Polyhalogenoheterocyclic Compounds. Part XXVI.[1] Nucleophilic Substitution in Trifluoropyrazines

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The orientation of substitution in trifluoropyrazines $C_4N_2F_3X$ (X = H, Cl, Br, OMe, or NMe_2) by methoxide and dimethylamine is described. Further attack *para* to H, Cl, or Br and *ortho* to OMe occurs; attack *ortho* to Me_2N is observed when steric factors permit. The synthesis of perfluorobipyrazin-2-yl is reported.

RECENT evidence [2,3] has cast more light on the substituent effects of halogen atoms at various positions in pyridines and benzenes. Here we describe further examples of the orientation of nucleophilic substitution in trifluoropyrazines. Halogenopyrazines are of special interest because all the carbon atoms are equivalently placed with respect to nitrogen, in the initial state, and the orientation of substitution would be expected, at first sight, to be governed by the halogeno- and other substituents. Some studies of further substitution in alkylmethoxy-trifluoropyrazines have been made previously.[4]

The Scheme shows the results of nucleophilic substitution in various trifluoropyrazines. Reaction of compounds (I)—(III) (X = H, Cl, or Br) with dimethylamine occurred in all cases with exclusive attack *para* to the substituent X. In comparison with compounds (I)—(III), the methoxy-derivative (IV) was much less reactive and gave, with dimethylamine, essentially one isomer (Va) but here arising from attack *ortho* to the substituent. The presence of one isomer was deduced from t.l.c. and ^{19}F n.m.r. data, and the structure (Va) was derived from ^{19}F chemical shifts (see later). The dimethylamino-compound (VI), prepared from dimethylamine and tetrafluoropyrazine, reacted with sodium methoxide in methanol to give predominantly (Va) along with *ca.* 10% of (Vb). However, the reaction of (VI) with dimethyl-

[1] Previous parts of this Series are entitled ' Polyfluoroheterocyclic Compounds; Part XXV, R. D. Chambers, M. Clark, J. R. Maslakiewicz, W. K. R. Musgrave, and P. G. Urben, *J.C.S. Perkin I*, 1974, 1513.

[2] R. D. Chambers, W. K. R. Musgrave, J. S. Waterhouse, D. L. H. Williams, J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J.C.S. Chem. Comm.*, 1974, 239.

