Polyfluoroheterocyclic Compounds. Part XV.[1] Formation and Nucleophilic Substitution of Polyfluoropyridazinium Cations

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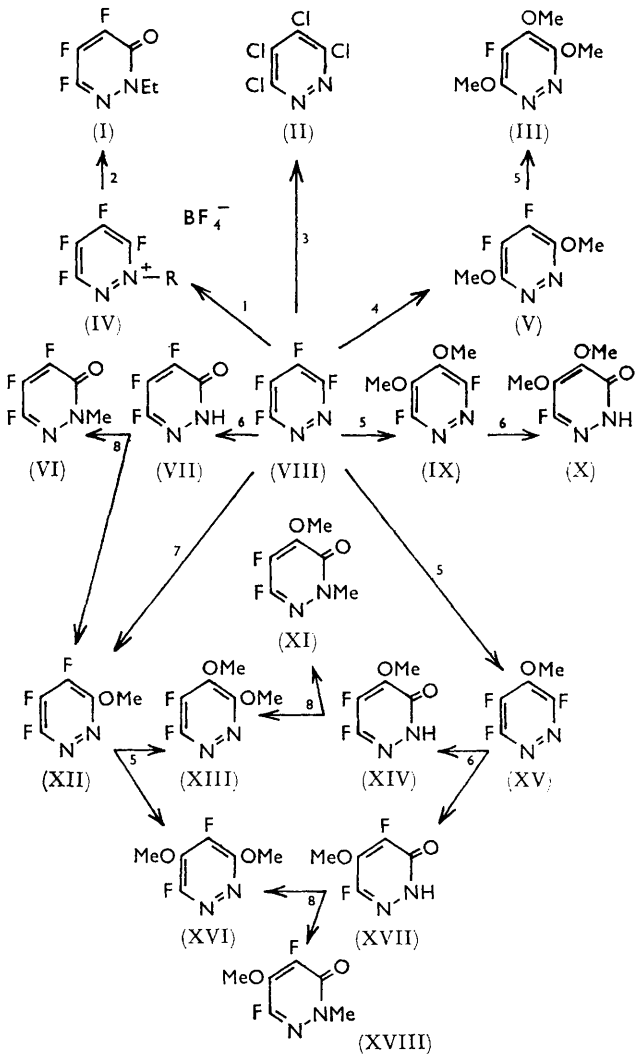
Under strongly acidic conditions, nucleophilic attack on tetrafluoropyridazine and on 3,5,6-trifluoro-4-methoxypyridazine by water or methanol leads to substitution of the fluorine atoms at C-3 and C-6 in preference to those at C-4 and C-5 which have previously been shown to be more reactive towards nucleophilic reagents under basic conditions. Treatment of tetrafluoropyridazine with water in sulphuric acid solution gives 3,4,5-trifluoro-1*H*-pyridazin-6-one, and similar treatment with methanol gives 3,4,5-trifluoro-6-methoxypyridazine (at 0°) or 4,5-difluoro-3,6-dimethoxypyridazine (at 20°). All four fluorine atoms of tetrafluoropyridazine are replaced by chlorine when it is treated with ethereal hydrogen chloride at 18°. Spectroscopic evidence suggests that the acid-catalysed reactions involve nucleophilic attack on protonated polyfluoropyridazinium cations, and two *N*-alkyl-tetrafluoropyridazinium tetrafluoroborates have been prepared and shown to give exclusively 1-alkyl-3,4,5-trifluoropyridazin-6-ones on treatment with water. Factors affecting the orientation of the products of nucleophilic attack on polyfluoropyridazinium cations are discussed. Structures have been assigned to the two isomeric difluoromethoxypyridazinones resulting from the acid-catalysed hydroxylation of 3,5,6-trifluoro-4-methoxypyridazine, by relating them to 3,4-difluoro-5,6-dimethoxypyridazine and 3,5-difluoro-4,6-dimethoxypyridazine.

RECENTLY we reported [2] the preparation of tetrafluoropyridazine and its nucleophilic substitution by amines and the anions of weak, or very weak, acids. Under these necessarily basic conditions the fluorine atoms at C-4 and C-5 of tetrafluoropyridazine are the most reactive. We now describe a different series of substitution reactions, which occur under acidic conditions, when nucleophilic attack occurs preferentially at C-3 and C-6, adjacent to the ring nitrogen atoms.

When water is added slowly to tetrafluoropyridazine (VIII) in concentrated sulphuric acid, 3,4,5-trifluoro-1*H*-pyridazin-6-one (VII) is obtained. This compound is also produced, autocatalytically, when tetrafluoropyridazine is exposed to atmospheric moisture, or when it is allowed to stand in contact with dilute sulphuric acid for a long time. Addition of methanol to tetrafluoropyridazine in concentrated sulphuric acid at 0° produces the 6-methoxy-compound (XII), while, if the reaction mixture is allowed to stand at 20°, the 3,6-dimethoxy-derivative (V) is the major product. When an ether solution of tetrafluoropyridazine is saturated with dry hydrogen chloride, no precipitate is noticeable but tetrachloropyridazine (II) is formed.

