Polyhalogenoheterocyclic Compounds. Part XXVII.[1] Nucleophilic Substitution in Chlorofluoropyrazines and Tetrachloropyrazine

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Substitutions in tetrachloropyrazine by dimethylamine, hydrazine, and methoxide are described. The orientation of further substitution in the resulting trichloropyrazines is established by independent syntheses from known chlorofluoropyrazines. In the absence of dominating steric effects, nucleophilic attack *ortho* to the substituent in trichloropyrazines is preferred.

THE orientation of nucleophilic substitution in a range of highly fluorinated aromatic compounds has been established.[2] However there are relatively few cases where the corresponding behaviour of polychloroheterocyclic

[1] Part XXVI, R. D. Chambers, W. K. R. Musgrave, and P. G. Urben, preceding paper.

[2] See *e.g.* R. D. Chambers, ' Fluorine in Organic Chemistry,' Wiley–Interscience, New York, 1973 and references therein.

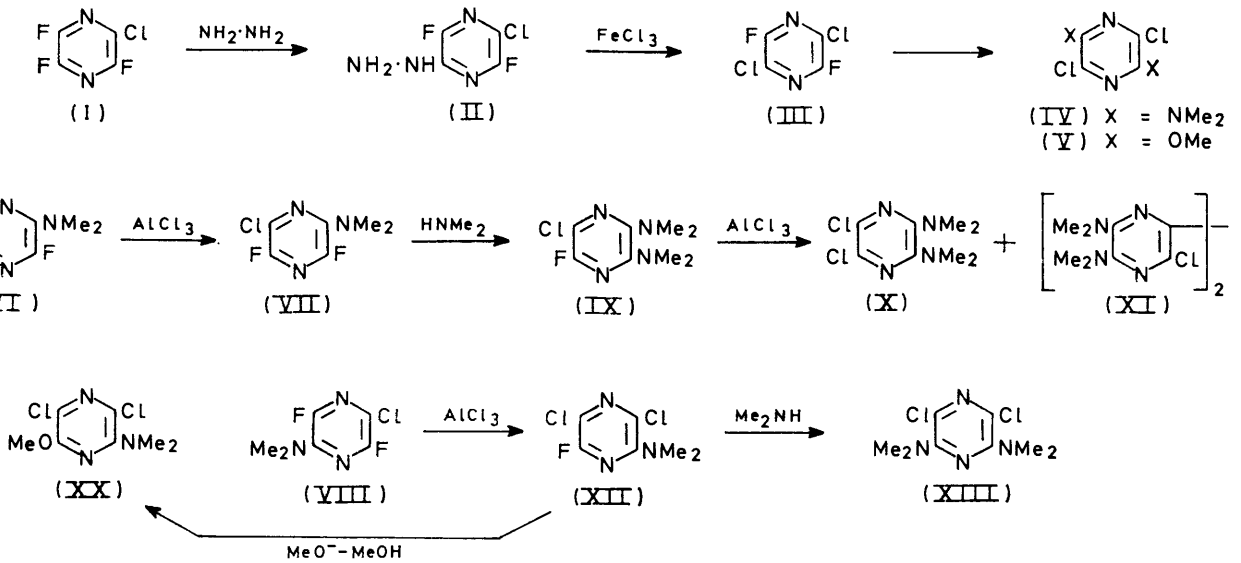
compounds has been ascertained unambiguously,[3-8] largely because of the dearth of structural probes available for investigation of polychlorinated compounds.

We describe here the syntheses and characterisation of various dichloropyrazines from chloro-fluoro-compounds, which enables us to establish the orientation of nucleophilic substitution in trichloropyrazines.

The reaction of hydrazine with chlorotrifluoropyrazine (I) gave one isomer (II) exclusively, as indicated by, for example, the characteristic *para* F,F coupling in the ^{19}F n.m.r. spectrum.[1,9] Compound (II) was then converted into the 2,5-dichlorodifluoropyrazine (III) with iron(III) chloride. Nucleophilic displacement of fluorine from (III) was achieved with either dimethylamine or sodium methoxide, giving the dichloropyrazine (IV) or (V), of known structure.

Replacement of fluorine by chlorine in some heterocyclic compounds has been achieved by using aluminium trichloride,[10] but no useful products could be obtained from such a reaction with chlorotrifluoropyrazine (I). Surprisingly, however, the reaction of the dimethylamino-derivative (VI) [1] with aluminium trichloride gave a modest yield of the chloro-derivative (VII).

