured at 100 Mc./sec. in deuteriochloroform solution with hexafluorobenzene as internal standard.

Reaction of Polyfluorobenzenes with Nitrogen-containing Heteroparaffins.—(*a*) A mixture of hexafluorobenzene (10·4 g.) and the required amine (7 ml.) was kept at 70—80° overnight. On pouring the reaction mixture into aqueous sodium carbonate solution (*ca.* 10%) an oil separated which was taken up in ether. The solvent was driven off and the amine obtained by distillation *in vacuo*. A small amount of *p*-disubstituted compound remained as a residue. Results are set out in Table 1. Reaction with pyrrolidine was exothermic and complete within 0·5 hr.

(*b*) A mixture of a pentafluorohalogenobenzene (10 g.) and required amine (20 ml.) was kept on a water-bath for *ca.* 5 hr., except for the reactions with pyrrolidine and piperidine which were exothermic and complete in 0·25 and 1 hr., respectively. The product was obtained as in (*a*) and results are given in Table 2.

(*c*) The pentafluorobenzenes listed in Table 1 and obtained in (*a*) were dissolved in an excess of the required secondary amine and kept under reflux for 6 hr. The reaction mixture was poured into water and the product obtained by extraction with ether followed by evaporation of the solvent and recrystallisation from light petroleum (b. p. 60—80°). Details of the compounds are given in Table 3.

TABLE 1

Pentafluorobenzenes with a heteroparaffinic substituent (I; R = F)

Product (I) X	Yield (%)	B. p.	Found (%) C	H	Formula	Reqd. (%) C	H
$[CH_2]_2$	70	76°/3 mm.	50·7	3·7	$C_{10}H_8F_5N$	50·6	3·4
$[CH_2]_3$	80	96/10 mm.	53·0	4·1	$C_{11}H_{10}F_5N$	52·6	4·0
$[CH_2]_4$	60	82/1 mm.	54·9	5·0	$C_{12}H_{12}F_5N$	54·4	4·5
$[CH_2{\cdot}O{\cdot}CH_2]$	67	77/2 mm.	47·6	3·6	$C_{10}H_8F_5NO$	47·5	3·2

Preparation of N-*Oxides.*—The required amine-substituted pentafluorobenzene (1 part) (cf. Tables 1 and 2) dissolved in formic acid (98%; 10 parts) and hydrogen peroxide (100 vol.; 1 part) was slowly added to the mixture with stirring. If any solid appeared at this stage, more formic acid was added to produce a solution. The reaction mixture was then kept in a refrigerator overnight and finally poured into twice its own volume of chloroform. An excess of a concentrated aqueous solution of potassium carbonate was added with stirring while keeping the temperature below 10°. The chloroform layer was separated and the aqueous layer extracted with small portions of chloroform (3×) which were combined with the main extract. The latter was then washed with dilute aqueous potassium carbonate, dried ($MgSO_4$), and finally evaporated under reduced pressure. The crude *N*-oxide thus obtained was purified by stirring its fine suspension in ether for 1—2 hr. It was then filtered off and if necessary recrystallised from a mixture of ethyl acetate and benzene or chloroform. Details of the various *N*-oxides and in some cases of their picrates prepared from benzene are given in Table 4. The pentafluorobenzenepyrrolidine *N*-oxide (III; $R = F$, $X = [CH_2]_2$) was unstable. Oxidation of the hexamethyleneimino-compounds (III; R = F or Cl, $X = [CH_2]_4$) gave the *pentafluorohydroxylamine* (IV), m. p. 38° (43%) (Found: C, 51·0; H, 4·5. $C_{12}H_{12}F_5NO$ requires C, 51·3; H, 4·3%) and the analogous *p-chlorotetrafluorohydroxylamine*, m. p. 51° (14%) (Found: C, 48·9; H, 4·5. $C_{12}H_{12}ClF_4NO$ requires C, 49·1; H, 4·1%).