The 4- and 5-fluorine atoms of the 6-methoxy-derivative (XII) and of the 3,6-dimethoxy-derivative (V) are easily substituted by nucleophiles under non-acidic conditions; thus, when treated with one molecular proportion of sodium methoxide at 0°, the 6-methoxy-compound (XII) gives a mixture of the dimethoxy-compounds (XIII) and (XVI), while the 3,6-dimethoxy-derivative (V) gives the 3,5,6-trimethoxy-compound (III).

The hydroxylation product of tetrafluoropyridazine has been shown to exist as the pyridazinone tautomer (VII), rather than the hydroxypyridazine, since its ultraviolet and ^{19}F n.m.r. spectra are closely similar to those of its *N*-methyl derivative (VI), and markedly different from those of its *O*-methyl derivative (XII). The infrared spectrum of the pyridazinone (VII) shows an N–H



Reagents: 1, $R_3O^+BF_4^-$–CH_2Cl_2; 2, H_2O; 3, HCl–Et_2O; 4, MeOH–H_2SO_4, 20°; 5, NaOMe–MeOH; 6, H_2O–H_2SO_4; 7, MeOH–H_2SO_4, 0°; 8, CH_2N_2–Et_2O

[1] Part XIV, R. D. Chambers, C. A. Heaton, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1968, 1933.

[2] R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1968, 2116, and references there cited.

stretching band at 3086 and a carbonyl band at 1701 cm.$^{-1}$, which is also shown by the *N*-methylpyridazinone (VI) but not by the *O*-methyl compound (XII), although this region of the spectrum is partly obscured by skeletal vibrations of the pyridazine ring. When the pyridazinone was treated with diazomethane, *N*- and *O*-methylation products were obtained in an approximate ratio of 4 : 1. The minor *O*-methyl derivative (XII) was identical with that obtained when tetrafluoropyridazine was treated with sulphuric acid and methanol at 0°.

3,5,6-Trifluoro-4-methoxypyridazine [2] (XV) is also hydroxylated by slowly diluting its solution in concentrated sulphuric acid with water, giving a mixture of the isomeric methoxypyridazones (XIV) and (XVII) in the ratio 8 : 3 approximately. Similarly, 3,6-difluoro-4,5-dimethoxypyridazine (IX) gives the dimethoxypyridazinone (X). The spectroscopic properties of each of these derivatives (X), (XIV), and (XVII) again indicate that they exist as the pyridazinone tautomers.

The major isomer (m.p. 134—136°) obtained when 3,5,6-trifluoro-4-methoxypyridazine (XV) is hydroxylated by this method has been shown to be the 5-methoxypyridazin-6-one (XIV), and the minor isomer (m.p. 162—164°) the 4-methoxypyridazin-6-one (XVII), by relating them to their *O*-methyl derivatives. Each compound was methylated with diazomethane, and the total reaction mixtures were found by ^{19}F n.m.r. spectroscopy each to contain two products in the ratio *ca.* 3 : 1. The resonances of the major product in both experiments were within 1·2 p.p.m. of those of the starting pyridazinones, and are due to the *N*-methylpyridazinones (XI) and (XVIII), while the minor methylation products are the *O*-methyl ethers (XIII) and (XVI). This conclusion is confirmed by comparison with the ^{19}F n.m.r. spectrum of the mixture of difluorodimethoxypyridazines (XIII) and (XVI), obtained when one molecular proportion of sodium methoxide was added to 3,4,5-trifluoro-6-methoxypyridazine (XII). The ^{19}F n.m.r. spectrum of this mixture showed four doublets of approximately equal intensity, one pair at −7·3 and −59·9 p.p.m., from hexafluorobenzene (J_{FF} 29 c./sec.), and the other pair at −13·5 and −67·6 p.p.m. (J_{FF} 26 c./sec.). The pair with J 29 was coincident with the resonances of the minor methylation product from the more abundant methoxypyridazinone (m.p. 134—136°), and the pair with J 26 coincided with the resonances of the *O*-methyl derivative obtained by methylation of the less abundant methoxypyridazinone (m.p. 162—164°). The shifts of the fluorine resonances of the isomeric dimethoxy-compounds (XIII) and (XVI) can be calculated approximately from those observed in 6-methoxy- and 4-methoxy-trifluoropyridazine, shown relative to the corresponding resonances of tetrafluoropyridazine in Table 1.