Replacement of fluorine in an unsaturated system by chlorine with Lewis acids is well known,[11] but the orientating influence of a dimethylamino-group in the process has not been reported previously. Nevertheless, we are unable at present to advance a convincing explanation of this effect. The structure of (VII) follows from the fact that it is different from the isomer (VIII) [1] and the observed ^{19}F chemical shifts agree closely with values calculated for (VII), from known substituent chemical shifts arising from a dimethylamino-group,[1] with reference to compound (I). Dimethylamine reacts with (VII) by displacement of fluorine, giving a compound which is assigned structure (IX). Treatment of (IX) with aluminium trichloride gives the dichloro-compound (X), together with a compound whose mass spectrum indicates a bipyrazinyl structure (XI). The alternative structure for (IX), with dimethylamino-groups *para* to each other, is ruled out because (X) is not identical with (IV). Finally, the remaining dichlorobis(dimethylamino)-pyrazine isomer (XIII) was obtained by the route



(I) (II) (III) (IV) X = NMe2; (V) X = OMe (VI) (VII) (IX) (X) (XI) (XX) (VIII) (XII) (XIII)

SCHEME 1

(VIII) ⟶ (XII) ⟶ (XIII). Compound (XIII) differed from the isomers (IV) and (X); its structure was thus established and this in turn proved the structure of (XII).

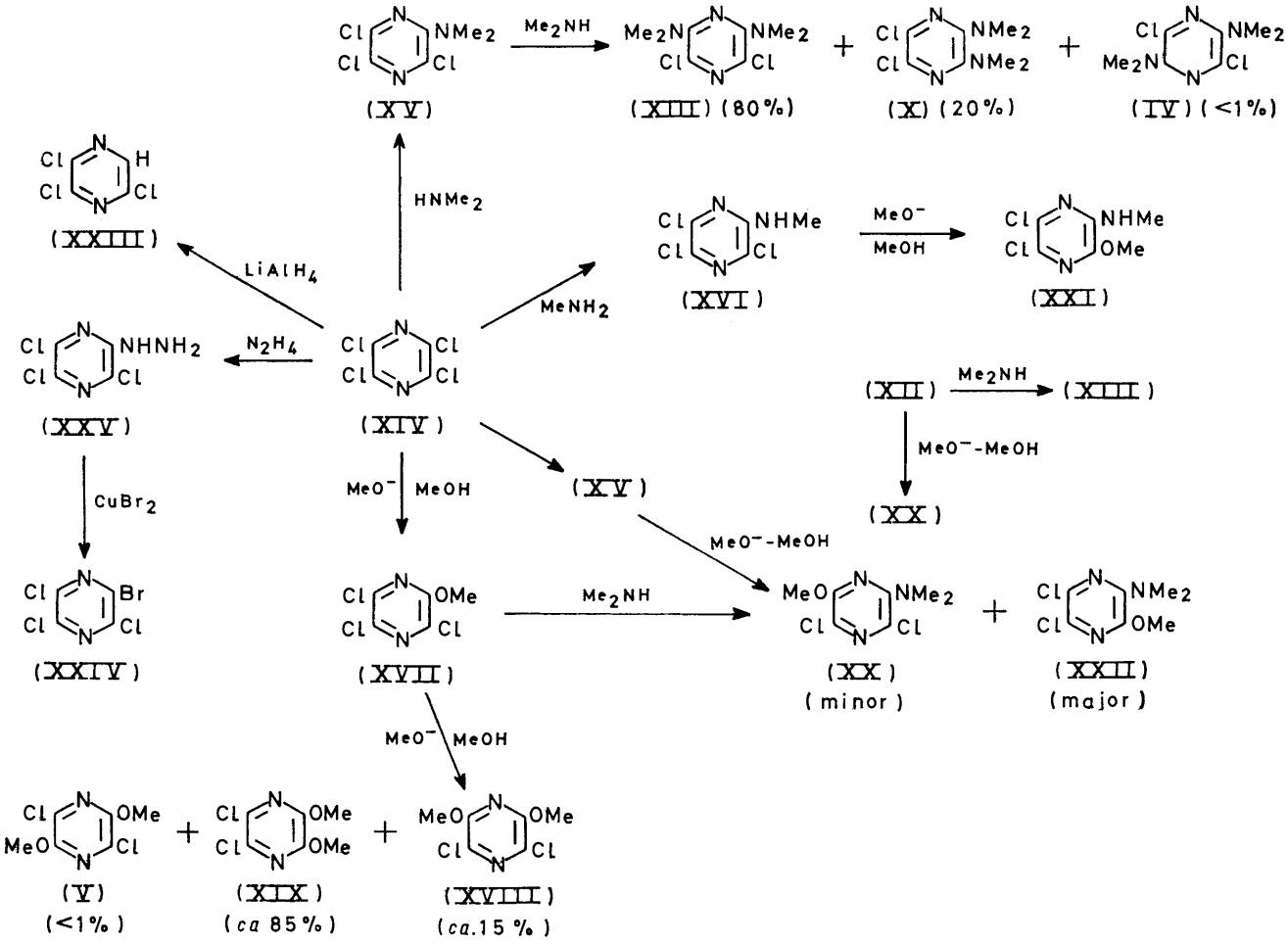
Tetrachloropyrazine (XIV) reacts rapidly with nucleophiles: treatment with dimethylamine gave a dimethylamino-derivative (XV) which, under more vigorous conditions, gave a mixture of dichloro-derivatives, (IV), (X), and (XIII), identified as described above, with isomer (XIII) as the major product. Methylamine reacts similarly with (XIV) giving (XVI), further reaction of which with methylamine led to an unstable product which we have been unable to characterise.

