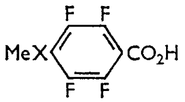
1178. *Aromatic Polyfluoro-compounds. Part XXIX.*[1] *Nucleophilic Replacement Reactions of Pentafluorobenzoic Acid*

By J. Burdon, W. B. Hollyhead, and J. C. Tatlow

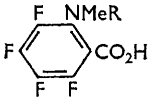
Sodium methoxide and sodium thiomethoxide reacted with pentafluorobenzoic acid to replace mainly (>90%) the fluorine *para* to the carboxyl group. Methylamine and dimethylamine gave comparable amounts of *ortho*- and *para*-replacement and also some decarboxylation to pentafluorobenzene, which reacted further with the nucleophiles.

In our studies [2] on the nucleophilic replacement reactions of pentafluorophenyl derivatives (C_6F_5X), we have so far found only one compound, pentafluoronitrobenzene, which gives substantially different isomer ratios with different nucleophiles.[3] We have now found that pentafluorobenzoic acid behaves similarly.

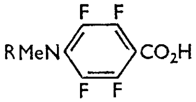
Pentafluorobenzoic acid reacted with sodium methoxide and with sodium thiomethoxide, both in methanol, to give mainly (>90%) products (I, II) in which the fluorine *para* to the carboxyl group had been replaced. The fluorine and proton nuclear magnetic resonance (n.m.r.) spectra (Table 2) of both compounds were consistent only with these *para* structures. Additional chemical evidence was provided in the methoxyl case (I) by heating with ammonia (see later), when decarboxylation to the known [4] 2,3,5,6-tetrafluoroanisole occurred.



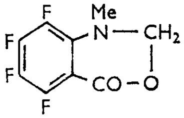
(I : X = O)
(II: X = S)



(III: R = H)
(IV: R = Me)



(V: R = H)
(VI: R = Me)



(VII)

Pentafluorobenzoic acid gave both acidic and neutral products with methylamine. The acidic products were 6- and 4-(methylamino)tetrafluorobenzoic acids, (III) and (V), respectively, and their relative amounts varied with the temperature of the reaction (Table 1). The structure of the *ortho*-acid (III) was proved by cyclisation with formaldehyde to compound (VII); anthranilic acid and many of its derivatives undergo a similar

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[1] Part XXVIII, D. Callandar, P. L. Coe, and J. C. Tatlow, *Tetrahedron*, 1965, in the press.

[2] J. C. Tatlow, *Endeavour*, 1963, **22**, 89, and other Parts in this Series.

[3] G. M. Brooke, J. Burdon, and J. C. Tatlow, *J.*, 1961, 802; J. G. Allen J. Burdon, and J. C. Tatlow, *J.*, 1965, 1045.

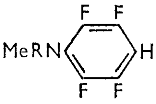
[4] R. Stephens and J. C. Tatlow, *Chem. and Ind.*, 1957, 821; G. M. Brooke, E. J. Forbes, R. D. Richardson, M. Stacey, and J. C. Tatlow, *J.*, 1965, 2088.

[5] V. Villiger, *Ber.*, 1909, **42**, 3529: V. Villiger and L. Blangey, *ibid.*, p. 3549; P. Friedlander and K. Kunz, *Ber.*, 1922, **55**, 1597.

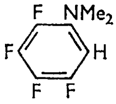
reaction.[5] The *para*-acid (V) was methylated[6] with formic acid and formaldehyde, in low yield, to 4-(dimethylamino)tetrafluorobenzoic acid (VI), whose structure has been proved chemically (see later). Consistent proton and fluorine n.m.r. spectra were obtained from both acids (Table 2).