TABLE 1

^{19}F N.m.r. chemical shifts of trifluoromethoxypyridazines

Compound	Solvent	Shifts relative to hexafluorobenzene (p.p.m.)	Effect of methoxy-substituent relative to tetrafluoropyridazine: High field 4-F	High field 5-F	Low field 3-F	Low field 6-F
Tetrafluoropyridazine	None	−18·1, −71·7	0		0	
3,4,5-Trifluoro-6-methoxypyridazine (XII)	$CDCl_3$	−9·1, −14·9, −64·7	+9·0	+3·2	+7·0	—
3,5,6-Trifluoro-4-methoxypyridazine (XV)	None	−15·0, −65·5, −73·7	—	+3·1	−2·0	+6·2

TABLE 2

^{19}F N.m.r. chemical shifts of difluorodimethoxypyridazines

Compound	Shifts relative to hexafluorobenzene (p.p.m.)	Effect of methoxy-substituents relative to tetrafluoropyridazine: High field 4-F	High field 5-F	Low field 3-F	Low field 6-F
Calculated:					
3,4-Difluoro-5,6-dimethoxypyridazine (XIII)	−6·0, −58·5	+12·1	—	+13·2	—
3,5-Difluoro-4,6-dimethoxypyridazine (XVI)	−11·8, −66·7	—	+6·3	+5·0	—
Observed:					
Isomer J 29 (in CCl_4)	−7·3, −59·9	10·8		11·8	
Isomer J 26 (in CCl_4)	−13·5, −67·6	4·6		4·1	

If these fluorine shifts due to methoxy-substituents are assumed to be additive, the shifts in 3,4-difluoro-5,6-dimethoxypyridazine (XIII) and 3,5-difluoro-4,6-dimethoxypyridazine (XVI) should be as shown in Table 2. The observed shifts of the dimethoxy-compounds, shown relative to tetrafluoropyridazine in Table 2, show that the isomer with J 29 is 3,4-difluoro-5,6-dimethoxypyridazine (XIII), and therefore that the corresponding, more abundant, pyridazinone (m.p. 134—136°) produced by the hydroxylation of 3,5,6-trifluoro-4-methoxypyridazine (XV) must be 3,4-difluoro-5-methoxy-1*H*-pyridazin-6-one (XIV).

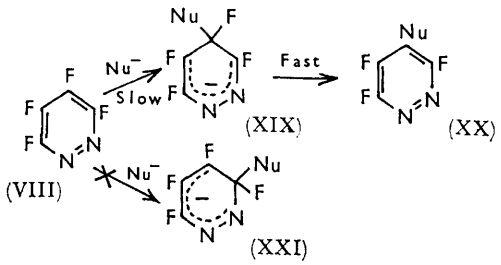
Acid catalysis in nucleophilic attack on nitrogen heterocyclic compounds, which has been shown [3] to proceed by attack on the protonated cations, is well known, but is less expected in the very weakly basic perfluoro-series.

[3] J. W. Bunting and D. D. Perrin, *J. Chem. Soc.* (*B*), 1967, 950, and references there cited.

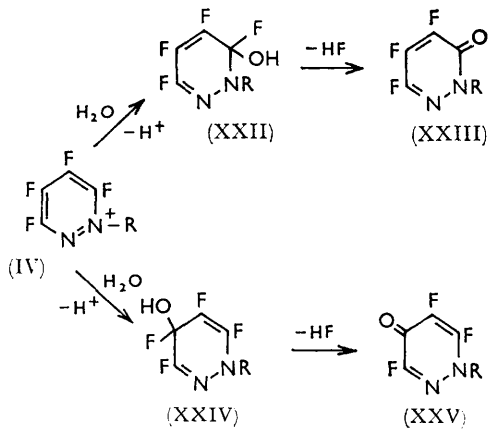
Nevertheless, we have previously reported the substitution of heptafluoroquinoline [4] by adding nucleophilic reagents to its solution in concentrated sulphuric acid. The catalytic effect of the acid in these reactions could also be attributed to assistance in the elimination of fluoride ion, by hydrogen-bonding, rather than to protonation of nitrogen. It is unlikely, however, that a mechanism of this type could cause the change from unique substitution at C-4, or C-4 and C-5, by nucleophilic attack on tetrafluoropyridazine in basic solution, to unique substitution at C-3, or C-3 and C-6, under acid catalysis. We consider, therefore, that the reacting species in the acid-catalysed reactions described in this paper are initially formed tetrafluoropyridazinium cations [or cations derived from the methoxy-compounds (IX) and (XV)]. The hypothesis that these reactions of the fluoropyridazines involve initial protonation is supported by the ^{19}F n.m.r. spectrum of tetrafluoropyridazine in concentrated sulphuric acid, which shows two multiplet bands at −43·4 and −85·7 p.p.m. (from hexafluorobenzene, external), compared with those of pure tetrafluoropyridazine at −18·1 and −71·7 p.p.m. (from hexafluorobenzene, internal). Similar shifts are observed when the spectrum of trifluoro-4-methoxypyridazine (XV) is measured in concentrated sulphuric acid (−26·1, −75·8, and −86·8 p.p.m. compared with −15·0, −65·5, and −73·7 p.p.m.). These downfield shifts are consistent with protonated species, and the appearance of only two types of fluorine in the spectrum of the protonated tetrafluoro-compound indicates exchange of the proton between the two nitrogen atoms.