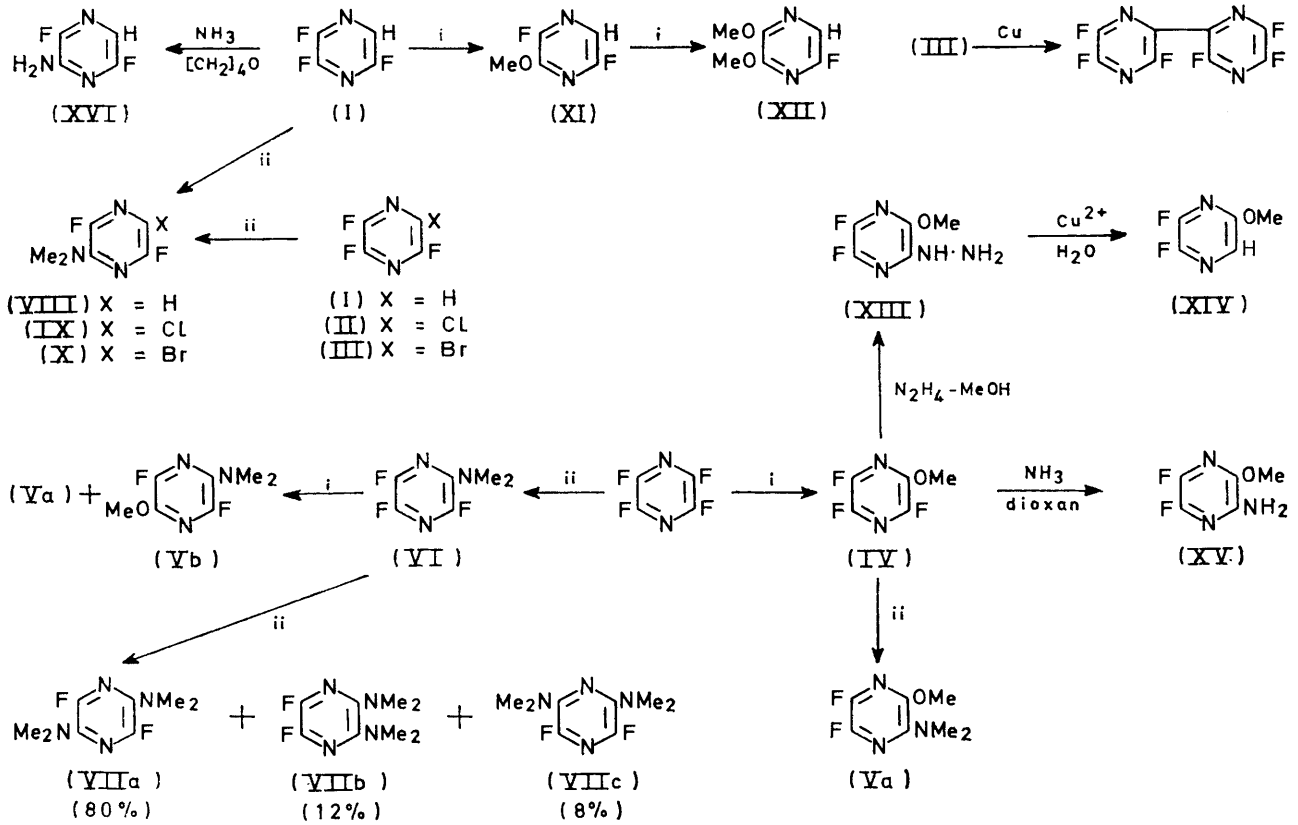
[3] J. S. Waterhouse, Ph.D. Thesis, Durham, 1973.

[4] C. G. Allison, R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1970, 1023.

amine in methanol gave contrasting results; a mixture of three isomers (VIIa—c) was obtained, with (VIIa) predominating, *i.e.* the isomer arising from attack *para* to the substituent.

and (III) as well as to hydrogen in (I) consequently maximises the activating influence of fluorine and the other halogen atoms.

Methoxy- and dimethylamino-groups in (IV) and (VI),



SCHEME i, NaOMe–MeOH; ii, Me_2NH–MeOH

Mechanism.—Attack *para* to H in (I) is consistent with the orientation of substitution in other fluorinated

(A)

aromatic systems [2-5] where it is evident that a fluorine atom *para* to the position of attack does not have a stabilising influence on the corresponding transition state (A; X = F). This arises because a fluorine atom does not necessarily stabilise an attached carbanion.[6] A fluorine atom *ortho* or *meta* to the point of attack is, however, known to be activating, the influence of *ortho*-fluorine probably stemming from an initial-state effect.[2-5] In contrast, bromo- and chloro-substituents are known invariably to increase the stability of attached carbanions, and therefore we would anticipate a similar effect in (A; X = Br or Cl). Attack *para* to these atoms in (II) respectively, are strongly deactivating and the magnitude of the effect indicates that these groups should either dominate the orientation of further substitution, leading to further attack at positions *meta* to these groups, or at least cause the rate of *meta*-attack to be comparable to the rate of attack *para* to these groups. The latter is the situation in the corresponding pentafluorobenzene derivatives.[7,8] It is surprising, therefore, that further nucleophilic attack on (IV) and (VI) with methoxide led to preferential *ortho*-attack, the least expected orientation. Further attack on the dimethylamino-derivative (VI) with dimethylamine led, principally, to *para*-attack [to give (VIIa)], the formation of (VIIb) obviously being inhibited by steric effects. Contrary to expectation, therefore, further substitution in (IV) and (VI) cannot be accounted for by the orientating influence of *either* the fluorine atoms *or* the other substituents (OMe or NMe_2). This point is further emphasised by the orientation of substitution in (XI), where both potential sites of substitution also have a *para*-fluorine atom: attack occurred exclusively *ortho* to OMe, giving (XII).