Sodium methoxide (1 equiv.) reacted with tetrachloropyrazine (XIV) to give mainly a methoxy-derivative (XVII); a mixture containing the isomeric dichlorodimethoxypyrazines (V), (XVIII), and (XIX) was

[3] G. G. Yakobson, L. S. Kobrina, T. D. Rubina, and N. N. Vorzhtsov, *J. Gen. Chem.* (*U.S.S.R.*), 1963, **33**, 1244, 3688.
[4] S. M. Shein and V. A. Ignatov, *J. Gen. Chem.* (*U.S.S.R.*), 1963, **33**, 2578.
[5] S. M. Roberts and H. Suschitzky, *J. Chem. Soc.* (*C*), 1968, 1537.
[6] W. T. Flowers, R. N. Haszeldine, and S. A. Majid, *Tetrahedron Letters*, 1967, 2503.
[7] R. S. Fənton, J. K. Landquist, and S. E. Meek, *J.C.S. Perkin I*, 1972, 2323, 2735.
[8] K. Gubler, R. Menasse, and K. Gaetzi, Swiss P., 484,156/1970 (*Chem. Abs.*, 1970, **73**, 14,866).
[9] C. G. Allison, R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1970, 1023.
[10] J. G. Thorpe, Ph.D. Thesis, Durham, 1969.
[11] G. A. Olah, W. S. Tolgyesi, and D. E. A. Dear, *J. Org. Chem.*, 1962, **27**, 3441.

obtained by using an excess of methoxide. Only a trace of (V) was present, detected by t.l.c.

The structure of the major dimethoxy-derivative (XIX) was deduced from the following set of observations. Reaction of the methoxy-derivative (XVII) with dimethylamine gave the same major product (XXII) as obtained by reaction of (XV) with methoxide; this indicates that, in the absence of dominating steric effects, the orienting influences of methoxy- and dimethylamino-groups are similar. Treatment of the fluoro-compound by reduction with lithium aluminium hydride, and the bromo-derivative (XXIV) was obtained from the corresponding hydrazino-compound (XXV) by reaction with copper(I) bromide. We have investigated the formation of organometallic compounds from (XXIV) but such reactions have been generally unsuccessful.[12] Exchange reactions of (XXIV) with butyl- and methyl-lithium led to the consumption of up to 4 equiv. of the alkyl-lithium and no identifiable products were isolated. Also, attempted trapping experiments gave no indication



SCHEME 2

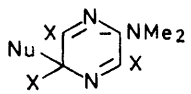
(XII) with methoxide gives (XX) and therefore establishes the structure of the latter, which is identical with the minor product (XX) obtained from substitution reactions involving (XV) or (XVII). Since we have established that neither methoxy- nor dimethylamino-groups direct substitution to the *para*-position in these chloropyrazines, the major product must be the *ortho*-isomer (XXII). Likewise, since methoxy is shown to be *ortho*-directing with dimethylamine it is reasonable to assume that the isomer obtained by reaction of (XVII) with methoxide is also an *ortho*-isomer, *i.e.* (XIX). The structure of (XXI) is assigned by analogy.

Trichloropyrazine (XXIII) was obtained from (XIV) of the intermediacy of arynes. Reactions of (XXIV) with magnesium were also unsuccessful. Furthermore, no significant quantities of bipyrazinyls were isolated from the reaction of (XXIV) with copper.

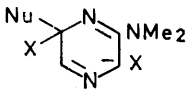
Mechanism.—A clear analogy now emerges between the orientations of nucleophilic substitution by methoxide ion in trifluoromethoxypyrazine and in trichloromethoxypyrazine (XVII): preferential attack *ortho* to methoxy occurs in each case. This directing effect can be attributed to the influence of ring nitrogen atoms, as discussed in the preceding paper.[1] Reactions of dimethylamine

[12] See also D. J. Barry, J. D. Cook, and B. J. Wakefield, *J.C.S. Perkin I*, 1972, 2190.

with trifluoro- and trichloro-dimethylaminopyrazines do show a difference, however. In each of these cases, formation of the *ortho*-isomer is inhibited by steric effects and the difference in orientation of the products obtained in the two reactions may be understood by comparing transition states like (A) and (B), corresponding to *para*- and *meta*-attack. The greater difference in stability between the transition states for the chloro- and fluoro-derivatives, will occur in case (B), where chlorine *para* to the position of attack will be strongly stabilising relative



(A)



(B)

X = Cl or F

to fluorine in the same position.[13,14] Therefore, it is understandable that more *meta*-disubstitution product (XIII) is obtained from the chloro-compound (XV) than from the corresponding trifluoro-derivative.