Reactions of N-*Oxides with Secondary Bases.*—(*a*) The *N*-oxide (1 part) was dissolved in the required secondary amine (5 parts). After the exothermic reaction had subsided (10—20 min.) the solution was neutralised with aqueous sulphuric acid (4N). After addition of an aqueous, saturated solution of sulphurous acid (5 parts) the reaction mixture was stirred and warmed on a water-bath for 15 min. to effect deoxygenation. The solution was then made neutral with an aqueous solution of sodium hydroxide (10%) and the precipitated product filtered off, dried, and purified by recrystallisation (ethanol) and if necessary by sublimation. Results are summarised in Table 5.

(*b*) *Reactions in Various Solvents.*—The pentafluoropiperidine *N*-oxide and its morpholino-analogue were made to react with nucleophiles in various solvents. The results are set out in Table 7.

(*c*) *Miscellaneous Reactions.*—A solution of the *N*-oxide of pentafluoropiperidinobenzene (1·0 g.) in benzene was

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TABLE 2

Tetrafluorohalogenobenzenes with a heteroparaffinic substituent (I; R = halogen) and their ^{19}F chemical shifts from C_6F_6 (p.p.m.)

Product (I)		Yield	M. p. or	Found (%)			Reqd. (%)		^{19}F Chemical shifts	
R	X	(%)	b. p./mm.	C	H	Formula	C	H	F^1 *	F^2 *
Cl	$[CH_2]_2$	98	56°	47·6	3·1	$C_{10}H_8ClF_4N$	47·4	3·1	−7·8	−13·9
Cl	$[CH_2]_3$	81	82/1·2	49·9	3·7	$C_{11}H_{10}ClF_4N$	49·4	3·8	−10·4	−14·4
Cl	$CH_2{\cdot}O{\cdot}CH_2$	85	61	45·0	3·3	$C_{10}H_8ClF_4NO$	44·6	3·0	−10·7	−15·1
Cl	$[CH_2]_4$	67	108/1·5	51·6	4·6	$C_{12}H_{12}ClF_4N$	51·2	4·3	−11·4	−14·5
Br	$[CH_2]_3$	100	43	42·1	3·2	$C_{11}H_{10}BrF_4N$	42·3	3·2	−12·4	−26·1
I	$[CH_2]_3$	98	60	37·0	2·9	$C_{10}H_{10}F_4IN$	36·8	2·3	−13·3	−38·8
Br	$[CH_2]_2$	98	66	40·7	2·6	$C_{10}H_8BrF_4N$	40·3	2·7	−7·8	−24·2
Cl	$CH_2{\cdot}N(Me){\cdot}CH_2$	70	118/1·8	47·1	4·2	$C_{11}H_{11}ClF_4N_2$	46·7	3·9		

* Doublets.

TABLE 3

Tetrafluorobenzenes with two heteroparaffinic substituents (I; R = heteroparaffin) and their ^{19}F chemical shifts from C_6F_6 (p.p.m.)

Product (I)		Yield	M. p.	Found (%)			Reqd. (%)		^{19}F Chemical shifts	
R	X	(%)	(°c)	C	H	Formula	C	H	F^1	F^2
C_4H_8N	$[CH_2]_2$	80	88	58·7	5·8	$C_{14}H_{16}F_4N_2$	58·3	5·6	−7·7	−7·7
$C_5H_{10}N$	$[CH_2]_3$	80	130	60·4	6·6	$C_{16}H_{20}F_4N_2$	60·8	6·3	−8·9	−8·9
$C_6H_{12}N$	$[CH_2]_4$	11	52	62·6	7·1	$C_{18}H_{24}F_4N_2$	62·8	7·0	−9·8	−9·8
Morpholino	$CH_2{\cdot}O{\cdot}CH_2$	80	182	53·0	5·3	$C_{14}H_{16}F_4N_2O_2$	52·5	5·0	−9·5	−9·5
C_4H_8N	$[CH_2]_3$	63	70	59·2	6·2	$C_{15}H_{18}F_4N_2$	59·6	6·0	−9·7 *	−6·4 *
C_4H_8N	$[CH_2]_4$	77	49	61·2	6·2	$C_{16}H_{20}F_4N_2$	60·8	6·3	−10·5 *	−6·6 *
$C_5H_{10}N$	$CH_2{\cdot}O{\cdot}CH_2$	67	126	56·3	6·1	$C_{15}H_{18}F_4N_2O$	56·6	5·7	−9·7	−9·7

* Doublet bands J (c./sec.) ~20.