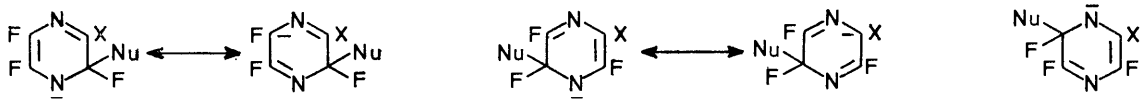
[5] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968.

[6] R. D. Chambers, 'Fluorine in Organic Chemistry,' Wiley-Interscience, New York, 1973, pp. 85, 89.

[7] J. Burdon, W. B. Hollyhead, and J. C. Tatlow, *J. Chem. Soc.*, 1965, 5152.

[8] J. G. Allen, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1965, 6329.

It is possible to explain these orientations on the basis of an effect which we tentatively put forward in a previous paper.[4] In transition states for nucleophilic substitution, a nitrogen atom *ortho* to the point of attack will be a position of high electron density as represented by (1)—(3), *i.e.* the nitrogen atoms are symmetrically situated in the initial state but unsymmetrical in the transition states. A fluorine atom attached to carbon which is adjacent to a negatively charged centre is very strongly stabilising,[6] and in both (1) and (2) the charged nitrogen has an adjacent fluorine atom whereas (3) has the substituent (OMe or BMe_2) in the adjacent position and, therefore, should be much less stable. The preference for (1) over (2) is less clear on this basis, however, but presumably there is also charge on the *para*-positions and the preference probably arises because (1a) will be more stable than (2a) when X = OMe or NMe_2.



(1) (1a) (2) (2a) (3)

tems, although magnitudes vary. The fluorine resonances from compounds (I)—(IV) and (VI) can be assigned on this basis and the relevant data are contained in the Table; the structures of (VIII)—(X) and (Vb) follow from the observation of a *para* F,F coupling. Observed chemical shifts for the structures established so far are in close agreement with values calculated from s.c.s. values but the calculated and observed values for (Va) differ. Nevertheless, the calculated shifts for (Va) are sufficient to distinguish this from the alternative structure, for which the difference between calculated and observed shifts is more marked. The s.c.s. values for the dimethylamino-group are large and distinctive and the differences amongst (VIIa), (VIIb), and (VIIc) are, consequently, considerable. Observed and calculated values for (VIIa) and (VIIc) are in reasonable agreement but for (VIIb) the values differ significantly. This is, indeed,

^{19}F N.n.r. shifts (solvent ether)

3,5,6-Trifluoropyrazines

Compound	Substituent	Shifts (p.p.m.) Downfield from external hexafluorobenzene			From internal tetrafluoropyrazine * (s.c.s.) 3-F	5-F	6-F	J/Hz for F atoms orientated o	m	p
(I)	F		70·0							
	H	69·9	*ca.* 76	*ca.* 77	*ca.* −7	*ca.* −6	+0·1	17	?	38
(II)	Cl	*ca.* 72	*ca.* 73	83·6	−13·6	*ca.* −3	*ca.* −2	16	?	38
(III)	Br	*ca.* 73	*ca.* 73	87·7	−17·2	*ca.* −3	*ca.* −3	17	?	48
(IV)	OMe				−1·7	+12·4	+4·9	15·1	12·3	51·2
(VI)	NMe_2	50·7	65·0	80·3	−10·0	+19·5	+5·0	18	18	48

Difluoropyrazines

Substituents	Shifts relative to external C_6F_6 Calculated for substituents orientated o		m		p		Observed		Compound	J/Hz
H, NMe_2	50·4	71·5	57·7	86·5	72·2	79·9	74·0	82·3	(VIII)	45
Cl, NMe_2	52·9	68·3	64·1	83·3	78·6	82·4	78·7	83·3	(IX)	48
Br, NMe_2	53·1	66·8	67·7	82·8	82·2	82·6	82·9	84·3	(X)	45
OMe, NMe_2	45·6	52·6	52·2	67·6	66·7	75·1	49·4	55·8	(Va)	10
							68·0	77·3	(Vb)	50
NMe_2, NMe_2	45·5		60·5		75·0		54·8		(VIIb)	
							64·7		(VIIc)	
							76·1		(VIIa)	
H, OMe	57·5	71·6	64·8	78·2	71·6	72·3	59·5	72·0	(XIV)	17
							71·0	72·3	(XI)	43

* Shifts relative to tetrafluoropyrazine for compounds (I) and (IV)[4] are interpolated from measurements using C_6F_6 as standard.