EXPERIMENTAL

Apparatus, solvents, and reagents used are described in the preceding paper.[1]

Molecular ions and molecular weights for chloro-compounds are given for the ^{35}Cl compound. Likewise for bromine compounds only ^{79}Br is considered. Normal isotope distributions may be presumed to have been present in all cases.

Procedure for the Reactions of Hydrazine and Alkylamines with Perhalogenopyrazines.—The pyrazine was treated with stirring with an aqueous solution of the amine (2·1 mol. equiv.) in methanol. The reaction was considered to be complete 30 min after all the starting material had dissolved, and the mixture was then added to several times its volume of water. If the product was precipitated as a solid, it was collected by filtration. In cases where the product was not precipitated, or came down as a liquid, it was extracted with ether–light petroleum (2 : 1). The organic layer was washed twice with water, dried ($MgSO_4$), and evaporated. The crude product was purified as appropriate.

Thus from tetrachloropyrazine (1 g) with dimethylamine was obtained *dimethylaminotrichloropyrazine* (XV) (750 mg), m.p. 85—86° (from methanol) (Found: C, 31·8; N, 18·7. $C_6H_6Cl_3N_3$ requires C, 31·8; N, 18·5%), τ 6·77, $\lambda_{max.}$ 271 (ε 16,000) and 350 nm (ε 6500), $\lambda_{max.}$ 6·41, 7·10, 7·47, 7·83, 8·35, 8·50, 9·23, 11·32, 14·69, 15·08, 15·33, and 20·56 μm.

Likewise from tetrachloropyrazine (1 g) and methylamine was obtained *methylaminotrichloropyrazine* (XVI) (600 mg), m.p. 88·5° (Found: C, 28·3; Cl, 50·6; N, 20·0%; M^+, 211. $C_5H_4N_3Cl_3$ requires C, 28·2; Cl, 50·1; N, 19·8%; *M*, 211), τ 6·85 (Me, d, *J* 5 Hz), $\lambda_{max.}$ 254 (ε 17,000) and 343 nm (ε 8400), $\lambda_{max.}$ 2·93, 6·27, 6·66, 6·98, 7·18, 7·89, 8·33, 8·74, 9·02, 9·40, 10·45, 13·13, and 15·07 μm.

From tetrachloropyrazine (5 g) and hydrazine was obtained crude *trichloro(hydrazino)pyrazine* (XXV) (4·2 g), which sublimed to give yellow blades, m.p. 172° (Found: C, 22·2; Cl, 50·1; N, 25·5. $C_4H_3Cl_3N_4$ requires C, 22·5; Cl, 49·9; N, 26·2%), $\lambda_{max.}$ 253·5 (ε 18,900) and 339 nm (ε 8700), $\lambda_{max.}$ 3·05, 6·35, 6·70, 7·45, 7·93, 8·69, 9·08, 9·89, 12·63, 14·58, 15·10, 15·75, 16·50, 19·07, and 21·30 μm.

From chlorotrifluoropyrazine [9] (I) (200 mg) and hydrazine was obtained 2-chloro-3,6-difluoro-5-hydrazinopyrazine (II) (120 mg), purified by sublimation to give an unstable yellow solid, m.p. 137°, ^{19}F δ 79·0 and 75·3 p.p.m. (both d, $J_{3,6}$ 43 Hz), $\lambda_{max.}$ 239·5 (ε 15,800) and 328 nm (ε 9000), $\lambda_{max.}$ 3·08, 6·18, 6·59, 7·07, 7·49, 8·19, 9·05, 10·42, 11·33, 13·60, 14·25, 15·15, 16·10, and 22·28 μm. The *acetonide*, obtained by recrystallisation of (II) from acetone, afforded white needles, m.p. 143—144° (Found: C, 38·4; Cl, 15·8; F, 17·7; N, 25·9%; M^+, 220. $C_7H_7ClF_2N_4$ requires C, 38·1; Cl, 16·1; F, 17·2; N, 25·4%; *M*, 220), τ 3·37 (s, $W_{\frac{1}{2}}$ *ca.* 15 Hz, NH), 7·87 (s, Me), and 8·00 (s, Me), $\lambda_{max.}$ 25·3 (ε 19,600) and 335·5 nm (ε 15,100).

From 2,5-dichloro-3,6-difluoropyrazine (III) and dimethylamine was obtained 2,5-*dichloro*-3-*dimethylamino*-6-*fluoropyrazine*, a liquid, purified by vacuum transfer (Found: C, 34·0; Cl, 33·2; F, 9·4; N, 20·4%; M^+, 208. $C_6H_6Cl_2FN_3$ requires C, 34·3; Cl, 33·8; F, 9·1; N, 20·0%; *M*, 208), ^{19}F δ 72 p.p.m., τ 6·97 (s), $\lambda_{max.}$ 255 (ε 14,700) and 343·5 nm (ε 7300), $\lambda_{max.}$ 3·41, 6·70, 7·15, 7·47, 8·56, 8·97, 10·80, 13·11, and 20·32 μm.