TABLE 4

Polyfluorophenyl-substituted *N*-oxides (III)

N-Oxide (III)		Yield	M. p.	Found (%)			Reqd. (%)	
R	X	(%)	(°c)	C	H	Formula	C	H
F	$[CH_2]_3$	85	126	49·5	4·1	$C_{11}H_{10}F_5NO$	49·5	3·8
Picrate		—	126	41·3	2·6	$C_{17}H_{13}F_5N_4O_8$	41·1	2·7
F	$CH_2{\cdot}O{\cdot}CH$	75	136	44·3	3·5	$C_{10}H_8F_5NO_2$	44·6	3·0
Picrate		—	146	38·9	2·2	$C_{16}H_{11}F_5N_4O_9$	38·6	2·2
Cl	$[CH_2]_3$	68	115	46·6	3·7	$C_{11}H_{10}ClF_4NO$	46·6	3·6
Picrate		—	111	40·1	2·9	$C_{17}H_{13}ClF_4N_4O_8$	39·8	2·5
Cl	$[CH_2]_2$	65	104	42·8	3·6	$C_{10}H_8ClFNO,0{\cdot}5H_2O$	43·1	3·2
Cl	$CH_2{\cdot}O{\cdot}CH_2$	64	116	42·1	2·9	$C_{10}H_8ClF_4NO_2$	42·1	2·8
Picrate		—	143	37·5	1·9	$C_{16}H_{11}ClF_4N_4O_9$	37·4	2·2
Br	$[CH_2]_3$	81	126	40·0	3·2	$C_{11}H_{10}BrF_4NO$	40·2	3·0
I	$[CH_2]_3$	77	140	34·9	2·6	$C_{11}H_{10}F_4INO$	35·2	2·7
Br	$[CH_2]_2$	80	115	37·2	2·7	$C_{10}H_8BrF_4NO,0{\cdot}5H_2O$	37·2	2·8

TABLE 5

vic-Trisubstituted tri- and di-fluorobenzenes (V)

Product (V)			Yield	M. p.	Found (%)			Reqd. (%)	
R^1	R^2	R^3	(%)	(°c)	C	H	Formula	C	H
$C_5H_{10}N$	$C_5H_{10}N$	F	65	143	66·2	8·1	$C_{21}H_{30}F_3N_3$	66·1	7·9
$C_5H_{10}N$	Me_2N	F	85	35	59·7	7·8	$C_{15}H_{12}F_3N_3$	59·8	7·4
$C_5H_{10}N$	Morpholino	F	60	200	59·2	6·6	$C_{19}H_{26}F_3N_3O_2$	59·2	6·8
Morpholino	Morpholino	F	70	228	56·2	6·6	$C_{18}H_{24}F_3N_3O_3$	55·8	6·2
Morpholino	Me_2N	F	80	54	55·5	7·0	$C_{14}H_{20}F_3N_3O$	55·5	6·6
$C_5H_{10}N$	$C_5H_{10}N$	Cl	85	126	63·8	7·7	$C_{21}H_{30}ClF_2N_3$	63·4	7·6
$C_5H_{10}N$	Me_2N	Cl	80	78	56·4	6·9	$C_{15}H_{22}ClF_2N_3$	56·7	7·0
Morpholino	Morpholino	Cl	85	214	53·9	6·0	$C_{18}H_{24}ClF_2N_3O_3$	53·5	6·0
Morpholino	Me_2N	Cl	90	102	52·8	6·3	$C_{14}H_{20}ClF_2N_3O$	52·6	6·3
$C_5H_{10}N$	$C_5H_{10}N$	Br	80	135	57·5	7·1	$C_{21}H_{30}BrF_2N_3$	57·0	6·8
C_4H_8N	C_4H_8N	Br	50	154	54·4	6·1	$C_{18}H_{24}BrF_2N_3$	54·0	6·0

