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POLYFLUOROHETEROCYCLIC COMPOUNDS—X[1]

2,3,5,6-TETRAFLUORO-4-METHYLPYRIDINE AND RELATED COMPOUNDS

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Abstract—The hydrogen atoms of the Me group in tetrafluoro-4-methylpyridine (I) are much less acidic than those of 4-picoline because of the Iπ effect of the fluorine atoms in positions 3 and 5. Free radical halogenation of the side chain of I occurs less readily than for 4-picoline and the resulting di- and trichloromethyl-tetrafluoropyridines can be hydrolysed to the corresponding aldehyde and acid.

THE papers in this series have, so far, dealt mainly with reactions involving the nucleophilic replacement of fluorine in a highly fluorinated aromatic nucleus, the position at which reaction occurs, and the influence on the reactivity of the starting material of the nitrogen atom in the ring system and the rest of the fluorine atoms. We now wish to consider the influence of the same factors on the reactions of an alkyl group attached to position 4 of the pyridine ring. Such compounds can be prepared in excellent yield by treating pentafluoropyridine with the theoretical amount of the appropriate lithium alkyl, and the preparations of 4-methyl- and 4-n-butyl-tetrafluoropyridines are described. As in the case of hexafluorobenzene, when MeMgI is used,[2] only a trace of the 4-Me derivative is obtained. When more than one molecular proportion of the lithium reagent is used the second alkyl group enters position 2 as would be expected from investigations described in earlier papers of this series. Similarly, other nucleophiles such as ethoxide ion and ammonia react with the 4-alkyltetrafluoropyridines in positions 2 and 6 as shown in Fig. 1.

In the hydrocarbon analogue of I, 4-picoline, the Me hydrogens are acidic, can be metallated,[3] and will undergo aldol condensations in acetic anhydride solution with benzaldehyde[4] and in water with formaldehyde.[5] This reactivity is due to the electronegative heterocyclic ring system to which the Me group is attached and, at first sight, it would appear that the acidity of the Me hydrogens of tetrafluoro-4-methylpyridine would be enhanced because of the extra electron withdrawal caused by the four fluorine atoms. However, when this compound is treated with n-BuLi the first reaction is to replace the 2-fluorine atom by the Bu group and further treatment of the 2-n-butyl-3,5,6-trifluoro-4-methylpyridine with n-BuLi and carbonation of the product gives only starting material together with valeric acid. Nor will tetrafluoro-4-methylpyridine condense with benzaldehyde or formaldehyde under conditions which are successful for 4-picoline. Similarly, selenium dioxide, a reagent which readily attacks active methylene groups and oxidizes 4-picoline to isonicotinic

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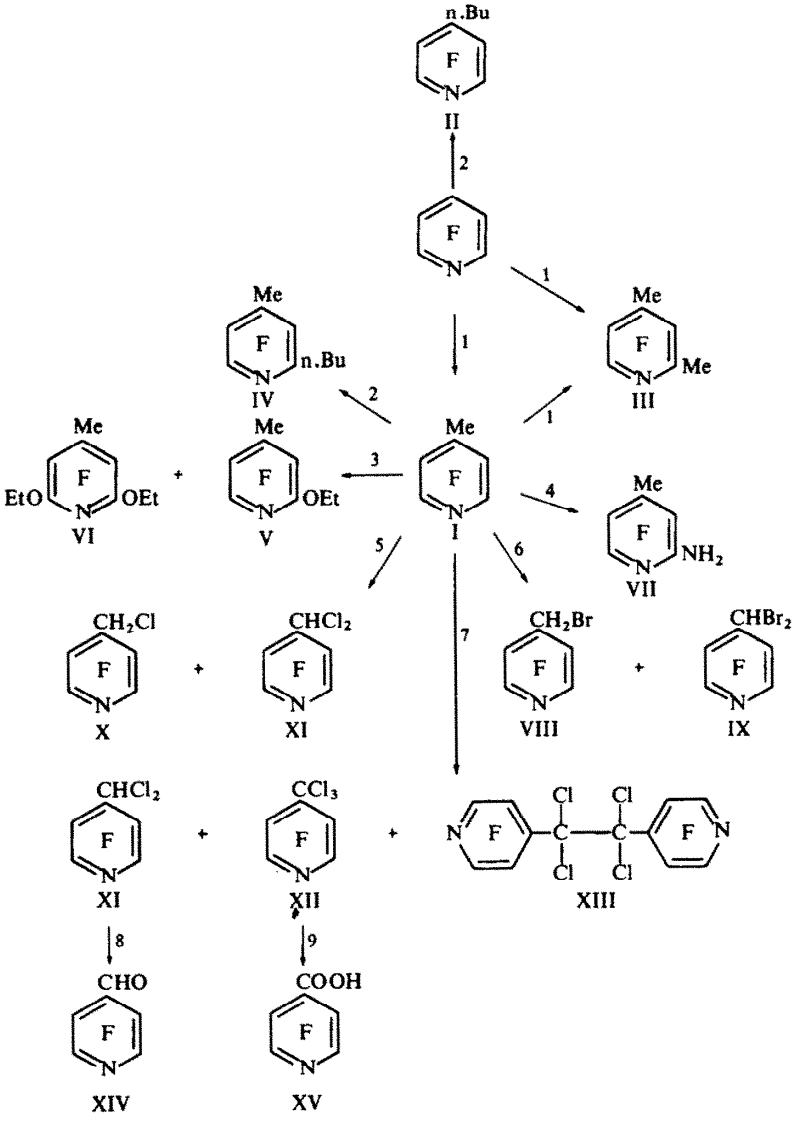
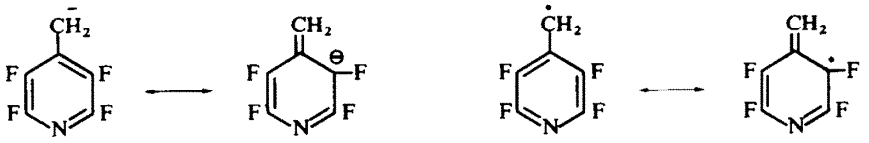