Procedure for the Reactions of Dimethylamine with Trihalogenopyrazines.—The general method was closely similar to that employed for perhalogenopyrazine except that an excess of dimethylamine was used, and the reaction was continued overnight. In some cases it was necessary to heat the reactants in a sealed tube, in which case pyridine, not methanol, was sometimes employed as solvent. Work-up procedure was identical to that described above. The reaction was sometimes performed starting from the perhalogenopyrazine without isolating the intermediate alkylaminotrihalogenopyrazine.

Thus from dimethylaminotrichloropyrazine (XV) (5 g), treated with dimethylamine in a sealed tube at 100 °C, was obtained, after recrystallisation of the crude product twice from aqueous methanol, 2,6-*dichloro*-3,5-*bis*(*dimethylamino*)-*pyrazine* (XIII) (2·5 g) as pale yellow needles, m.p. 88·5—89·5° (Found: C, 40·85; N, 23·6%; M^+, 234. $C_8H_{12}Cl_2N_4$ requires C, 40·8; N, 23·8%; *M*, 234), τ 6·80, $\lambda_{max.}$ 237 (ε 12,000) and 354 nm (ε 10,000) $\lambda_{max.}$ 3·45, 6·52, 6·75, 7·18, 7·80, 8·44, 8·65, 9·20, 9·48, 11·35, 14·30, and 20·05 μm. From the residues left by evaporation of the mother liquors, other products were obtained by chromatography over silica in light petroleum containing a trace of ether; in order of elution from the column these were: 2,3-*dichloro*-5,6-*bis*-(*dimethylamino*)*pyrazine* (X) (1 g after evaporation of solvent) which was recrystallised from light petroleum (b.p. 60—80 °C) to give yellow plates (850 mg), m.p. 86·5—87° (Found: C, 40·9; N, 23·7%; M^+, 234. $C_8H_{12}Cl_2N_4$ requires C, 40·8; N, 23·8%; *M*, 234), τ 7·05, $\lambda_{max.}$ 224 (ε 8200), 281 (ε 12,900), and 351 nm (ε 8100), $\lambda_{max.}$ 3·40, 6·48, 6·64, 6·90, 7·02, 7·10, 7·19, 7·73, 8·24, 8·36, 8·43, 8·69, 8·84, 9·43, 10·14, 10·40, 11·28, 13·98, 15·05, 15·27, and 18·45 μm; 2,5-dichloro-3,6-bis(dimethylamino)pyrazine (IV) (*ca.* 1 mg), m.p. 64—65° (from aqueous methanol), identical (mixed m.p.) with an authentic sample (see below); and 2,6-dichloro-3,5-bis(dimethylamino)pyrazine (XIII) (1·3 g).

The proportions of (XIII), (X), and (IV) were *ca.* 80 : 20 : 1 when the reaction was performed in pyridine and the distribution appeared to be similar when methanol was used as solvent.

Similarly from 2,5-dichloro-3,6-difluoropyrazine (III) (200 mg) was obtained 2,5-*dichloro*-3,6-*bis*(*dimethylamino*)-*pyrazine* (IV), as yellow needles (150 mg), m.p. 64—65° (from aqueous methanol) (Found: C, 40·9; N, 23·8%; M^+,

[13] 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.

[14] J. Burdon, *Tetrahedron*, 1965, 3373.

234. $C_8H_{12}Cl_2N_4$ requires C, 40·8; N, 23·8%; *M*, 234), τ 6·97, $\lambda_{max.}$ 219 (ε 7000), 283 (ε 18,000), and 361 nm (ε 7500), $\lambda_{max.}$ 3·45, 6·72, 6·90, 7·18, 7·51, 8·02, 8·77, 9·09, 9·51, 10·50, 14·01, 14·32, and 20·57 μm.

Likewise from 2-chloro-6-dimethylamino-3,5-difluoropyrazine (VII) (150 mg) was obtained 2-*chloro*-5,6-*bis*(*dimethylamino*)-3-*fluoropyrazine* (IX) (100 mg), m.p. 50—51° (from methanol) (Found: C, 44·1; Cl, 15·7; N, 26·0%; M^+, 218. $C_8H_{12}ClFN_4$ requires C, 43·9; Cl, 16·2; N, 25·6%; *M*, 218), ^{19}F δ 72 p.p.m., τ 7·17 (s) and 7·30 (s), $\lambda_{max.}$ 209 (ε 7600), 271 (ε 11,600), and 348 nm (ε 7600), $\lambda_{max.}$ 6·47, 6·68, 6·91, 7·14, 7·50, 8·52, 8·73, 9·46, 10·39, 11·08, 13·04, and 21·75 μm.