made to react with excess of piperidine at room temperature for 6 days. Working-up in the usual way [cf. (*a*)] produced a solid which was purified by repeated recrystallisation from ethanol followed by vacuum sublimation. 1,5-*Difluoro*-2,3,4,6-*tetrapiperidinobenzene* had m. p. 153° (80%) (Found: C, 69·7; H, 9·1. $C_{26}H_{40}F_2N_4$ requires C, 70·0; H, 9·0%). In another experiment the same *N*-oxide (1·0 g.) dissolved in benzene (40 ml.) was treated with morpholine (1·4 g.) for 2 hr. at room temperature, and this was followed by addition of pyrrolidine (13 ml.) which was allowed to react for 48 hr. at room temperature. Working up as before gave a syrup (1·5 g.) which on repeated recrystallisation from aqueous acetone gave 1,5-*difluoro*-2,4-*dimorpholino*-3-*piperidino*-6-*pyrrolidinobenzene*, m. p. 176° (Found: C,

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63·2; H, 7·7. $C_{23}H_{34}F_2N_4O_2$ requires C, 63·3; H, 7·8%). When the piperidine *N*-oxide (1·0 g.) was treated with pyrrolidine (0·5 g.) in methanol (15 ml.) at room temperature for 1 hr. the *N*-oxide of tetrafluoro-1-piperidino-4-pyrrolidinobenzene (III; R = C_4H_8N, X = $[CH_2]_3$)

TABLE 6

^{19}F chemical shifts in *vic*-trisubstituted tri- and di-fluorobenzenes (V) in deuteriochloroform solution with C_6F_6 as internal standard

Compound (V)			Chemical shift	
R¹	R²	R³	(p.p.m.)	Bands
$C_5H_{10}N$	$C_5H_{10}N$	F	−15·1	Doublet
			+2·7	Triplet
$C_5H_{10}N$	Me_2N	F	−11·7	Doublet
			−0·8	Triplet
$C_5H_{10}N$	Morpholino	F	−16·6	Doublet
			+1·4	Triplet
Morpholino	Morpholino	F	−16·7	Doublet
			+0·3	Triplet
Morpholino	Me_2N	F	−11·9	Doublet
			−1·3	Triplet
$C_5H_{10}N$	$C_5H_{10}N$	Cl	−27·1	Singlet
$C_5H_{10}N$	Me_2N	Cl	−25·8	Singlet
Morpholino	Morpholino	Cl	−28·4	Singlet
Morpholino	Me_2N	Cl	−26·3	Singlet
$C_5H_{10}N$	$C_5H_{10}N$	Br	−45·6	Singlet
C_4H_8N	C_4H_8N	Br	−41·8	Singlet

TABLE 7

Reactions of the *N*-oxide (1 g.) of pentafluoropiperidinobenzene (A) and pentafluoromorpholinobenzene (B) with nucleophiles (5 g.) in various solvents (20 ml.) at room temperature for 1 hr.

N-Oxide	Nucleophile	Solvent	Position of substitution	Yield (%)
A	$C_5H_{10}N$	H_2O	4	80
A	$C_5H_{10}N$	C_6H_6	2, 6	90
A	$C_5H_{10}N$	MeOH	4	70
A	C_4H_8N	H_2O	4	80
B	C_4H_8NO	Benzene	2, 6	60
A	NaOMe	MeOH	4	95
A	NaOMe	Benzene *	4 and 2	66, 34

* Containing a small quantity of methanol.

separated as a brown syrup (0·75 g.) on driving off the solvent. This syrup was treated with excess of morpholine (2 ml.) for 18 hr. at room temperature. Working-up as in (*a*) gave 1,2,5-*trifluoro*-4-*morpholino*-3-*piperidino*-6-*pyrrolidinobenzene*, m. p. 92° (Found: C, 61·5; H, 7·1; N, 11·0. $C_{19}H_{26}F_3N_3O$ requires C, 61·8; H, 7·1; N, 11·2%).