Structural Assignments.—Structures were assigned largely on the basis of ^{19}F n.m.r. data, the most striking diagnostic feature being a large *para* F,F coupling, where this exists. This follows from earlier work [4] where the spectra of a range of fluoropyrazines were analysed and *para* F,F coupling values fell in the range 40—50 Hz, the corresponding *ortho*- and *para*-values always being much smaller and generally below 20 Hz. Also, the earlier work established that fluorine substituent chemical shifts (s.c.s.) are in the same directions for the pyrazine system as those observed for benzene and pyridine systems, although magnitudes vary. The fluorine resonances from compounds (I)—(IV) and (VI) can be assigned on this basis and the relevant data are contained in the Table; the structures of (VIII)—(X) and (Vb) follow from the observation of a *para* F,F coupling. Observed chemical shifts for the structures established so far are in close agreement with values calculated from s.c.s. values but the calculated and observed values for (Va) differ. Nevertheless, the calculated shifts for (Va) are sufficient to distinguish this from the alternative structure, for which the difference between calculated and observed shifts is more marked. The s.c.s. values for the dimethylamino-group are large and distinctive and the differences amongst (VIIa), (VIIb), and (VIIc) are, consequently, considerable. Observed and calculated values for (VIIa) and (VIIc) are in reasonable agreement but for (VIIb) the values differ significantly. This is, indeed, evidence for the *ortho*-arrangement of the dimethylamino-groups: additivity of the s.c.s. values may be expected to be influenced by steric effects.

ortho H,F coupling constants are distinctively larger than corresponding *meta* and *para* values and this feature has been useful in establishing the structures of various compounds having H attached to the pyrazine ring, *e.g.* (VIII), (XI), and (XII).

The structure of (XVI), which was too insoluble for an n.m.r. spectrum to be obtained, was assigned in the light of reactions of other nucleophiles with (I).

EXPERIMENTAL

Spectroscopic data were obtained using the following spectrometers: i.r. Grubb–Parsons Spectromaster; u.v. Unican SP 800; mass spectra A.E.I. M.S.9; n.m.r. Varian A56/60D. ^{19}F N.m.r. spectra were recorded for solutions in ether, with hexafluorobenzene as external reference, shifts to low field being positive. ^{1}H Spectra were recorded for solutions in carbon tetrachloride.

M.p.s were obtained with a Kofler hot-stage apparatus, if above 25 °C. If below 25 °C a sealed tube in an alcohol or water-bath was employed.

Chromatographic silica (100—200 mesh) was obtained from Reeve Angel. Light petroleum refers to redistilled fractions of b.p. 40—60 °C, unless otherwise stated. Ammonia, dimethylamine, and hydrazine were used as saturated aqueous solutions.

All reactions were performed at room temperature, unless otherwise stated.

General Procedure for Reactions with Amines and Hydrazines.—The pyrazine was dissolved in methanol and the amine (2·1 mol. equiv.) was added as an aqueous solution, with stirring. Cooling was employed as necessary, to moderate the heat of reaction. The reaction mixture was set aside for 10 min, and then partitioned between water (several times the volume of the reaction mixture) and light petroleum–ether (1 : 1). The organic layer was washed twice with water, dried ($MgSO_4$), and evaporated on a water-bath. The product was purified as appropriate.