1. MeLi; 2. n-BuLi; 3. NaOEt; 4. excess aq NH_3; 5. Cl_2, 150–190°; 6. Br_2, 150–170°; 7. Cl_2, 150–210°; 8. fuming H_2SO_4; 9. conc. H_2SO_4.

FIG. 1.

acid,[6] does not oxidize tetrafluoro-4-methylpyridine. Other oxidizing agents, chromium trioxide in glacial acetic acid, alkaline permanganate, and concentrated nitric acid in the presence of mercuric nitrate cause disruption of the fluorinated ring system. These results run parallel with those on pentafluorotoluene.[7]

The inactivity of the Me group in the fluorinated ring system in reactions involving anion formation can be explained on the basis of the destabilization, relative to the



XVI XVII

corresponding non-fluorinated anion, of the anion XVI due to repulsion of the π electrons by the lone pairs of the fluorine atoms in positions 3 and 5. This Iπ effect has been used to interpret the UV spectra of the halobenzenes,[8] to rationalize orientation and reactivity in nucleophilic substitution into polyhalobenzenes,[9] and to explain the decreased acidity of fluoronitromethanes relative to the chloronitromethanes and nitromethanes by destabilizing the carbanion conjugate base in which the carbon is sp^2 hybridized.[10]

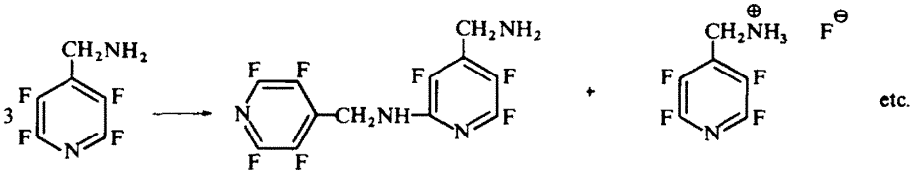
In the case of the free radical reactions of tetrafluoro-4-methylpyridine, since fluorine stabilises radicals such as XVII, easier reaction than in the case of 4-picoline would be expected. In fact, this is not so, and it may be that this is simply a steric effect due to the fluorine atoms in the 3 and 5 positions.

Thus, the peroxide-catalysed reaction between 4-picoline and N-bromo-succinimide[11] gives the tribromomethyl compound only and no mono- or di-bromo compounds, while tetrafluoro-4-methylpyridine gives only low yields of the momobromomethyl and no di- or tri-bromo derivatives. Direct bromination, in acetic acid, of 4-picoline is not possible[12] presumably not through any lack of reactivity but because of the side reactions of the brominated products which would give polycyclic nitrogen-bridged systems similar to those from 2-chloromethylpyridine.[13] On the other hand, light induced free-radical bromination of the tetrafluoro compound either in the presence or absence of a solvent proceeds slowly as far as a mixture of mono- and di-bromomethyl derivatives provided that the hydrogen bromide formed is removed on a stream of nitrogen as it is produced. These ring-fluorinated bromomethyl compounds can not undergo the same side-reactions as the unfluorinated analogues because the ring nitrogen has very limited basic strength[14] and can not form quaternary salts.