Reactions of N-Oxides with Primary Bases.—(*a*) The *N*-oxide (1·0 g.) dissolved in benzene (40 ml.) or without a solvent was made to react with the required amine (2·5 ml.) at room temperature overnight. The amine hydrofluoride which separated was filtered off and the benzene solution evaporated to dryness under reduced pressure to leave a crude *N*-oxide which was purified by trituration with hot petrol. The *N*-oxide was then dissolved in aqueous sulphuric acid and deoxygenated by passing SO_2 gas through the solution with stirring for 0·5 hr. The mixture was neutralised with aqueous sodium hydroxide solution and extracted with petrol (b. p. 60—80°) to give the corresponding tetrafluorobenzene (X; R¹ = tertiaryamino, R² = secondary amino, R³ = F) after driving off the solvent and purification of the residue from ethanol. Liquid products were purified by distillation and chromatography. Similar results were obtained without a solvent.

(*b*) The *N*-oxide (1·0 g.) was made to react as an aqueous solution (10 ml.) with the required primary amine (2·0 ml.) at room temperature overnight. Deoxygenation was effected as before and the product extracted and purified as in (*a*).

The various reactions are tabulated (Table 8).

(*c*) *Reaction with Ammonia.*—(*a*) Reaction of the piperidine *N*-oxide (III; R = F, X = $[CH_2]_3$) with an aqueous solution of ammonia or with liquid ammonia at various temperatures gave complex mixtures of products.

(*b*) Through a well-stirred solution of the piperidine *N*-oxide (10 g.) (III; R = F, X = $[CH_2]_3$) in benzene (450 ml.) containing anhydrous potassium carbonate (2·5 g.) ammonia gas was passed for 8 days at room temperature. Inorganic residues were filtered off and excess of ammonia was removed by passing nitrogen gas through the reaction mixture. The solvent was driven off and the brown residue extracted with ether (3 × 100 ml.) which left starting material. The ethereal layer was dried ($MgSO_4$) and on evaporation deposited the N-(2-*amino*-3,4,5,6-*tetrafluorophenyl*)*piperidine* N-*oxide* m. p. 130° (petrol) (Found: C, 50·2; H, 4·6; N, 10·3. $C_{11}H_{12}F_4N_2O$ requires C, 50·0; H, 4·5; N, 10·6%). The *N*-oxide was dissolved in dilute sulphuric acid and then treated with SO_2 gas for 5 min. to yield the parent *amine* (X; R¹ = $C_5H_{10}N$, R² = NH_2, R³ = F), m. p. 59° purified by sublimation (Found: C, 53·7; H, 5·3; N, 11·1. $C_{11}H_{12}F_4N_2$ requires C, 53·2; H, 4·8; N, 11·3%). Its ^{19}F n.m.r. spectrum in $CDCl_3$ with C_6F_6 as internal standard showed 4 bands namely at 12·9 (triplet), at 1·2 (triplet), at 0·7 (doublet), and at −10·3 p.p.m. (doublet) with J(c./sec.) = 20 in every case, indicative of *ortho*-coupling. The *diacetyl derivative* had m. p. 65° (Found: C, 53·8; H, 4·3. $C_{15}H_{16}F_4N_2O_2$ requires C, 54·2; H, 4·8%). The *trifluoroacetyl derivative* had m. p. 99—100°

TABLE 8

Reactions of pentafluoropiperidinobenzene *N*-oxide (III; R = F, X = $[CH_2]_3$) with the primary amines to give the *N*-oxides (XI) and diamines (X; R¹ = $C_5H_{10}N$, R² = secondary amino, R³ = F)

		Products				Found (%)				Reqd. (%)		
		(XI)	(X)	Yield	M. p. or							
Primary amine	Solvent	R	R²	(%)	b. p. (°c)/mm.	C	H	N	Formula	C	H	N
Benzylamine *	—	—	$PhCH_2NH$	90	154/0·9 (38)	64·0	5·2	8·4	$C_{18}H_{18}F_4N_2$	63·9	5·3	8·3
Benzylamine	Benzene	$Ph{\cdot}CH_2$	—	75	106	60·8	5·3	7·9	$C_{18}H_{18}F_4N_2O$	61·0	5·1	7·9
	,,	—	$Ph{\cdot}CH_2NH$	60	—	—	—	—		—	—	—
Cyclohexylamine	,,	C_6H_{11}	—	65	108	58·5	6·5	—	$C_{17}H_{22}F_4N_2O$	59·0	6·4	—
	,,	—	C_6H_{11}	52	154/3	62·0	6·7	8·5	$C_{17}H_{22}F_4N_2$	61·8	6·7	8·5
Butylamine	,,	C_4H_9	—	80	70	56·2	6·5	9·1	$C_{15}H_{20}F_4N_2O$	56·2	6·3	8·6
	,,	—	C_4H_9	85	135/3	59·2	6·6	9·1	$C_{15}H_{20}F_4N_2$	59·2	6·6	9·2