To confirm that nucleophilic attack on the perfluoropyridazinium cation occurs at the position adjacent to the positively charged nitrogen atom, rather than at C-4 or C-5 as it does in the neutral molecule, *N*-ethyl- and and *N*-methyl-tetrafluoropyridazinium tetrafluoroborate (IV; R = Et and Me) were prepared (by the action of the trialkyloxonium tetrafluoroborate on tetrafluoropyridazine) and treated with water, giving the expected *N*-ethyl- and *N*-methyl-trifluoropyridazinones (I) and (VI). The formation of the *N*-ethyl quaternary salt (IV; R = Et) was confirmed by its ^{19}F n.m.r. spectrum, which showed complex bands at −31·1, −40·0, −78·9, and −85·1 p.p.m., as well as the resonance of the tetrafluoroborate ion at −12·8 p.p.m. (from hexafluorobenzene). These compounds appear to be the first examples of *N*-alkyl quaternary salts of a perfluoroheterocyclic system.

The difference in orientation of nucleophilic substitution between the tetrafluoropyridazine molecule and its *N*-protonated, or *N*-alkylated, cation cannot be due to overall thermodynamic control of the acid-catalysed reaction, since treatment of 3,5,6-trifluoro-4-methoxypyridazine (XV) with sulphuric acid and methanol, under conditions which would convert tetrafluoropyridazine into its 6-methoxy-derivative (XII), gave a mixture of the unchanged 4-methoxy-compound (XV) and the two unsymmetrical dimethoxy-compounds (XIII) and (XVI). No 6-methoxy- or 3,6-dimethoxy-pyridazines could be detected in the product by ^{19}F n.m.r. spectroscopy. Furthermore, it is unlikely that 'quenching' of the quaternary salts with water would give, exclusively, the product of thermodynamic control. The other possibility, that the 4- and 4,5-substituted compounds, obtained [2] by nucleophilic attack on the neutral perfluoropyridazine molecule, are the result of a thermodynamically controlled reaction, is also ruled out since no rearranged compounds, *e.g.*, the 4,5-dimethoxy-compound (IX), were detected when the 6-methoxy-compound (XII) was treated with methoxide ion in methanol; again only the two dimethoxy-derivatives (XIII) and (XVI) were detected. The orientation of nucleophilic substitution in the neutral tetrafluoropyridazine molecule has been discussed in previous papers,[2] in terms of the factors affecting the relative stabilities of transition states resembling the Wheland intermediates (XIX) and (XXI).



Nucleophilic attack on the tetrafluoropyridazinium cation, on the other hand, could give either, or both, of the *uncharged* intermediates exemplified by (XXII) and (XXIV), followed by the elimination of hydrogen fluoride to give the pyridazinones (XXIII) or (XXV).



Since, theoretically, each of the intermediates (XXII) and (XXIV) would probably be able to eliminate hydrogen fluoride equally easily, it is unlikely that the elimination step is rate- and product-determining. It is probable, therefore, that the relative energy of the transition states leading to these intermediates is the

[4] R. D. Chambers, M. Hole, B. Iddon, W. K. R. Musgrave, and R. A. Storey, *J. Chem. Soc.* (*C*), 1966, 2328.

deciding factor in the orientation of substitution of the tetrafluoropyridazinium cation. If the transition states are similar to these intermediates, the conjugated diene nature of (XXII) probably lowers its energy compared with the unconjugated diene (XXIV). Nucleophilic attack would also be expected to be easiest at C-6, adjacent to the positive nitrogen atom, since this is the position of lowest electron-density. The relative electron densities at the ring carbon atoms are assumed to be indicated, to a first approximation, by the chemical shifts of the ^{19}F resonances of their attached fluorine atoms; assignment of the lowest-field resonances, and therefore the lowest electron densities, of the protonated and alkylated tetrafluoropyridazinium ions to the fluorines adjacent to nitrogen, as in the neutral molecule, is supported by the spectrum of protonated 3,5,6-trifluoro-4-methoxypyridazine (XV), which lacks one of the high-field bands. It appears, therefore, that both conjugation and electron-density effects could combine to lower the activation energy of the reaction path through the intermediate (XXII), resulting in the observed attack at the position adjacent to the positively charged nitrogen atom.

EXPERIMENTAL

Infrared spectra were measured on either a Grubb-Parsons Spectromaster or GS2A spectrophotometer, ultraviolet spectra on a Unicam SP 800, mass spectra on an A.E.I. M.S.9 spectrometer, and n.m.r. spectra on a Perkin-Elmer R10 operating at 60 Mc./sec., using hexafluorobenzene as internal standard (downfield shifts are quoted as negative). Solvents were evaporated off using a rotary evaporator, and ether solutions were dried over sodium sulphate.

Tetrafluoropyridazine (VIII).—Tetrafluoropyridazine was prepared as previously described,[2] with the modification that the reaction was conducted using a nickel-lined autoclave (240 ml. capacity); tetrachloropyridazine (20 g.) and potassium fluoride (150 g.) were heated to 295—300° for 7 hr., and the contents of the autoclave were pumped out into a cold trap. The condensate (9·0 g., 65%) was almost pure (g.l.c.) tetrafluoropyridazine.