The neutral product of the pentafluorobenzoic acid–methylamine reaction was 2,3,5,6-tetrafluoro-*N*-methylaniline (VIII), since the same compound was obtained from the reaction of pentafluorobenzene with methylamine. Because pentafluorobenzene has so far reacted with all nucleophiles,[2] and in particular with ammonia,[7] at the position *para* to the hydrogen, it seems unlikely that it would behave differently with methylamine. Once again, n.m.r. indicated the *para*-structure (VIII). Increasing amounts of this decarboxylation product (VIII) were formed from the acid with increasing temperature of reaction; at 70° there was virtually none, but at 100° it comprised over half the product. However, when a mixture of the acids (III) and (V) was heated with methylamine at 100°, no neutral product formed. Decarboxylation to pentafluorobenzene must therefore be competitive with nucleophilic replacement in unsubstituted pentafluorobenzoic acid, and must be followed by replacement in pentafluorobenzene in the normal way.

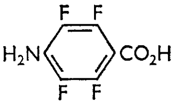
The reaction of pentafluorobenzoic acid with dimethylamine was very similar to that with methylamine; 2- and 4-(dimethylamino)tetrafluorobenzoic acids, (IV) and (VI), were obtained, together with neutral products. Once again, the amount of the neutral products increased with increasing temperature of reaction, as did the ratio of the isomeric acids in favour of the *ortho*-acid (IV). However, two neutral products, in the ratio 4 : 1, were formed in this reaction. The major neutral component, 2,3,5,6-tetrafluoro-*NN*-dimethylaniline (IX), was produced also from pentafluorobenzene and dimethylamine; an attempted synthesis by methylation of 2,3,5,6-tetrafluoroaniline with formic acid and formaldehyde[6] failed, as reaction with the aromatic hydrogen appeared to be taking place. The minor neutral component showed a doublet in the dimethylamino-region of its proton n.m.r. spectrum, indicating[8] one *ortho*-fluorine; it was therefore 2,3,4,5-tetrafluoro-*NN*-dimethylaniline (X). This compound was probably formed by decarboxylation of the *ortho*-acid (IV), since this acid, and to a lesser extent the *para*-acid (VI), both decarboxylated to some extent on being heated with dimethylamine. The *ortho*-acid (IV) decarboxylated more readily than the *para*-acid (VI), and the major decarboxylation product (IX) must therefore have been formed almost entirely *via* pentafluorobenzene, as in the methylamine reaction. The greater ease of decarboxylation of the dimethylamino-acid (IV) as compared with the methylamino-acid (III) can be attributed to steric acceleration.



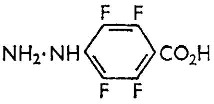
(VIII: R = H)
(IX: R = Me)



(X)



(XI)



(XII)

The structure of the *ortho*-dimethylamino-acid (IV) follows from a synthesis from its methylamino-analogue (III) by methylation with formic acid and formaldehyde. The fluorine n.m.r. spectrum of the *para*-acid (VI) was unambiguous (Table 2), and some chemical evidence has also been obtained for the same structure. Treatment of pentafluorobenzoic acid with hydrazine gave a low yield of 2,3,5,6-tetrafluoro-4-hydrazinobenzoic acid (XII); although this compound could not be purified satisfactorily, it gave a benzaldehyde derivative, and also reacted with aqueous copper sulphate, a reagent which

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[6] J. G. Allen, J. Burdon, and J. C. Tatlow, preceding Paper.
[7] G. M. Brooke, J. Burdon, M. Stacey, and J. C. Tatlow, *J.*, 1960, 1768.
[8] J. Burdon, *Tetrahedron*, 1965, **21**, 1101.

replaces hydrazino-groups by hydrogen,[9] to give the known [10] 2,3,5,6-tetrafluorobenzoic acid, thus showing that the fluorine *para* to the carboxyl was indeed the one replaced. As the yield of the hydrazino-acid (XII) was low, and as much intractable material was formed, it is quite possible that an *ortho*-hydrazino-acid formed as well, and was lost or destroyed in the reaction or the isolation procedure. Reduction of the benzaldehyde derivatived of the hydrazino-acid (XII) gave 4-aminotetrafluorobenzoic acid (XI), which methylate to give the *para*-dimethylamino-acid (VI), thus proving this structure chemically.