* In water as solvent the *benzylamino*-2,3,5,6-*tetrafluoro*-4-*piperidinobenzene*, m. p. 62° (Found: C, 63·5; H, 5·6; N, 8·2. $C_{18}H_{18}F_4N_2$ requires C, 63·9; H, 5·3; N, 8·3%) was formed.

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(Found: C, 45·4; H, 3·5; N, 8·1. $C_{13}H_{11}F_7N_2O$ requires C, 45·4; H, 3·2; N, 8·1%).

Reactions with Methoxide.—(a) *In methanol:* A solution of the piperidine *N*-oxide (III; R = F, X = $[CH_2]_3$) in dry methanol (25 ml.) was treated with sodium methoxide in methanol (8·3 ml.; 1·2N) and kept at room temperature for 1 hr. The solvent was removed at room temperature *in vacuo* and the white residue taken up in chloroform to separate it from sodium fluoride. Evaporation of the chloroform gave the p-*methoxy-compound*, m. p. 134° (2·7 g.) (III; R = OMe, X = $[CH_2]_3$) (Found: C, 52·1; H, 4·9; N, 4·7. $C_{12}H_{13}F_4NO_2$ requires C, 51·6; H, 4·6; N, 5·0%). Its *picrate* had m. p. 120° (Found: C, 42·8; H, 2·9. $C_{18}H_{16}F_4N_4O_9$ requires C, 42·5; H, 3·2%). It was dissolved in 2N-sulphuric acid and deoxygenated by passing sulphur dioxide through the solution for 10 min. Neutralisation with sodium hydroxide followed by ether extraction gave *tetrafluoro*-p-*methoxypiperidinobenzene* as a colourless oil, b. p. 108°/2 mm. (Found: C, 54·7; H, 5·3. $C_{12}H_{13}F_4NO$ requires C, 54·8; H, 5·0%). Its ^1H n.m.r. spectrum showed the protons of the piperidine ring at τ 6·88 (4H) and 8·39 (6H) and the methoxy-protons at τ 6·00 (3H). Its ^{19}F n.m.r. spectrum showed bands at −15·08 and −7·02 p.p.m. consistent with *p*-substitution. Since piperidinopentafluorobenzene, when dissolved in excess of methanolic sodium methoxide and heated under reflux for 24 hr., gave the same methoxypiperidinobenzene as above, the *p*-orientation is further supported.

The above piperidine *N*-oxide (1·0 g.) was treated with an excess of methanolic sodium methoxide at room temperature for 6 hr. On working up the reaction mixture as before **3,5-*difluoro*-2,4,6-*trimethoxypiperidinobenzene*** (0·7 g.) was obtained (Found: C, 58·5; H, 7·0. $C_{14}H_{19}F_2NO_3$ requires C, 58·5; H, 6·6%). Its ^1H n.m.r. spectrum showed absorption bands at τ 6·88 (4H) and 8·38 (6H) corresponding to the piperidine ring and methoxy-protons at τ 6·04 (3H) and at 6·15 (6H).

(b) *In benzene:* The above piperidine *N*-oxide (2·67 g.) was dissolved in dry benzene (200 ml.) and a solution of sodium methoxide in methanol (8·3 ml.; 1·2N) was then added. The mixture was stirred overnight at room temperature and worked up as before. A mixture of 2-methoxytetrafluoro- and 4-methoxytetrafluoro-piperidinobenzene was obtained which could not be separated quantitatively by chromatography on a silica column with benzene as eluant. The two compounds were in the ratio of 34 : 66 respectively based on the intensity ratio of the *o*-methoxy- and *p*-methoxy-peaks in the ^1H n.m.r. of the mixture.

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