3,4,5-*Trifluoro*-6-*methoxypyridazine* (XII).—Tetrafluoropyridazine (628 mg.) in conc. sulphuric acid (5·0 ml.) was treated dropwise with a mixture of methanol (2·5 ml.) and conc. sulphuric acid (2·5 ml.) during 15 min. with stirring at 0°. After 5 min., methanol (5·0 ml.) was added during 30 min.; the mixture was stirred for a further 20 min. at 0°, diluted with ether, and poured into ice–water. The organic layer was washed with water and dried, and the solvent was evaporated off. The residue (560 mg.) was sublimed at 30°/*ca.* 20 mm., to give the 6-*methoxy-derivative* (438 mg., 65%), m.p. 54—56° [Found: C, 36·3; H, 2·0; F, 35·3%; *M* (mass spectrum), 164. $C_5H_3F_3N_2O$ requires C, 36·6; H, 1·85; F, 34·8%; *M*, 164], $\nu_{max.}$ (KBr) 3003, 2950, 1661, 1575, 1466, 1403, 1362w, 1311w, 1290, 1261w, 1214, 1171, 1115vs, 1038, 985, 943, 900, 751, 702, 666, and 492 cm.$^{-1}$, $\lambda_{max.}$ (cyclohexane) 263·5 and 285infl. mμ (log ε 3·27 and 2·83). The ^{19}F n.m.r. spectrum ($CDCl_3$) showed absorption at −9·1, −14·9, and −64·7 p.p.m.

4,5-*Difluoro*-3,6-*dimethoxypyridazine* (V).—Tetrafluoropyridazine (4·02 g.) in conc. sulphuric acid (30 ml.) was treated dropwise with a mixture of methanol (15 ml.) and conc. sulphuric acid (15 ml.) during 15 min. with stirring at 0°. After 5 min., methanol (30 ml.) was added during 30 min.; the mixture was stirred at 0° for a further 4 hr. and then at *ca.* 20° for 66 hr. Water (350 ml.) was added slowly, and the mixture was stirred for 30 min. The precipitate was dried (P_2O_5/*ca.* 400 mm.), to give colourless plates of 4,5-*difluoro*-3,6-*dimethoxypyridazine* (1·73 g., 35%), m.p. 115—117° unchanged on recrystallisation from cyclohexane [Found: C, 41·1; H, 3·5; F, 22·0%; *M* (mass spectrum), 176. $C_6H_6F_2N_2O_2$ requires C, 40·9; H, 3·4; F, 21·6%; *M*, 176], $\nu_{max.}$ (KBr) 3008w, 2899w, 2342w, 1672, 1484, 1431, 1399, 1279w, 1232, 1163, 1124, 1074, 1056sh, 1017, 1000w, 962w, 840, 826, 781, 752, 725, 702, 676w, 662, 652w, 599, 565w, and 448 cm.$^{-1}$, $\lambda_{max.}$ (cyclohexane) 272·5 mμ (log ε 3·34). ^{19}F N.m.r. (acetone) showed absorption at −7·8 p.p.m. (singlet).

3,4,5-*Trifluoro*-1H-*pyridazin*-6-*one* (VII).—Tetrafluoropyridazine (2·0 g.) in conc. sulphuric acid (20 ml.) was treated dropwise with water (80 ml.) during 1·5 hr. with vigorous stirring; the addition was regulated to keep the temperature below 60°. The mixture was stirred for a further 1·5 hr. at *ca.* 20° and extracted repeatedly with ether; the extract was washed with saturated sodium sulphate solution and dried, and the ether was evaporated off. The residue (1·87 g.) was sublimed at 100°/0·5 mm. and recrystallised from benzene, to give the *pyridazinone* (1·50 g., 75%), m.p. 129—131° [Found: C, 32·1; H, 0·7; F, 37·7%; *M* (mass spectrum), 150. $C_4HF_3N_2O$ requires C, 32·0; H, 0·7; F, 38·0%; *M*, 150], $\nu_{max.}$ (KBr) 3086, 3030, 2907, 2353, 1701, 1667, 1597, 1475, 1364w, 1299, 1279, 1232, 1129, 1020, 1016, 881, 781, 752, 662, and 654 cm.$^{-1}$ $\lambda_{max.}$ (ethanol) 277·5 mμ (log ε 3·43), $\lambda_{max.}$ (cyclohexane) 276 mμ. ^{19}F n.mr. (acetone) showed absorption at −16·6, −23·5, and −59·6 p.p.m.