The light induced chlorination in the absence of a solvent proceeds rather more readily than does bromination and can be regulated to give either a mixture of mono- and di- or di- and tri-chloromethyl derivatives together with a small amount of 1,1,2,2-tetrachlorobis(tetrafluoro-4-pyridyl)ethane. Mass spectral data indicate that 4-trichloromethyltetrafluoropyridine readily loses a chlorine atom to give this dipyridylethane. Peroxide catalysed chlorination using sulphuryl chloride is much less successful, giving only partial conversion to 4-chloromethyl- together with a little 4-dichloromethyl-tetrafluoropyridine. These results are very similar to those obtained with pentafluorotoluene[7] in which, it is stated, the hydrogen is less susceptible to free radical attack than the corresponding hydrogen atoms in toluene itself. In this compound too the lower activity may be due to the steric hindrance of the *ortho* fluorines.

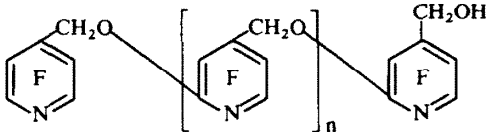
The 4-bromomethyltetrafluoropyridine reacts with aqueous ammonia, under conditions such that no nuclear substitution occurs, to give 4-aminomethyltetrafluoropyridine. This amine reacts with benzoyl chloride very readily to give the benzoyl derivative; it is not very stable and on standing deposits a white solid

possibly because of polymer, (XVIII), or simply quaternary salt, (XIX) formation (compare Ref.7).



XVIII XIX

The tetrafluoro-4-chloromethylpyridine can not be hydrolysed by acid, and heating it with aqueous sodium carbonate gives what is presumably a polyether (XX), by



XX

nucleophilic attack of the alkoxide ion formed, at position 2 of the ring system. Mass spectral measurements showed molecular weights corresponding to n = 3, 2, and 1.

The tetrafluoro-4-dichloromethylpyridine is hydrolysed by fuming sulphuric acid to tetrafluoro-4-formylpyridine which gives the usual reactions of an aldehyde, and tetrafluoro-4-trichloromethylpyridine is hydrolysed by concentrated sulphuric acid to 4-carboxy-tetrafluoropyridine.

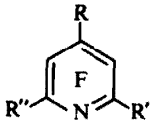
EXPERIMENTAL

^{19}F NMR measurements, used to identify the compounds described, were made on an A.E.I. R.S.2 spectrometer operating at 60 Mc/s and are shown in Table 1.

Reactions of pentafluoropyridine

(a) *With methyllithium.* (i) An ice-cold solution of MeLi[17] (125 mmoles) in anhyd ether (100 ml) was added over 1½ hr to a stirred soln of pentafluoropyridine (21·13 g, 125 mmoles) in anhyd ether (150 ml) at −60° under N. Cooling was discontinued, and stirring was continued for a further 1 hr after which the reaction mixture was poured onto ice and 2N HCl. The ethereal layer was separated, the aqueous layer was extracted with ether (3 times), the combined ethereal extracts washed with water, dried (Na_2SO_4) and, after removal of the ether, fractional distillation of the residue gave 2,3,5,6-*tetrafluoro-4-methylpyridine* (I; 18·6 g, 90%) as a colourless liquid, b.p. 130–131°/760 mm, n_D^{20} 1·4109, d^{20} 1·44 g/ml, λ_{max} (in cyclohexane) 209 and 266 mμ. (Found: C, 43·6; H, 2·1; F, 46·1. $C_6H_3F_4N$ requires: C, 43·6; H, 1·8; F, 46·0%.) (ii) An ice-cold soln of MeLi (70 mmoles) in anhyd ether (50 ml) was added to a stirred soln of pentafluoropyridine (5·9 g, 35 mmoles) in anhyd ether (100 ml) at −60° under N. Cooling was discontinued and the reaction mixture was stirred for a further 3 hr after which it was treated as in (i). Distillation of the product gave a fraction (4·0 g), b.p. 130–144°/760 mm, which was shown by analytical-scale GLC (di-n-decylphthalate on Celite at 100° or silicone elastomer on Celite at 75°) to consist of 2,3,5,6-tetrafluoro-4-methylpyridine (12 mole %) and 3,5,6-*trifluoro*-2,4-*dimethylpyridine* (III; 88 mole %), and a higher-boiling fraction (0·30 g), b.p. 146–150°/760 mm, which was shown by analytical-scale GLC (silicone elastomer on Celite at 150°) to consist of several products which were not investigated further. The 3,5,6-trifluoro-2,4-dimethylpyridine was separated by preparative-scale GLC (silicone elastomer on Celite at 110°) and had b.p. 148–150°/760 mm, n_D^{20} 1·4366, d^{20} 1·27 g/ml, λ_{max} (in cyclohexane) 204 and 267 mμ. (Found: C, 52·4; H, 3·6; F, 35·3. $C_7H_6F_3N$ requires: C, 52·2; H, 3·8; F, 35·4%.)