Reaction of pentafluorobenzoic acid with ammonia gave no acidic products, only pentafluorobenzene. Since decarboxylation, which is competitive with nucleophilic replacement, presumably takes place *via* the pentafluorobenzoate anion, and since the three amines will be approximately equally effective in forming this anion, the rate of decarboxylation should be largely independent of the amine. However, as the nucleophilicity of the amines decreases in the order, $Me_2NH > MeNH_2 > NH_3$, the ability of the nucleophile to compete with the decarboxylation should also decrease in the same order; in the case of ammonia, it seems that the lowest temperature at which replacement will occur at an appreciable rate is higher than the temperature at which the decarboxylation proceeds rapidly. That pentafluorobenzene and not tetrafluoroaniline was produced is another indication that ammonia is a poorer nucleophile than methylamine or dimethylamine. Heating a polyfluoro-aromatic carboxylic acid with ammonia at 120° may, in some cases, provide a useful method of decarboxylation; we have used it to convert the methoxy-acid (I) to tetrafluoroanisole in high yield.

Methyl-lithium reacted with pentafluorobenzoic acid, but as almost all the products were neutral, attack at the carboxyl group must have predominated over nucleophilic replacement; the reaction has not, therefore, been investigated further.

All the nucleophilic replacement reactions of pentafluorobenzoic acid presumably proceed *via* the pentafluorobenzoate anion. This seems to be true even with the amines, where salt hydrolysis or alcoholysis back to the free acid might just possibly be significant. However, sodium pentafluorobenzoate and methylamine gave the same product distribution as did pentafluorobenzoic acid and methylamine. The Hammett σ value (0·0 for *para*) of the carboxylate ion group suggests that this group should be neither strongly electron-donating, nor -attracting, and that pentafluorobenzoic acid should therefore react with nucleophiles at much the same rate as does pentafluorobenzene. This appears, qualitatively, to be so.

In its reactions with methoxide and thiomethoxide, pentafluorobenzoic acid follows the pattern [2] of many C_6F_5X compound in which X is not a powerful electron donor, in reacting at the position *para* to X. With amines, however, it parallels pentafluoronitrobenzene [3] in giving high *ortho*-replacement, although the amounts are not perhaps as significant as might first appear. The pentafluoronitrobenzene–amine reactions were carried out [3] at room temperature, and an approximate extrapolation for the pentafluorobenzoic acid–amine reactions indicates that only about 10% *ortho*-replacement would occur at 15° as opposed to 20—70% (the rest being *para*) with pentafluoronitrobenzene.[3] Nevertheless, the amount of *ortho*-replacement is significant, and requires an explanation. In the pentafluoronitrobenzene cases, we postulated [3] hydrogen-bonding between the nitro-group and the amines, and a similar rationalisation is possible with pentafluorobenzoic acid. There are three factors, however, which, while not invalidating the hydrogen-bonding theory, lead us to suggest that these high *ortho*-replacements are more complex than was first apparent. First, the pentafluorobenzoic acid–dimethylamine reaction gave more *ortho*-acid (IV) (45% at 70°) than did the methylamine [37% of (III) at 70°], whereas the reverse (20 and 70%, respectively, in 3% ethanol–ether) was true for pentafluoronitrobenzene.[3] Secondly, there was a hint of a solvent effect in the pentafluorobenzoic acid–methylamine reaction, as the amount of *ortho*-acid (III) decreased in the presence of

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[9] J. M. Birchall, R. N. Haszeldine, and A. R. Parkinson, *J.*, 1962, 4966.
[10] D. J. Alsop, J. Burdon, and J. C. Tatlow, *J.*, 1962, 1801.

water (Table 1), although this can be rationalised on the basis of the Hughes–Ingold theory[11] of solvent effects. Thirdly, we recently discovered[12] a solvent effect in the pentafluoronitrobenzene–sodium methoxide reaction; 50% *ortho*-replacement occurred in 3·8% methanol in ether, as compared with 8% in methanol alone, the remaining product being the *para*-isomer. We therefore defer a discussion of high *ortho*-replacement until we have more data.