3,4-*Difluoro*-5-*methoxy*-1H-*pyridazin*-6-*one* (XIV) *and* 3,5-*Difluoro*-4-*methoxy*-1H-*pyridazin*-6-*one* (XVII).—3,5,6-Trifluoro-4-methoxypyridazine [2] (765 mg.) in conc. sulphuric acid (7·6 ml.) was treated dropwise with water (30 ml.) during 1 hr. with vigorous stirring at *ca.* 18°. The mixture was stirred for a further 3 hr. and extracted repeatedly with ether. The extract was washed with saturated sodium sulphate solution and dried, and the ether was evaporated off, to give a mixture of isomeric methoxypyridazinones (611 mg.). The ^{19}F n.m.r. spectrum of the crude product was recorded. The mixture was recrystallised successively from benzene and a mixture of acetone and cyclohexane, to give 3,4-*difluoro*-5-*methoxy*-1H-*pyridazin*-6-*one* (105 mg.), m.p. 134—136° [Found: C, 36·8; H, 2·3; F, 24·2%; *M* (mass spectrum), 162. $C_5H_4F_2N_2O_2$ requires C, 37·0; H, 2·45; F, 23·5%; *M*, 162], $\nu_{max.}$ (KBr) 3160, 3012w, 2865w, 1689, 1634, 1592, 1456, 1300w, 1269, 1227, 1111, 1021, 950sh, 942, 866w, 825, 770, 757w, 629sh, and 615 cm.$^{-1}$, $\lambda_{max.}$ (ethanol) 237·5 and 271·5 mμ (log ε 3·13 and 3·36). ^{19}F N.m.r. (acetone) showed absorption at −13·1 and −56·1 p.p.m. (doublets, J_{FF} 28 c./sec.). The mother-liquors from the two recrystallisations were concentrated, and a second crop of crystals was obtained from each; these were combined and twice recrystallised from a mixture of acetone and cyclohexane, to give 3,5-*difluoro*-4-*methoxy*-1H-*pyridazin*-6-*one* (20 mg.), m.p. 162·5—164° (Found: C, 37·3; H, 2·1%), $\nu_{max.}$ (KBr) 3155, 2976, 2874, 1647, 1592, 1473, 1414, 1381w, 1361w, 1276, 1225, 1196, 1143, 1013, 957, 885, 771, 745, and 673 cm.$^{-1}$, $\lambda_{max.}$ (ethanol) 237 and 273 mμ (log ε 3·48 and 3·43). ^{19}F N.m.r. (acetone) showed absorption at −19·6 and −61·9 p.p.m. (doublets,

J_{FF} 22 c./sec.); comparison with the spectrum of the total product showed that the 4-methoxy- and 5-methoxypyridazinones were present in the ratio *ca.* 3 : 8 respectively.

3-*Fluoro*-4,5-*dimethoxy*-1H-*pyridazin*-6-*one* (X).—3,6-Difluoro-4,5-dimethoxypyridazine [2] (250 mg.) in conc. sulphuric acid (3·0 ml.) was treated dropwise with water (10 ml.) during 45 min. with vigorous stirring; the addition was regulated to keep the temperature below 60°. The mixture was stirred for a further 3 hr. at *ca.* 20° and extracted repeatedly with ether; the extract was washed with saturated sodium sulphate solution and dried, and the ether was evaporated off. The residue was recrystallised from a mixture of cyclohexane and benzene, to give the *dimethoxypyridazinone* (107 mg., 45%), m.p. 138—140°; sublimation at 20°/0·2 mm. raised the m.p. to 139—141° [Found: C, 41·4; H, 4·0%; *M* (mass spectrum), 174. $C_6H_7FN_2O_3$ requires C, 41·4; H, 4·0%; *M*, 174], $\nu_{max.}$ (KBr) 3155w, 3012w, 2890w, 1661, 1575, 1477, 1447w, 1416, 1342w, 1277, 1235, 1200, 1185, 1129vs, 1047, 960, 926, 830, 782, 763, 695w, 692, 630w, and 570 cm.$^{-1}$, $\lambda_{max.}$ (ethanol) *ca.* 252infl. and 277 mμ (log ε 3·42 and 3·60). ^{19}F N.m.r. (acetone) showed absorption at −60·0 p.p.m.

3,4,5-*Trifluoro*-1-*methylpyridazin*-6-*one* (VI).—(a) *From* 3,4,5-*trifluoro*-1H-*pyridazin*-6-*one* (VII). 3,4,5-Trifluoro-1*H*-pyridazin-6-one (664 mg.) in ether (10 ml.) was treated with ethereal diazomethane with stirring at *ca.* 20°, until there was no further effervescence and the pale yellow colour persisted. The mixture was stirred for a further 75 min. at *ca.* 20° and the ether was evaporated off. The solid residue was shown, by g.l.c. on silicone elastomer at 150°, to contain two components, and its ^{19}F n.m.r. spectrum was recorded. Two recrystallisations from cyclohexane and sublimation at 60°/20 mm. gave 3,4,5-*trifluoro*-1-*methylpyridazin*-6-*one* (440 mg., 60%) as lustrous leaves, m.p. 74—76° [Found: C, 36·4; H, 1·8; F, 35·2%; *M* (mass spectrum), 164. $C_5H_3F_3N_2O$ requires C, 36·6; H, 1·85; F, 34·8%; *M*, 164], $\nu_{max.}$ (KBr) 3289w, 2967, 2915, 2857sh, 1802w, 1706sh, 1695, 1664, 1650, 1613, 1585, 1481, 1387w, 1330, 1307, 1290, 1282, 1212w, 1166, 1109, 1010, 962, 943, 752, 730w, 705, 672, 667, 577, 538w, and 446 cm.$^{-1}$, $\lambda_{max.}$ (cyclohexane) 220infl., 281, 289·5, 300infl., and 314infl. mμ (log ε 3·26, 3·45, 3·47, 3·36, and 2·94). ^{19}F N.m.r. (acetone) showed absorption at −14·8, −24·2, and −58·5 p.p.m. Comparison with the n.m.r. spectrum and g.l.c. of the crude material revealed that the resonances and retention time of the minor product (*ca.* 20%) were identical with those of 3,4,5-trifluoro-6-methoxypyridazine.