Preparation of Trifluoropyrazine (I).—Tetrafluoropyrazine (5·0 g) in methanol (*ca.* 50 ml) was treated with hydrazine as above. No attempt was made to purify the crude hydrazinopyrazine obtained, but hydrated copper sulphate (30 g) in water (300 ml) was added to it.[9,10] The mixture was gently warmed in a distillation apparatus until frothing subsided, and then water (20 ml) was distilled off, carrying the trifluoropyrazine (I) with it. The trifluoropyrazine was extracted into ether, the ether layer was dried ($MgSO_4$), and then ether was removed by fractional distillation through a short Vigreux column. A further fraction, b.p. 89 °C, was collected. The n.m.r. spectrum of this product (1·2 g) indicated it to be *trifluoropyrazine* (I) containing 5—10% of ether. A portion purified by preparative g.l.c. had m.p. 0—1° (Found: C, 35·8; H, 0·4; N, 21·5%; M^+, 134. $C_4HF_3N_2$ requires C, 35·8; H, 0·7; N, 20·9%; *M*, 134), τ 2·33 (complex m, $W_{\frac{1}{2}}$ 14 Hz) [this signal simplifies towards a doublet (*J* 6 Hz) at −5 °C, and approaches a double doublet (*J* 7 and 2 Hz) at 105 °C], $\lambda_{max.}$ 247 nm (ε 4800), $\lambda_{max.}$ 6·21, 6·32, 6·85, 6·90, 7·56, 7·81, 8·33, 8·52, 9·74, 11·2, 12·4, 13·8, and 19·9 μm.

Methoxytrifluoropyrazine [4] (IV) (1 g) was similarly treated with hydrazine (reaction time 2 h). A small proportion of the hydrazino-derivative, which crystallised from the reaction mixture, was filtered off and purified by sublimation to give *2,3-difluoro-5-hydrazino-6-methoxypyrazine* (XIII), m.p. 155° (decomp.) (Found: C, 34·1; H, 3·8; N, 32·2%. $C_5H_6F_2N_4O$ requires C, 34·1; H, 3·4; N, 31·8%). The bulk of the hydrazino-compound was not purified however, but treated with copper sulphate and worked up as above to give crude methoxydifluoropyrazine which was purified by preparative g.l.c. to give *2,3-difluoro-5-methoxypyrazine* (XIV) (300 mg), a liquid (Found: C, 40·9; H, 2·47; N, 19·7. $C_5H_4F_2N_2O$ requires C, 41·1; H, 2·75; N, 19·2%), τ 2·63 (1H, t, *J* 2 Hz) and 6·22 (3H, s), $\lambda_{max.}$ 295 nm (ε 6000), $\lambda_{max.}$ 6·42, 6·71, 6·97, 7·50, 7·79, 8·45, 8·63, 9·68, 12·3, and 20·1 μm.

Reaction of Trifluoropyrazines with Dimethylamine.—Trifluoropyrazine (I) (0·5 g), obtained as described above, gave *3-dimethylamino-2,5-difluoropyrazine* (VIII) (350 mg), after removal of remaining solvents from the crude product at water-pump pressure, followed by vacuum transfer (0·2 mmHg) to give the pure compound, m.p. 16° (Found: C, 44·9; H, 4·05; F, 24·1%; M^+, 159. $C_6H_7F_2N_3$ requires C, 45·2; H, 4·35; F, 23·9%; *M*, 159), τ 3·33 (1H, dd, $J_{H,F}$ 8 and 3·5 Hz), and 7·30 (6H, d, $J_{H,F}$ 2 Hz), $\lambda_{max.}$ 275 nm (ε 6500); $\lambda_{max.}$ 6·18, 6·53, 6·91, 7·08, 7·46, 8·23, 8·84, 9·72, 12·05, 12·83, 14·64, and 20·2 μm.

Chlorotrifluoropyrazine [4] (II) (300 mg) gave *2-chloro-5-dimethylamino-3,6-difluoropyrazine* (IX) (280 mg), m.p. 14—15° (Found: C, 37·4; H, 3·5; N, 22·1%; M^+, 193. $C_6H_6ClF_2N_3$ requires C, 37·2; H, 3·1; N, 21·7%; *M*, 193), τ 6·78 (d, $J_{H,F}$ 2·0 Hz), $\lambda_{max.}$ 250 (ε 18,000) and 336 nm (ε 9000), $\lambda_{max.}$ 6·20, 6·64, 6·97, 7·47, 8·14, 8·65, 10·69, 12·19, 13·45, 14·48, and 20·15 μm.