From 2,6-dichloro-3-dimethylamino-5-fluoropyrazine (XII) (50 mg) was obtained 2,6-dichloro-3,5-bis(dimethylamino)pyrazine (XIII) (25 mg), m.p. 87—88°, identical (mixed m.p.) with an authentic sample obtained from tetrachloropyrazine (see earlier).

From methoxytrichloropyrazine (XVII) (200 mg), after reaction in a sealed tube at 100 °C for 4 h, was obtained 2,3-*dichloro*-5-*dimethylamino*-6-*methoxypyrazine* (XXII) (140 mg), m.p. 93—94° (recrystallised twice from methanol) (Found: C, 38·4%; M^+, 220. $C_7H_9Cl_2N_3O$ requires C, 38·0%; *M*, 220), τ 6·00 (3H) and 6·85 (6H), $\lambda_{max.}$ 264 (ε 13,900) and 331 nm (ε 8400), $\lambda_{max.}$ 3·40, 6·39, 6·53, 6·62, 7·04, 7·12, 7·27, 7·64, 7·83, 8·06, 8·51, 8·60, 9·92, 10·2, 10·9, 12·9, 15·1, and 20·0 μm.

Preparation of Methoxytrihalogenopyrazines.—Tetrachloropyrazine (1 g) dissolved in methanol–ether was treated with sodium methoxide (1·1 mol. equiv.) in methanol. After 10 min the mixture was poured into water and extracted into light petroleum. The organic layer was separated and evaporated. The residue was purified by chromatography through silica in light petroleum solution. The major component was sublimed (40 °C; 0·1 mmHg) to give pure *methoxytrichloropyrazine* (XVII) (750 mg), m.p. 29·0—30·5° (Found: C, 28·1; Cl, 50·3; N, 13·4%; M^+, 212. $C_5H_5Cl_3N_2O$ requires C, 28·1; Cl, 49·9; N, 13·1%; *M*, 212), τ 6·17, $\lambda_{max.}$ 237 (ε 9900) and 316 nm (ε 10,000), $\lambda_{max.}$ 6·42, 6·79, 7·20, 7·48, 7·90, 8·45, 8·93, 9·83, 10·57, 13·15, 15·02, and 20·78 μm.

Reactions of Sodium Methoxide with Trihalogenopyrazines.—The pyrazine, dissolved in methanol, was treated with an excess of sodium methoxide, also in methanol, for 3 h. The mixture was then poured into water and the crude product filtered off and recrystallised from methanol in all cases. In some cases the reaction was performed with the perhalogenopyrazine, the intermediate methoxytrihalogenopyrazine not being isolated.

Thus from tetrachloropyrazine (2 g) was obtained, after two recrystallisations, 2,3-*dichloro*-5,6-*dimethoxypyrazine* (XIX) (900 mg), m.p. 131·5—132° (Found: C, 34·2; Cl, 33·7; N, 13·2%; M^+, 208. $C_6H_6Cl_2N_2O_2$ requires C, 34·5; Cl, 34·0; N, 13·4%; *M*, 208), τ 5·90, $\lambda_{max.}$ 236·5 (ε 12,000) and 309 nm (ε 8700), $\lambda_{max.}$ 6·38, 6·65, 6·90, 7·10, 7·38, 7·63, 7·80, 8·09, 8·48, 9·87, 10·49, 12·08, 14·38, 15·07m, and 20·10 μm. The residue from evaporation of the mother liquors of the recrystallisation was chromatographed over silica in light petroleum. The first few fractions contained a component with the same R_F value as 2,5-dichloro-5,6-dimethoxypyrazine (V) but not in sufficient quantity for isolation. Then the remaining (XIX) (800 mg) was eluted. The final fractions afforded 2,5-*dichloro*-3,6-*dimethoxypyrazine* (XVIII) (250 mg) (220 mg after recrystallisation; m.p. 138·5°) (Found: C, 34·7; N, 13·6%; M^+, 208. $C_6H_6Cl_2N_2O_2$ requires C, 34·5; N, 13·4%; *M*, 208), τ 5·88, $\lambda_{max.}$ 236 (ε 13,000) and 319 nm (ε 11,000), $\lambda_{max.}$ 6·33, 6·44, 6·68, 6·78, 6·86, 7·20, 7·60, 8·08, 8·37, 8·88, 9·97, 12·57, 13·21, and 20·35 μm.

Likewise from the dichlorodifluoropyrazine (III) (300 mg) was obtained, after recrystallisation, 2,5-*dichloro*-3,6-*dimethoxypyrazine* (V) (210 mg), as white needles, m.p. 151—152° (Found: C, 34·7; Cl, 33·5; N, 14·1%; M^+, 208. $C_6H_6Cl_2N_2O_2$ requires C, 34·5; Cl, 34·0; N, 13·4%; *M*, 208), τ 5·89, $\lambda_{max.}$ 323 (ε 13,200) and 330 nm (ε 10,000), $\lambda_{max.}$ 6·75, 7·22, 7·39, 8·23, 8·55, 8·78, 10·00, 12·27, 14·61, and 20·80 μm.