(b) *From tetrafluoropyridazine* (VIII). Tetrafluoropyridazine (820 mg.) in methylene chloride (2·0 ml.) was added to trimethyloxonium tetrafluoroborate [5] (4·5 g.) and methylene chloride (10·0 ml.), under an atmosphere of dry nitrogen, and refluxed for 2 hr. The mixture was allowed to cool, and treated successively with wet ether (20 ml.) and water (20 ml.) with vigorous stirring at *ca.* 20°. The organic layer was separated, washed with water, and dried, and the solvent was evaporated off. The crystalline residue (651 mg.) was sublimed at 60°/20 mm., and twice recrystallised from cyclohexane, to give 3,4,5-trifluoro-1-methylpyridazin-6-one (202 mg., 25%), m.p. and mixed m.p. with a sample obtained from the previous experiment 74—76°. The i.r. spectra of the two samples were identical.

3,4,5-*Trifluoro*-1-*ethylpyridazin*-6-*one* (I).—Tetrafluoropyridazine (790 mg.) in dry methylene chloride (1·5 ml.) was added to triethyloxonium tetrafluoroborate [6] (3·0 g.) under an atmosphere of dry nitrogen. The mixture was refluxed for 45 min. and allowed to cool. In an identical experiment, a sample of this soluton was withdrawn and quickly sealed in a n.m.r. tube; its ^{19}F n.m.r. spectrum showed complex bands centred at −31·1, −40·0, −78·9, and −85·1 p.p.m., and a singlet at −12·8 p.p.m. (BF_4^-). The mixture was treated successively with wet ether (10 ml.) and water (5 ml.) with stirring at *ca.* 20°. The organic layer was separated, washed with water and dried, and the solvent was evaporated off. The ^{19}F n.m.r. spectrum of the oily residue was recorded, and then the residue (636 mg.) was distilled *in vacuo*, to give 3,4,5-*trifluoro*-1-*ethylpyridazin*-6-*one* as a colourless liquid (556 mg., 60%), b.p. 75—77°/10 mm. [Found: C, 41·4; H, 2·8%; *M* (mass spectrum), 178. $C_6H_5F_3N_2O$ requires C, 40·5; H, 2·8%; *M*, 178], $\nu_{max.}$ (film) 2985, 2933, 2874w, 1695, 1670, 1580, 1475, 1385w, 1340, 1316, 1287, 1221, 1157, 1119, 1089w, 1027, 997, 929w, 899, 746, 725w, 696, 668, and 585 cm.$^{-1}$, $\lambda_{max.}$ (cyclohexane) 221infl., 282·5, 291, 301infl., and 315infl. mμ. ^{19}F N.m.r. showed absorption at −14·7, −25·1, and −59·2 p.p.m., identical with that of the crude material.

3,4-*Difluoro*-5-*methoxy*-1-*methylpyridazin*-6-*one* (XI)—3,4-Difluoro-5-methoxy-1*H*-pyridazin-6-one (102 mg.) in ether (5·0 ml.) was treated with an excess of ethereal diazomethane with stirring at 0°. The mixture was allowed to reach room temperature with stirring during 3 hr. The ether was evaporated off, and the ^{19}F n.m.r. spectrum (in acetone) of the residue (120 mg.) showed absorption at −8·4 and −59·8 p.p.m. (doublets, J_{FF} 29 c./sec., relative intensity 1) and at −12·1 and −56·6 p.p.m. (doublets, J_{FF} 29 c./sec., relative intensity *ca.* 3). Evaporation of the solvent and two recrystallisations of the residue from di-isopropyl ether gave colourless rhombic plates of 3,4-*difluoro*-5-*methoxy*-1-*methylpyridazin*-6-*one* (42 mg.), m.p. 57—59° [Found: C, 41·5; H, 3·2%; *M* (mass spectrum), 176. $C_6H_6F_2N_2O_2$ requires C, 40·9; H, 3·4%; *M*, 176], $\nu_{max.}$ (KBr) 3270w, 3030, 3003, 2959, 2849, 1898w, 1634vs, 1580, 1466, 1443, 1410, 1342, 1318sh, 1307, 1208, 1127vs, 1026, 990, 903, 754, 732, 714w, 651, 570, and 542w cm.$^{-1}$, $\lambda_{max.}$ (ethanol) 237 and 279·5 mμ (log ε 3·4 and 3·75). The ^{19}F n.m.r. spectrum of the pure compound showed bands at −12·1 and −56·6 p.p.m. identical with those observed for the crude product.