Bromotrifluoropyrazine [4] (III) (300 mg) gave *2-bromo-5-dimethylamino-3,6-difluoropyrazine* (X) (270 mg) after purification by sublimation (0·05 mmHg; 30 °C), m.p. 30—33° (slowly becomes a green liquid under ambient conditions) (Found: C, 30·6; H, 2·55; Br, 33·1; F, 15·9; N, 17·6. $C_6H_6BrF_2N_3$ requires C, 30·7; H, 2·5; Br, 33·6; F, 16·0; N, 17·6%), τ 6·76 (t, $J_{H,F} = J_{H,F}$ = 0·8 Hz), $\lambda_{max.}$ 253 (ε 17,000) and 337 nm (ε 10,000), $\lambda_{max.}$ 6·20, 6·64, 6·97, 7·47, 8·14, 8·65, 10·80, 12·38, 14·57, and 20·2 μm.

Preparation of Dimethylaminotrifluoropyrazine (VI).—Tetrafluoropyrazine (500 mg) was treated with dimethylamine (2·1 equiv.) in the usual fashion and the crude product was recrystallised from light petroleum at −70 °C and then from methanol. The product was dried (P_2O_5) to give *dimethylaminotrifluoropyrazine*, (VI) (160 mg), m.p. −23°, a pale yellow liquid showing strong violet fluorescence in solution (Found: F, 32·7%; M^+, 177. $C_6H_6F_3N_3$ requires F, 32·2%; *M*, 177), τ 6·80 (d, *J* 1·8 Hz), $\lambda_{max.}$ 242 (ε 12,800) and 333 nm (ε 6500), $\lambda_{max.}$ 6·50, 6·90, 7·02, 7·77, 8·08, 8·44, 10·28, 11·62, and 19·85 μm.

Reactions of Dimethylaminotrifluoropyrazine (VI) *and Methoxytrifluoropyrazine* (IV) *with Sodium Methoxide.*—Dimethylaminotrifluoropyrazine (200 mg) was treated with the solution obtained by dissolving sodium (30 mg) in methanol (10 ml). The mixture was worked up by partition between ether and water, the ether layer being dried and evaporated. The crude product (200 mg) showed ^{19}F δ 49·4 and 55·8 p.p.m. (both d, *J* 19 Hz) and very much weaker signals (10%) at 77·3 and 68·0 p.p.m. (both d, *J* 50 Hz); t.l.c. showed only a trace of impurity but this could not be removed by recrystallisation several times from methanol at low temperatures.

Methoxytrifluoropyrazine (IV) [4] (400 mg) was treated with an excess of dimethylamine (*ca.* 2 ml of aqueous solution) in methanol (10 ml) for 2 days. The crude product (430 mg), obtained by the usual work-up, was examined by ^{19}F n.m.r. spectroscopy. Only the signals of 2-dimethylamino-5,6-difluoro-3-methoxypyrazine (Va) (^{19}F δ 49·4 and 55·8 p.p.m.) were observed. T.l.c. showed traces of the isomer (Vb) obtained in the foregoing reaction and elemental analysis of the mixture excluded the possibility that significant amounts of material not containing fluorine were present. This mixture was sublimed (0·01 mmHg; 90 °C)

[9] I. Collins, S. M. Roberts, and H. Suschitzky, *J. Chem. Soc.* (*C*), 1971, 167.

[10] D. G. Holland, G. J. Moore, and C. Tamborski, *J. Org. Chem.*, 1964, **29**, 3042.

to give a moderate quantity of solid 2-*dimethylamino*-5,6-*difluoro*-3-*methoxypyrazine* (Va), m.p. 21° (Found: F, 19·8%; M^+, 189. $C_7H_9F_2N_3O$ requires F, 20·1%; *M*, 189), τ 5·98 (3H, s) and 6·90 (6H, s), $\lambda_{max.}$ 247 (ε 10,700) and 333 μm (ε 7100), $\lambda_{max.}$ 3·37, 3·46, 6·12, 6·36, 6·58, 6·77, 7·04, 7·65, 8·10, 8·38, 8·44, 9·87, 10·40, 11·61, 13·65, and 14·40 μm.