From dimethylaminotrichloropyrazine (XV) (200 mg) was obtained 2,3-*dichloro*-5-*dimethylamino*-5-*methoxypyrazine* (XXII) (120 mg), m.p. 93—94°, unchanged by admixture with a sample prepared from methoxytrichloropyrazine (XVII). The same minor product appeared on t.l.c. of the crude products from the two methods of preparation.

The residues from evaporation of the mother liquors of recrystallisation from several such preparations were chromatographed over silica, with light petroleum as eluant. The first compound eluted was present in negligible quantity, then followed the remaining 2,3-dichloro-5-dimethylamino-6-methoxypyrazine (XXII), and finally 2,6-*dichloro*-3-*dimethylamino*-5-*methoxypyrazine* (XX) (15—20% of the residues from recrystallisation). This was recrystallised from methanol, twice, to give pure material, m.p. 68·5—70° (Found: C, 38·0; N, 19·3%; M^+, 221. $C_7H_9Cl_2N_3O$ requires C, 38·0; N, 19·0%; *M*, 221), τ 6·04 (3H) and 6·90 (6H), $\lambda_{max.}$ 263 (ε 12,300) and 341 nm (ε 9000), $\lambda_{max.}$ 6·42, 6·54, 6·74, 6·90, 7·14, 7·30, 8·48, 9·07, 10·25, 11·05, 13·00, 13·38, and 20·0 μm.

Treatment of 2,6-dichloro-3-dimethylamino-5-fluoropyrazine (XII), slightly contaminated by dimethylaminotrifluoropyrazine (XV), with sodium methoxide in methanol gave a mixture of two products. The minor one was indistinguishable on t.l.c. from (XXII), and the major indistinguishable from (XX), with respect to R_F, fluorescence, and photochromic properties.

Preparation of 2,3-*Dichloro*-5-*methoxy*-6-*methylaminopyrazine.*—Methylaminotrichloropyrazine (XVI) (200 mg) was treated with a strong aqueous solution of sodium hydroxide (2 pellets) in methanol (10 ml) under reflux for 10 min. On cooling crystals appeared and were filtered off. Recrystallisation (three times from methanol) gave 2,3-*dichloro*-5-*methoxy*-6-*methylaminopyrazine* (XXI) (60 mg) as greenish plates, m.p. 164° (Found: C, 34·8; H, 3·58; N, 20·3%; M^+, 207. $C_6H_7Cl_2N_3O$ requires C, 34·6; H, 3·37; N, 20·0%; *M*, 207), τ 5·92 (OMe) and 6·90 (NMe, d, *J* 5 Hz), $\lambda_{max.}$ 252 (ε 15,000) and 326 nm (ε 9200).

Reactions of Dimethylaminofluoropyrazines with Aluminium Trichloride.—All these reactions were performed in sealed tubes.

Dimethylaminotrifluoropyrazine (VI) (1·5 g) and aluminium trichloride (3 g) were heated to 100 °C for 36 h. The product was then added to water, and sodium hydroxide solution was added until aluminium hydroxide was precipitated. The mixture was extracted with ether and the extract was dried ($MgSO_4$) and evaporated. The residue was purified by vacuum transfer to give 2-*chloro*-6-*dimethylamino*-3,5-*difluoropyrazine* (VII) (0·6 g), m.p. 6—7° (Found: C, 37·5; N, 22·3. $C_6H_6ClF_2N_3$ requires C, 37·2; N, 21·7%), ^{19}F δ 65·7 (d, *J* 10 Hz) and 83·5 p.p.m. (d, *J* 10 Hz), τ 6·87 (d, *J* 2·3 Hz), $\lambda_{max.}$ 248·5 (ε 15,000) and 342 nm (ε 6400), $\lambda_{max.}$ 3·40, 6·21, 6·60, 7·03, 7·38, 7·85, 8·15, 8·32, 8·67, 9·33, 10·41, 12·82, 14·23, and 20·10 μm.

Likewise from 2-chloro-5-dimethylamino-3,6-difluoropyrazine (VIII) (200 mg) and aluminium trichloride (500 mg), after heating to 100 °C for 5 days, was obtained 2,6-*dichloro*-3-*dimethylamino*-5-*fluoropyrazine* (XII) (110 mg), m.p. 52—60° (Found: C, 34·5; N, 20·6%; M^+, 209. $C_6H_6Cl_2FN_3$ requires C, 34·3; N, 20·1%; M, 209), ^{19}F δ 72 p.p.m., τ 6·80 (s), $\lambda_{max.}$ 265 (ε 25,000) and 345 nm (ε 11,000), $\lambda_{max.}$ 3·40, 6·37, 6·60, 7·10, 7·20, 7·44, 7·68, 7·83, 8·07, 8·53, 9·08, 9·23, 10·96, 11·30, 13·29, 13·60, 14·60, 15·32, 15·90, 18·7, 20·17, and 20·50 μm. Although analytically not significant, the mass spectrum also revealed a trace of trichlorodimethylaminopyrazine which was not removed by recrystallisation.