TABLE 1. ^{19}F CHEMICAL SHIFTS IN DERIVATIVES OF PENTAFLUOROPYRIDINE, RELATIVE TO $CFCl_3$ (p.p.m.)* (POSITIONS OF THE FLUORINE NUCLEI OR SUBSTITUTED GROUPS IN PARENTHESES)



	R	R'	R''	Chemical shifts (+ve shifts are measured to high field)			Effect of substituted group on ^{19}F shifts				Reference Compound
A[15]	F	F	F	87·6 (2,6)	162·0 (3,5)	134·2 (4)					
B	Me	F	F	92·5 (2,6)	144·0 (3,5)		Me (4)	−18 (3,5)	+5 (2,6)		A
C	Me	Me	F	90·9 (6)	144·25 (5)	128·65 (3)	Me (2)	−15 (3)	−2 (6)	0 (5)	B
D	n-Bu	F	F	91·9 (2,6)	144·2 (3,5)		n-Bu (4)	−18 (3,5)	+4 (2,6)		A
E	Me	n-Bu	F	90·7 (6)	144·3 (5)	130·6 (3)	n-Bu (2)	−13 (3)	−2 (6)	0 (5)	B
F[14]	NH_2	F	F	95·7 (2,6)	165·9 (3,5)		NH_2 (4)	+4 (3,5)	+8 (2,6)		A
G[16]	NH_2	NH_2	F	96·4 (6)	175·2 (5)	164·1 (3)	NH_2 (2)	−2 (3)	+1 (6)	+9 (5)	F
H[a]	Me	NH_2	F	94·9 (6)	160·1 (5)	145·8 (3)	NH_2 (2)	+2 (5)	+2 (6)	+16 (5)	B
I	Me	OEt	F	95·1 (6)	154·1 (5)	144·3 (3)	OEt (2)	0 (3)	+3 (6)	+10 (5)	B
J[b]	Me	OEt	OEt		152·5 (3,5)		OEt (2)	−2·0 (3)		+8 (5)	I
K	CH_2Cl	F	F	89·7 (2,6)	143·1 (3,5)		CH_2Cl (4)	−1 (3,5)	−3 (2,6)		B
L	$CHCl_2$	F	F	87·8 (2,6)	140·7 (3,5)		$CHCl_2$ (4)	−3 (3,5)	−5 (2,6)		B
M	CCl_3	F	F	87·1 (2,6)	140·1 (3,5)		CCl_3 (4)	−4 (3,5)	−5 (2,6)		B
N	CH_2Br	F	F	89·75 (2,6)	143·0 (3,5)		CH_2Br (4)	−1 (3,5)	−3 (2,6)		B
O	$CHBr_2$	F	F	88·1 (2,6)	139·9 (3,5)		$CHBr_2$ (4)	−4 (3,5)	−4 (2,6)		B
P	CHO	F	F	90·4 (2,6)	146·8 (3,5)		CHO (4)	−15 (3,5)	+3(2,6)		A

* Spectra were recorded using pure liquids with the exception of (*a*) in ether and (*b*) in acetone.

(b) *With n-butyllithium.* An ice-cold soln of n-BuLi (15 mmoles) in anhyd ether–hexane (4/6 ml) was added over 30 min to a stirred soln of pentafluoropyridine (2·54 g, 15 mmoles) in anhyd ether (10 ml) at −70° under N. The reaction mixture was stirred for a further 30 min at −70° followed by 30 min at 20°. After working up the reaction mixture in the manner described above, the product obtained was vacuum transferred and further purified by preparative-scale GLC (silicone elastomer on Celite at 110°) to give *4-n-butyl-2,3,5,6-tetrafluoropyridine* (II; 2·2 g, 71%) as a colourless liquid, b.p. 185–186°/758 mm, n_D^{20} 1·4249, λ_{max} (in cyclohexane) 206 and 266 mμ. (Found: C, 52·6; H, 4·1; F, 36·3. $C_9H_9F_4N$ requires: C, 52·2; H, 4·4; F, 36·7%.)