Reaction of Dimethylaminotrifluoropyrazine (VI) *with Dimethylamine.*—The pyrazine (VI) (1 g) was treated with an excess of dimethylamine in methanol for 2 days; the usual work-up gave a liquid crude product (1·2 g), ^{19}F δ 54·8, 64·7, and 76·1 p.p.m. (*ca.* 12 : 8 : 80). The three bis(dimethylamino)difluoropyrazines were separated by chromatography on silica, with light petroleum containing a trace of ether as eluant. The grouped fractions containing each of the three products were evaporated to dryness and the residues were recrystallised from methanol. In order of appearance from the column these were: 2,3-*bis*(*dimethylamino*)-5,6-*difluoropyrazine* (VIIb), yellow needles with greenish fluorescence, m.p. 52—53° (Found: C, 47·4; N, 28·1%; M^+, 202. $C_8H_{12}F_2N_4$ requires C, 47·5%; N, 27·7%; *M*, 202), τ 7·10 (s), $\lambda_{max.}$ 216, 267, and 344 nm, $\lambda_{max.}$ 3·37, 3·49, 6·23, 6·42, 6·69, 6·90, 7·10, 7·50, 7·60, 8·15, 8·53, 8·71, 8·97, 9·08, 10·24, 10·95, 11·98, 12·90, 14·22, and 21·10 μm; 2,6-*bis*(*dimethylamino*)-3,5-*difluoropyrazine* (VIIc), white needles, fluorescence similar to that of (VI), m.p. 70° (Found: C, 47·3; N, 27·5%; M^+, 202), τ 6·90 (t, *J* 1·0 Hz), $\lambda_{max.}$ 220, 251, and 352 nm, $\lambda_{max.}$ 3·45, 6·20, 6·39, 6·59, 7·01, 7·10, 7·87, 8·26, 8·64, 10·30, 14·10, 14·21, and 20·25 μm; and 2,5-*bis*(*dimethylamino*)-3,6-*difluoropyrazine* (VIIa), which may also be obtained by direct recrystallisation of the reaction product, yellow plates with blue-green fluorescence, m.p. 34° (Found: C, 47·7; N, 27·6; F, 19·2%; M^+, 202), τ 6·98 (t, *J* 0·3 Hz), $\lambda_{max.}$ 266 and 356 nm, $\lambda_{max.}$ 3·38, 3·49, 6·60, 7·03, 7·13, 7·79, 8·33, 8·75, 9·45, 10·19, 12·18, and 20·05 μm.

All the dimethylamino-di- and -tri-fluoropyrazines are light-sensitive, especially in solution or in the liquid phase.

Reaction of Trifluoropyrazine with Sodium Methoxide.—Trifluoropyrazine (I) (400 mg) was treated with the solution obtained by dissolving sodium (75 mg) in methanol (10 ml). The resultant solution was added to water, and the mixture extracted with ether. The extract was dried ($MgSO_4$) and evaporated. The residue was purified by preparative g.l.c. to give 2,5-*difluoro*-3-*methoxypyrazine* (XI) (280 mg), m.p. 1—3° (Found: C, 41·1; H, 2·6; N, 19·6. $C_5H_4F_2N_2O$ requires C, 41·1; H, 2·75; N, 19·2%), τ 2·92 (1H, dd, *J* 8 and 3 Hz) and 6·35 (3H, s), $\lambda_{max.}$ 287 nm (ε 6500), $\lambda_{max.}$ 6·21, 6·39, 6·71, 6·92, 7·13, 7·55, 7·8br, 8·19, 8·42, 8·57, 9·66, 10·3, 11·6, 12·3, 14·1, 17·5, and 20·0 μm.