2-Chloro-5,6-bis(dimethylamino)-3-fluoropyrazine (IX) (250 mg) was heated to 140 °C for 3 h with aluminium trichloride (0·5 g). The product was partitioned between sodium hydroxide solution and ether and the ether layer was then separated, dried, and evaporated. The residue was dissolved in light petroleum–ether (95 : 5) and filtered through activated alumina; the filtrate was evaporated and the residue (30 mg) was recrystallised from light petroleum (b.p. 60—80 °C) to give plates, m.p. 85—86°, not depressed by admixture with 2,3-dichloro-5,6-bis(dimethylamino)-pyrazine (X) obtained from tetrachloropyrazine (see earlier). Washing the alumina from which (X) had been eluted with light petroleum–ether (80 : 20) gave another yellow crystalline solid (15 mg). This was recrystallised [light petroleum (60—80°)] giving needles, m.p. 173—175°, of a bipyrazinyl, probably (XI) (Found: M^+, 398. Calc. for $C_{16}H_{24}Cl_2N_8$: M, 398).

Preparation of 2,5-*Dichloro*-3,6-*difluoropyrazine* (III).—Chlorotrifluoropyrazine (I) [9] (5 g) was converted into the crude hydrazino-derivative (II) and to this was added with cooling a solution of anhydrous iron(III) chloride (30 g) in dilute hydrochloric acid (150 ml). The mixture was warmed gently until frothing subsided, and then water (50 ml) was distilled off, carrying the dichlorodifluoropyrazine with it. The mixture of pyrazine and water was shaken with ether, the layers were separated, and the ethereal layer was dried ($MgSO_4$) and evaporated. The residue was purified by sublimation (60 °C; 0·05 mmHg) to give pure 2,5-*dichlorodifluoropyrazine* (III) (2·3 g), m.p. 89—90° (Found: F, 20·8%; M^+, 184. $C_4Cl_2F_2N_2$ requires F, 20·6%; M, 184), ^{19}F δ 84·8 p.p.m., $\lambda_{max.}$ 214 (ε 8600), 252 (ε 1100), and 294 nm (ε 9400), $\lambda_{max.}$ 6·94, 7·05, 7·38, 8·40, 8·80, 12·03, 14·87, 17·60, and 20·50 μm.

Preparation of Bromotrichloropyrazine (XXIV).—Trichloro(hydrazino)pyrazine (XXV) (500 mg) was dissolved in *ca.* 15% hydrobromic acid (20 ml) and copper(II) bromide (1 g) was added. The mixture was stirred, and 30% hydrogen peroxide (5 ml) was added dropwise. Next day the precipitate was filtered off and sublimed (80 °C; 0·05 mmHg) to give crude *bromotrichloropyrazine* (510 mg). A sample recrystallised from ethanol had m.p. 85—86° (Found: C, 18·3; N, 10·9%; M^+, 260. $C_4BrCl_3N_2$ requires C, 18·3; N, 10·7%; M, 260), $\lambda_{max.}$ 237·5 (ε 10,900), 270·5 (ε 1800), 310·5 (ε 9300), and 315·5 nm (ε 8600), $\lambda_{max.}$ 7·7, 8·6, 9·3, 16·0, and 21·2 μm.

Preparation of Trichloropyrazine (XXIII).—Tetrachloropyrazine (1 g) was dissolved in 1 : 1 ether–tetrahydrofuran (20 ml) and cooled to −70 °C. A considerable excess of lithium aluminium hydride was added, and the mixture allowed to warm slowly, until at *ca.* 0 °C the solution became brown and effervescence was observed. The mixture was maintained at 0 °C for 2 h, then several drops of water were added to destroy any remaining hydride. The organic layerwas separated and evaporated to dryness. The residue was chromatographed over activated alumina. Light petroleum eluted tetrachloropyrazine (700 mg). Light petroleum containing a trace of ether eluted the trichloropyrazine. Other minor products were not isolated. The fractions containing trichloropyrazine were evaporated to dryness and the residue (200 mg) recrystallised at −70 °C from light petroleum and then from methanol to give trichloropyrazine (XXIII) (80 mg), m.p. 33° (Found: M^+, 182. Calc. for $C_4HCl_3N_2$: M, 182), τ 2·00 (s, $W_{\frac{1}{2}}$ 10 Hz), $\lambda_{max.}$ 229 (ε 7300) and 299·5 nm (ε 7700), $\lambda_{max.}$ 7·15, 7·62, 8·30, 8·52, 9·55, 11·60, 17·20, and 21·4 μm. Trichloropyrazine could not be made from the reaction of trichloro(hydrazino)-pyrazine (XXV) with copper(II) sulphate.

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