EXPERIMENTAL

Pentafluorobenzoic Acid and Sodium Methoxide.—The acid (2·04 g.) was heated under reflux with 0·45N-sodium methoxide (50 ml.) for 36 hr. The mixture was poured into water, acidified, and the crude product (2·0 g.) isolated by ether extraction. Crystallisation from toluene gave 2,3,5,6-*tetrafluoro*-4-*methoxybenzoic acid* (I) (1·50 g.), m. p. 122—123° (Found: C, 43·3; H, 1·9. $C_8H_4F_4O_3$ requires C, 42·9; H, 1·8%). The ^1H n.m.r. spectrum of the crude product, in acetone, showed only (>90%) a triplet (J = 1·8 c./sec.) at 4·15.

The acid gave an S-*benzylthiuronium salt*, m. p. 183—184° (from aqueous ethanol) (Found: C, 49·5; H, 3·6. $C_{16}H_{14}F_4N_2O_3S$ requires C, 49·2; H, 3·6%).

Decarboxylation of 2,3,5,6-*Tetrafluoro*-4-*methoxybenzoic Acid.*—The acid (1·0 g.) and aqueous ammonia (7·5 ml., 1·2%) were heated in a sealed tube at 125° for 16 hr. The reaction mixture was poured into water, when ether extraction yielded the liquid 2,3,5,6-tetrafluoroanisole (0·4 g.), identified by infrared (i.r.) spectroscopy.[4] Acidification of the remaining aqueous solution, followed by ether extraction, gave the starting acid (0·3 g.), identified by its i.r. spectrum.

Pentafluorobenzoic Acid and Sodium Thiomethoxide.—The acid (3·0 g.) was added to 0·6N-sodium methoxide in methanol (50 ml.) in which methanethiol (1·5 g.) had been dissolved. The mixture was heated under reflux for 16 hr., and the crude product (3·0 g.) isolated as in the first experiment. Crystallisation from toluene gave 2,3,5,6-*tetrafluoro*-4-(*methylthio*)*benzoic acid* (II) (2·5 g.), m. p. 133° (Found: C, 39·8; H, 1·7. $C_8H_4F_4O_2S$ requires C, 40·0; H, 1·7%). The ^1H n.m.r. spectrum of the crude product, in acetone, showed no absorption in the methoxyl region[8] (3·7—4·3) and only (>90%) a triplet (J = 1·2 c./sec.) at 2·65 in the methylthio region[8] (2·3—2·7).

The thio-acid gave an S-*benzylthiuronium salt*, m. p. 182° (from aqueous ethanol) (Found: C, 47·5; H, 3·9. $C_{16}H_{14}F_4N_2O_2S_2$ requires C, 47·3; H, 3·5%).

Pentafluorobenzoic Acid and Methylamine.—The acid (4·25 g.) and 16% w/w ethanolic methylamine (20 ml.) were heated in a sealed tube at 80° for 20 hr. The mixture was poured into water and extracted with ether (3 × 50 ml.) (extracts A). The aqueous layer was acidified and also extracted with ether (4 × 50 ml.) (extracts B).

Distillation of dried ($MgSO_4$) extracts A yielded 2,3,5,6-*tetrafluoro*-N-*methylaniline* (VIII) (1·1 g.), b. p. 159°, pure (>98%) by gas chromatography, as a colourless liquid which darkened so rapidly that a satisfactory analysis could not be obtained (Found: C, 47·8; H, 3·5. $C_7H_5F_4N$ requires C, 46·9; H, 2·8%).