Treatment of trifluoropyrazine (I) (200 mg) with an excess of sodium methoxide solution, followed by work-up as above and purification by sublimation gave 5-*fluoro*-2,3-*dimethoxypyrazine* (XII) (200 mg), m.p. 63·5—64·5° (Found: C, 45·3; H, 4·8; N, 18·4. $C_6H_7FN_2O_2$ requires C, 45·6; H, 4·45; N, 17·7%), ^{19}F δ 64·3 p.p.m. (d, *J* 9 Hz), τ 2·85 (1H, d, *J* 8 Hz), 6·45 (3H, s), and 6·48 (3H, s), $\lambda_{max.}$ 297 nm (ε 6400), $\lambda_{max.}$ 6·41, 6·73d, 6·89, 7·18, 7·47, 7·76, 8·45, 9·68, 10·2, 12·5, and 14·2 μm.

Preparation of Aminopyrazines. Methoxytrifluoropyrazine (IV) [4] (200 mg) was dissolved in dioxan (5 ml) and treated overnight with an excess of aqueous ammonia. The dioxan and water were evaporated off at reduced pressure and the residue sublimed (0·05 mmHg; 130 °C) to give crude amino-difluoro-methoxypyrazine. This was recrystallised from chloroform–carbon tetrachloride to give pure 2-*amino*-5,6-*difluoro*-3-*methoxypyrazine* (XV) (100 mg), m.p. 127° (Found: C, 37·5; H, 3·3; N, 25·8. $C_5H_5F_2N_3O$ requires C, 37·3; H, 3·05; N, 26·1%), ^{19}F δ 47·0 (d, *J* 16 Hz) and 53·4 (d, *J* 16 Hz) p.p.m., τ 5·1 (2H, $W_{\frac{1}{2}}$ 15 Hz) and 6·00 (3H, s). $\lambda_{max.}$ 225 (ε 10,500) and 318 nm (ε 7200), $\lambda_{max.}$ 2·87, 3·00, 6·17, 7·15, 7·68, 3·00, 9·92, 10·9, 13·7, and 20·4 μm.

Trifluoropyrazine (150 mg) was dissolved in tetrahydrofuran (2 ml) and treated with an excess of aqueous ammonia for 10 min. Ammonia and solvent were then evaporated off at reduced pressure, and the residue sublimed (0·05 mmHg; 110 °C) to give 3-*amino*-2,5-*difluoropyrazine* (XVI) (120 mg), sublimes *ca.* 170° (Found: C, 36·3; H, 2·25; N, 31·6. $C_4H_3F_2N_3$ requires C, 36·6; H, 2·3; N, 32·1%), $\lambda_{max.}$ 303 nm (ε 6300), $\lambda_{max.}$ 2·96, 3·00, 3·14, 6·08, 6·69, 6·92, 7·55, 7·74, 8·18, 12·0, 13·7d, and 19br μm.

Preparation of Hexafluorobipyrazin-2-yl.—Bromotrifluoropyrazine [4] (III) (500 mg) was heated with an excess of copper bronze powder (*ca.* 200 mg) in a sealed tube at 190 °C for 24 h. The resultant black solid was powdered, and the product sublimed (0·03 mmHg; 100 °C) from it onto a cold finger. The sublimate was dissolved in light petroleum and filtered through activated alumina. Material eluted by petroleum was mostly residual bromotrifluoropyrazine. The alumina was then washed with ether and the material obtained sublimed to give *hexafluorobipyrazinyl* (110 mg), m.p. 89—90° (Found: C, 36·4; F, 43·0%; M^+, 266. $C_8F_6N_4$ requires C, 36·1; F, 42·8%; *M*, 266), ^{19}F δ 72·5 (dd, 6-F), 80·2 (d, 5-F), and 84·3 p.p.m. (d, 3-F) ($J_{3,6}$ 40, $J_{5,6}$ 20, $J_{3,5} < 5$ Hz), $\lambda_{max.}$ 301 (ε 7600) and 225 nm (ε 16,600), $\lambda_{max.}$ 6·28, 6·34, 6·85, 7·09, 7·15 7·52, 8·20, 8·37, 9·63, 12·28, 13·94, 17·66, and 20·1 μm.

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