Methylation of 3,5-*Difluoro*-4-*methoxy*-1H-*pyridazin*-6-*one* (XVII) *with Diazomethane*.—3,5-Difluoro-4-methoxy-1*H*-pyridazin-6-one (95 mg.) was treated with diazomethane as in the previous experiment. The ^{19}F n.m.r. spectrum of the total product (in acetone) showed absorption at −14·3 and −67·6 p.p.m. (doublets, J_{FF} 26 c./sec., relative intensity 1) also at −21·1 and −62·6 p.p.m. (doublets, J_{FF} 20 c./sec., relative intensity *ca.* 3). No crystalline product was obtained from the mixture.

Tetrachloropyridazine (II) *from Tetrafluoropyridazine* (VIII).—Tetrafluoropyridazine (500 mg.) in dry ether (10 ml.) was saturated with dry hydrogen chloride and set aside for a total of 2 hr. The solution was washed with water and dried, and the ether was evaporated off. The residue (687 mg.) was recrystallised from ethanol, to give tetrachloropyridazine (512 mg., 70%), m.p. 85—86·5°. A second recrystallisation raised the m.p. to 87—89° undepressed by admixture with an authentic sample.[2] The i.r. spectra of the two samples were identical.

A Mixture of 3,5-*Difluoro*-4,6-*dimethoxypyridazine* (XVI) *and* 3,4-*Difluoro*-5,6-*dimethoxypyridazine* (XIII).—(a) *From*

[5] H. Meerwein, *Org. Synth.*, 1966, **46**, 120.
[6] H. Meerwein, *Org. Synth.*, 1966, **46** 113.

3,4,5-*trifluoro*-6-*methoxypyridazine* (XII). 3,4,5-Trifluoro-6-methoxypyridazine (256 mg.) in dry methanol (1·3 ml.) was treated dropwise with methanolic sodium methoxide (1·0 mol.) during 45 min. with stirring at 0°. The mixture was stirred for a further 10 min. at 0°, allowed to reach room temperature during 10 min., evaporated to *ca.* 0·5 ml. and extracted with ether. The extract was washed with water, and dried, and the solvent was evaporated off, to give a pale yellow liquid (268 mg.) which was shown by g.l.c., on didecyl phthalate at 150°, to contain two components. The ^{19}F n.m.r. spectrum of this mixture (diluted with CCl_4) showed absorption at −7·3 and −59·9 p.p.m. (doublets, J_{FF} 29 c./sec.) also at −13·5 and −67·6 p.p.m. (doublets, J_{FF} 26 c./sec.); in acetone the absorptions were at −8·3 and −59·6 p.p.m. (J 29), and at −14·6 and −67·5 p.p.m. (J 26). Distillation at 0·3 mm. from a bath at *ca.* 70° gave a colourless analytical sample of isomeric dimethoxypyridazinones (Found: C, 41·1; H, 3·6; F, 21·9. $C_6H_6F_2N_2O_2$ requires C, 40·9; H, 3·4; F, 21·6%).

(b) *From* **3,5,6-*trifluoro*-4-*methoxypyridazine*** (XV). 3,5,6-Trifluoro-4-methoxypyridazine [2] (616 mg.) in conc. sulphuric acid (5·0 ml.) was treated dropwise with a mixture of methanol (2·5 ml.) and conc. sulphuric acid (2·5 ml.) during 15 min. with stirring at 0°. After 5 min., methanol (5·0 ml.) was added during 30 min.; the mixture was stirred for a further 20 min., diluted with ether, and poured into ice–water. The organic layer was washed with water and dried, and the ether was evaporated off, to give a pale yellow liquid (545 mg.). The ^{19}F n.m.r. spectrum showed absorptions with the shifts and fine-structure expected for 3,5,6-trifluoro-4-methoxypyridazine, 3,4-difluoro-5,6-dimethoxypyridazine, and 3,5-difluoro-4,6-dimethoxypyridazine in the ratio *ca.* 3 : 3 : 1.

4-*Fluoro*-3,5,6-*trimethoxypyridazine* (III).—4,5-Difluoro-3,6-dimethoxypyridazine (352 mg.) in methanol (1·8 ml.) was treated dropwise with methanolic sodium methoxide (1·0 mol.) during 20 min. with stirring at 0°. The mixture was stirred for a further 10 min. at 0°, allowed to reach room temperature during 10 min., evaporated to *ca.* 1 ml., and extracted with ether. The extract was washed with water and dried, and the solvent was evaporated off. The residue was sublimed at 100°/0·1 mm., to give the *trimethoxy-derivative* (270 mg., 75%), m.p. 83—85°; recrystallisation from cyclohexane raised the m.p. to 85—87° [Found: C, 44·9; H, 4·6; F, 10·3%; M (mass spectrum), 188. $C_7H_9FN_2O_3$ requires C, 44·7; H, 4·8; F, 10·1%; M, 188], $\nu_{max.}$ (KBr) 3040w, 2967, 2899w, 1626, 1468, 1389, 1372, 1279, 1208, 1196, 1178, 1143, 1117, 1067, 993, 954, 923, 756, 707w, and 682 cm.$^{-1}$, $\lambda_{max.}$ (cyclohexane) 271 mμ (log ε 3·33). ^{19}F N.m.r. (acetone) showed absorption at −9·1 p.p.m.

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