Reactions of 2,3,5,6-tetrafluoro-4-methylpyridine

(a) *With sodium ethoxide.* (i) Na (0·46 g, 20 mmoles) was added to anhyd EtOH (20 ml) followed by 2,3,5,6-tetrafluoro-4-methylpyridine (1·65 g, 10 mmoles) and the mixture was refluxed for 3 hr after which it was poured into ice-cold water (100 ml). Extraction of the product with CH_2Cl_2 and distillation of the dried (Na_2SO_4) extracts gave *2,6-diethoxy-3,5-difluoro-4-methylpyridine* (VI; 2.1 g, 97%) as a colourless liquid, b.p. 48–50°/0·3 mm. The product solidified in the receiver and was further purified by sublimation under reduced press (40°/0·04 mm) to give white crystals, m.p. 43–44°, λ_{max} (in cyclohexane) 217 and 291 mμ. (Found: C, 54·9; H, 5·7; F, 17·3. $C_{10}H_{13}F_2NO_2$ requires: C, 55·3; H, 6·0; F, 17·5%.)

(ii) Na (0·35 g, 15 mmoles) was added to anhyd EtOH (10 ml) and the resulting soln of EtONa was added slowly, with stirring, to a soln of 2,3,5,6-tetrafluoro-4-methylpyridine (2·5 g, 15 mmoles) in anhyd EtOH (20 ml) at 0°. The mixture was stirred for a further 1 hr at 0° and then at 20° for 3 hr after which it was worked up in the manner described above. Distillation of the product gave a colourless oil (2·4 g, 83%), b.p. 178–180°, which was shown by analytical-scale GLC (silicone elastomer on Celite at 175°) to contain <1% of 2,6-diethoxy-3,5-difluoro-4-methylpyridine. Purification by preparative-scale GLC (silicone elastomer on Celite at 170°) gave *2-ethoxy-3,5,6-trifluoro-4-methylpyridine*, (V) b.p. 178–180°, n_D^{20} 1·4450, d^{20} 1·28 g/ml, λ_{max} (in EtOH) 213 and 278 mμ. (Found: C, 50·3; H, 4·1; F, 30·2. $C_8H_8F_3NO$ requires: C, 50·3; H, 4·2; F, 29·8%.)

(b) *With ammonia.* 2,3,5,6-Tetrafluoro-4-methylpyridine (1·65 g, 10 mmoles) and ammonia (5·0 g; 0·88 *s.g.*, large excess) were sealed in a Carius tube, and heated at 150° for 4 hr. On cooling the tube to room temp, the white solid which had formed was filtered off, dried (over P_2O_5 *in vacuo*), and sublimed under reduced press (60°/0·04 mm) to give a product (0·80 g, 49%) which was shown by analytical-scale GLC (silicone elastomer on Celite at 150°) to be slightly impure. Further purification by preparative-scale GLC (silicone elastomer on Celite at 150°) followed by crystallization from light petroleum (b.p. 40–60°) gave *2-amino-3,5,6-trifluoro-4-methylpuridine*, (VII) m.p. 106–107°, λ_{max} (in cyclohexane) 220 and 293 mμ. (Found: C, 44·6; H, 3·2; F, 34·8. $C_6H_5F_3N_2$ requires: C, 44·45; H, 3·1; F, 35·2%.)

(c) *With n-butyllithium.* (i) An ice-cold soln of n-BuLi (10 mmoles) in anhyd ether–hexane (2·5/2·5 ml) was added over 30 min to a stirred soln of 2,3,5,6-tetrafluoro-4-methylpyridine (1·65 g, 10 mmoles) in anhyd ether (5 ml) at −60° under N. The reaction mixture was worked up as described for the preparation of tetrafluoro-4-methylpyridine and afforded a single product (1·72 g, 85%) which was shown to be *2-n-butyl-3,5,6-trifluoro-4-methylpyridine*, (IV) b.p. 206–207° (with slight decomp), n_D^{20} 1·4453, λ_{max} (in cyclohexane) 205 and 268 mμ. (Found: C, 59·2; H, 5·6; F, 28·2. $C_{10}H_{12}F_3N$ requires: C, 59·1; H, 6·0; F, 28·05%.)

(ii) The product from (c) (i) (1·02 g, 5 mmoles) was treated with n-BuLi (5 mmoles) in anhyd ether at −60° under N. After stirring for 30 min at −60° dry CO_2 was passed into the reaction mixture for 30 min and it was then allowed to warm to room temp while the introduction of CO_2 continued. After working up as described for tetrafluoro-4-methylpyridine it afforded, besides valeric acid, only starting material.

(d) *With bromine.* (i) A stream of dry N was bubbled through 2,3,5,6-tetrafluoro-4-methylpyridine (4·95 g, 30 mmoles) heated under reflux on a bath at 150° and irradiated by a 200 w. bulb. Br_2 (a large excess) was added at intervals and the course of the reaction was followed by analytical-scale GLC (silicone elastomer on Celite at 100°). The temp of the bath was raised slowly to 170° during the course of the reaction. The results of a typical reaction are given in Table 2.

When no starting material could be detected by GLC the excess of Br_2 was removed by increasing the flow of N_2. The reaction mixture was vacuum transferred to give a product (6·8 g) which was separated by preparative-scale GLC (silicone elastomer on Celite at 110°) into *4-bromomethyl-2,3,5,6-tetrafluoropyridine* (VIII; 77 mole %, 4·9 g) a strongly lachrymatory liquid with b.p. 187–188°/760 mm, n_D^{20} 1·4802. (Found: C, 29·5; H, 0·76; F, 31·0; Br, 32·4. $C_6H_2F_4BrN$ requires: C, 29·5; H, 0·83; F, 31·15; Br, 32·75%); and *4-dibromomethyl-2,3,5,6-tetrafluoropyridine* (IX; 23 mole %, 1·9 g) a lachrymatory liquid with b.p. 208–209°/758 mm (with slight decomp), n_D^{20} 1·5185, λ_{max} (in cyclohexane) 213 and 272 mμ. (Found: C, 22·7;

TABLE 2. ELEMENTAL BROMINATION OF TETRAFLUORO-4-METHYLPYRIDINE

Reaction time hr	Products		
	Starting material mole %	Bromomethyl deriv mole %	Dibromomethyl deriv mole %
10	47·8	52·2	trace
18	9·4	80·4	10·2
30	0	77	23

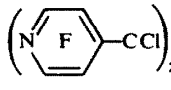
H, 0·27; F, 22·8; Br, 49·1. $C_6HF_4Br_2N$ requires: C, 22·3; H, 0·3; F, 23·5; Br, 49·5%.) (ii) 2,3,5,6-Tetrafluoro-4-methylpyridine (1·65 g, 10 mmoles) and bromine (4·8 g, 30 mmoles) were sealed in a silica tube and irradiated by a 750 W Hanovia mercury discharge tube for 72 hr. The product was dissolved in ether, the ethereal soln was washed successively with 2% Na_2CO_3 aq, 2% Na_2SO_3 aq, and water, and dried (Na_2SO_4). After removal of the ether, analytical-scale GLC showed the product (1·8 g) to be a mixture of starting material (76 mole %) and 4-bromomethyl-2,3,5,6-tetrafluoropyridine (24 mole %).

(e) *With N-bromosuccinimide.* A mixture of 2,3,5,6-tetrafluoro-4-methylpyridine (1·65 g, 10 mmoles), N-bromosuccinimide (2·0 g, 11·2 mmoles), and benzoyl peroxide (0·024 g, 0·1 mmole) in anhyd CCl_4 (15 ml) was heated under reflux for 17 hr after which time all the N-bromosuccinimide had been consumed. The succinimide was filtered off and the filtrate was washed successively with 2% Na_2CO_3 aq, 2% Na_2SO_3 aq, and water, and dried (Na_2SO_4). The CCl_4 was distilled off and the residue was vacuum transferred to give a product (1·62 g) which was shown by analytical-scale GLC to be a mixture of starting material (65 mole %) and 4-bromomethyl-2,3,5,6-tetrafluoropyridine (35 mole %) together with traces of two other unidentified compounds.

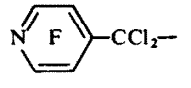
(f) *With chlorine.* (i) A stream of dry Cl_2 was passed into 2,3,5,6-tetrafluoro-4-methylpyridine (3·30 g, 20 mmoles) heated under reflux on a bath at 150° and irradiated by a 200 W bulb. The bath temp was raised slowly to 190° and the course of the reaction was followed by analytical-scale GLC (silicone elastomer on Celite at 100°). After 90 min, when all the starting material had been consumed, the reaction mixture was vacuum transferred to give a product (3·7 g) which was shown by GLC to be a mixture of 4-*chloromethyl*-2,3,5,6-*tetrafluoropyridine* (X; 75 mole %, 2·66 g) and 4-*dichloromethyl*-2,3,5,6-*tetrafluoropyridine* (XI, 25 mole %, 1·04 g); total yield 88·5%.

The products were separated by preparative-scale GLC (silicone elastomer on Celite at 110°). 4-Chloromethyl-2,3,5,6-tetrafluoropyridine is lachrymatory and has b.p. 167·5/758 mm, n_D^{20} 1·4512, λ_{max} (in cyclohexane) 212 and 274 mμ. (Found: C, 36·2; H, 1·0; F, 18·3; Cl, 37·8. $C_6H_2F_4ClN$ requires: C, 36·1; H, 1·0; F, 38·1; Cl, 17·8%.) 4-Dichloromethyl-2,3,5,6-tetrafluoropyridine is slightly lachrymatory and has b.p. 179°/758 mm, n_D^{20} 1·4684, λ_{max} (in cyclohexane) 211 and 279 mμ. (Found: C, 30·8; H, 0·52; F, 33·0; Cl, 30·4. $C_6HF_4Cl_2N$ requires: C, 30·8; H, 0·43; F, 32·5; Cl, 30·3%). (ii) 2,3,5,6-Tetrafluoro-4-methylpyridine (6·0 g, 36·4 mmoles) was chlorinated as above except that the bath temp was raised slowly to 210° over 18 hr. A small amount of white solid had separated; on cooling to 0° more of the solid crystallized and the liquid was decanted from the solid and vacuum transferred to give a product shown by GLC to be a mixture of 4-dichloromethyl-2,3,5,6-tetrafluoropyridine (75·5 mole %, 4·34 g) and 4-*trichloromethyl*-2,3,5,6-*tetrafluoropyridine* (XII; 24·5 mole %, 1·66 g) together with traces of two other compounds; one of these had the same retention time as that of 4-chloro-2,3,5,6-tetrafluoropyridine.

The solid was triturated with light petroleum (b.p. 40–60°) and filtered off to give what was shown by NMR to be 1,1,2,2-*tetrachlorobis*(2,3,5,6-*tetrafluoro*-4-*pyridyl*)*ethane* (XIII; 0·35 g, 0·75 mmoles) which, on further purification by recrystallization from ethyl methyl ketone, had m.p. 288–289° (sealed tube). (Found: C, 31·0. $C_{12}F_8Cl_4N_2$ requires: C, 30·9%.) In the mass spectrum the parent ion peak (mass number 464) and the P + 2, P + 4, and P + 6 peaks showed up in the correct isotopic abundance ratio. The P + 8 peak could not be seen. Fragment ion peaks at mass numbers 394, 396, and 398



; and 232, 234, and 236



had the isotopic abundance ratio expected for two chlorine atoms and the latter combination indicated the ready fission of the compound into two equivalent fragment ions. The peak at mass number 197 corresponded to the fragment ion formed by loss of one chlorine atom from the fission ions and the peaks at mass numbers 197 and 199 had the isotopic abundance ratio expected for the presence of one chlorine atom. The IR spectrum of this compound was also consistent with its structure.

The chloromethyl compounds were separated by preparative-scale GLC (silicone elastomer on Celite at 110°). 4-Trichloromethyl-2,3,5,6-tetrafluoropyridine has b.p. 197–198°/740 mm, n_D^{20} 1·4820. (Found: C, 26·9; F, 28·2; Cl, 39·0. $C_6F_4Cl_3N$ requires: C, 26·8; F, 28·3; Cl, 39·6%.) The mass spectrum of this compound was obtained using a cold inlet system; when a hot inlet system was employed the resulting spectrum was very similar to that obtained for 1,1,2,2-tetrachloro-bis(2,3,5,6-tetrafluoro-4-pyridyl)ethane. When the cold inlet system was used the parent ion peak was present at mass number 267 and this and the peaks at 269, 271, and 273 had the isotopic abundance ratio expected for the presence of three chlorine atoms. The base peak was present at mass number 232 corresponding to the loss of one chlorine atom from the sterically strained parent ion. The peaks at 232, 234, and 236 had the isotopic abundance ratio expected for the presence of two chlorine atoms. Peaks were also present at 197 and 162 corresponding to the loss of two and three chlorine atoms, respectively, from the parent ion.

(g) *With sulphuryl chloride.* A mixture of 2,3,5,6-tetrafluoro-4-methylpyridine (1·65 g, 10 mmole), SO_2Cl_2 (1·35 g, 10 mmoles), and benzoyl peroxide (0·024 g, 0·1 mmole) was heated under reflux. After 21 hr, and again after 50 hr, further amounts of SO_2Cl_2 (1·35 g, 10 mmoles) were added. The course of the reaction was followed by analytical-scale GLC. After 5 days the excess SO_2Cl_2 was distilled off and the reaction mixture vacuum transferred to give a product (1·9 g) which was shown by analytical-scale GLC to be a mixture of starting material (37 mole %), 4-chloromethyl-2,3,5,6-tetrafluoropyridine (58·7 mole %), and 4-dichloromethyl-2,3,5,6-tetrafluoropyridine (4·3 mole %) together with traces of SO_2Cl_2, chlorobenzene, and benzoyl chloride.

Hydrolysis of 4-trichloromethyl-2,3,5,6-tetrafluoropyridine

4-Trichloromethyl-2,3,5,6-tetrafluoropyridine (0·29 g, 1·08 mmoles) was heated at 150–160° with conc H_2SO_4 (1 ml) for 2 hr, the reaction mixture was cooled and poured onto ice. The resulting aqueous soln was extracted with ether (5 times), the ethereal extracts were combined, washed with water, and dried (Na_2SO_4). The ether was distilled off and the residue was sublimed at 80° (bath temp)/0·3 mm. A white solid was obtained which was further purified by recrystallisation from hexane to give 4-carboxy-2,3,5,6-tetrafluoropyridine (0·14 g, 67%), the m.p., mixed m.p., and the IR spectrum of which were identical with those of an authentic sample.

Hydrolysis of 4-dichloromethyl-2,3,5,6-tetrafluoropyridine

4-Dichloromethyl-2,3,5,6-tetrafluoropyridine (1·7 g, 7·3 mmoles) was heated at 150° with fuming H_2SO_4 (2·6 ml) for 20 hr in a Carius tube after which the reaction mixture was cooled and poured onto ice. The product was extracted with ether, the ethereal extracts were washed with water, and dried ($MgSO_4$). The ether was distilled off and the residue (0·8 g) was purified by large-scale GLC (silicone elastomer on Celite at 175°) to give 2,3,5,6-*tetrafluoro-4-formylpyridine* (XIV; 0·40 g, 31%), a liquid with b.p. 173–174°/734 mm, n_D^{20} 1·4557 (Found: C, 40·1; H, 0·6; F, 41·9. C_6HF_4NO requires: C, 40·25; H, 0·6; F, 42·4%), carbonyl vibration frequency 1724 cm^{-1}. In the mass spectrum of this compound the parent ion peak (base peak) was present at mass number 179. Other prominent peaks present at mass numbers 178, 160, 151, and 150, supported the structure.

The product gave a silver mirror with ammoniacal $AgNO_3$ and a 2,4-*dinitrophenyl hydrazone* m.p. 232°. (Found: C, 40·3; H, 1·5; F, 20·6; M, 359. $C_{12}H_5F_4N_5O_4$ requires: C, 40·1; H, 1·4; F, 21·2%; M, 359.) A mixture of the aldehyde (0·5 g) and aniline (0·5 g) was warmed at 100° for 30 min; the solid product (0·5 g) was filtered off and recrystallized from EtOH to give 2,3,5,6-*tetrafluoroisonicotinylidene aniline* (0·2 g) m.p. 111°. (Found: C, 56·8; H, 2·4; F, 29·1; M, 254. $C_{12}H_6F_4N_2$ requires: C, 56·7; H, 2·4; F, 29·5%; M, 254.)

Hydrolysis of 4-chloromethyl-2,3,5,6-tetrafluoropyridine

4-Chloromethyltetrafluoropyridine (4 g, 20·0 mmoles) was heated at 100° with K_2CO_3 (7 g) in water (25 ml) for 6 hr. After cooling, the reaction mixture was extracted with ether (4 × 25 ml), dried ($MgSO_4$), and the ether distilled. The residue (2·2 g), a very viscous liquid, had, among others, peaks with mass numbers at 825, 664, and 503 corresponding to polymers of the formula XX with n = 3, 2 and 1 respectively.

Reaction of 4-bromomethyl-2,3,5,6-tetrafluoropyridine with aqueous ammonia

A mixture of 4-bromomethyltetrafluoropyridine (1·76 g, 7·2 mmoles) and aqueous ammonia (4 ml, *s.g.* 0·88) in EtOH (~3 ml, sufficient to make the system homogeneous) was stirred at 20° for 20 hr and the reaction mixture was then poured into water. The product was extracted with ether, the extract washed with water, and dried (Na_2SO_4) and, after removal of the ether by distillation, the residual oil was vacuum transferred to give crude *4-aminomethyl-2,3,5,6-tetrafluoropyridine* (0·66 g, 32%). The amine reacted immediately with benzoyl chloride at room temp in the absence of NaOH to give *N-benzoyl-4-aminomethyl-2,3,5,6-tetrafluoropyridine* which, after recrystallization from EtOH, had m.p. 185–186°. (Found: C, 54·8; H, 2·9; F, 27·7; M, 284. $C_{13}H_8F_4ON_2$ requires: C, 54·9; H, 2·8; F, 26·8%; M, 284.)

The amine is unstable and begins to deposit a white solid after about 1 hr; it is all converted into solid after a few days. It forms a hydrochloride.

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