Evaporation of dried ($MgSO_4$) extracts B yielded a solid (2·50 g.), whose ^1H n.m.r. spectrum, in acetone, indicated the presence of tetrafluoro-6- and -4-(methylamino)benzoic acids (40 and 60%, respectively). Chromatography of the mixed acids on silica gel (1 in. × 2 ft.) in 0·8 g. portions gave, on elution with acetone–light petroleum (b. p. 40—60°) (1 : 1), 2,3,4,5-*tetrafluoro*-6-(*methylamino*)*benzoic acid* (III) (1·38 g.), m. p. 163—165° [80% recovery from toluene–light petroleum (b. p. 40—60°)] (Found: C, 43·1; H, 2·1. $C_8H_5F_4NO_2$ requires C, 43·1; H, 2·3%). Further elution with acetone alone gave 2,3,5,6-*tetrafluoro*-4-(*methylamino*)-*benzoic acid* (V) (1·10 g.), m. p. 153—154° [81% recovery from toluene–light petroleum (b. p. 40—60°)] (Found: C, 43·0; H, 2·5%). The reaction was repeated as shown in Table 1.

On heating under reflux with trifluoroacetic anhydride for 8 hr., the 6-(methylamino)-acid gave an N-*trifluoroacetyl derivative*, m. p. 101—102° [from toluene–light petroleum (b. p. 60—80°)] (Found: C, 37·7; H, 1·3. $C_{10}H_4F_7NO_3$ requires C, 37·6; H, 1·3%).

The 4-(methylamino)-acid gave an S-*benzylthiuronium salt*, m. p. 176—178° (from aqueous ethanol) (Found: C, 49·6; H, 4·3. $C_{16}H_{15}F_4N_3O_2S$ requires C, 49·4; H, 3·9%).

2,3,5,6-*Tetrafluoro*-N-*methylaniline* (VIII).—Pentafluorobenzene (3·89 g.) and 33% w/w ethanolic methylamine (5·0 ml.) were heated in a sealed tube at 105° for 20 hr. The mixture

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[11] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons, London, 1953, p. 345.

[12] J. Burdon, D. Fisher, D. King, and J. C. Tatlow, *Chem. Comm.*, 1965, 65.

TABLE 1

Pentafluoro-benzoic acid (g.) [a]	Temp.	2,3,5,6-Tetrafluoro-*N*-methylaniline (g.)	Acidic products (g.)	6-(Methyl amino)-acid (%) [b]
4·52	125°	2·75	0·48	57
4·40	100	2·12	1·58	45
4·60	70	0·0	4·10	37
1·10 [c,d]	70	0·0	0·87	22
1·00 [c]	70	0·0	0·85	22

[a] Treated with ethanolic methylamine (16% w/w; 20 ml.) at the temperature given for *ca.* 16 hr. unless otherwise stated. [b] Obtained from ^{1}H n.m.r. spectra, in acetone, of crude acidic products; accuracy ±5%; remainder was tetrafluoro-4-(methylamino)benzoic acid. [c] Treated with ethanolic methylamine (16% w/w; 5·0 ml.) and water (5·0 ml.) for *ca.* 16 hr. [d] Sodium pentafluorobenzoate was the starting material.

was poured into water, and the product isolated by ether extraction; it was 2,3,5,6-tetrafluoro-*N*-methylaniline (VIII) (3·35 g.), b. p. 159°, identical (i.r.) with the compound obtained above.

Reaction of 2,3,4,5-*Tetrafluoro*-6-(*methylamino*)*benzoic Acid* (III) *with Formaldehyde*.—The acid (0·45 g.), water (40 ml.), and 40% formalin (1·0 ml.) were heated on a steam-bath, and ethanol (*ca.* 1 ml.) was added to homogenise the solution. After 1 hr. at 100° the reaction mixture was cooled, when colourless crystals (0·35 g.), m. p. 95°, were deposited. Recrystallisation from toluene–light petroleum (b. p. 40—60°) gave 2,3,4,5-*tetrafluoro*-6-(N-*hydroxymethyl*-N-*methyl*)*aminobenzoic acid lactone* (VII) (0·23 g.), m. p. 98—99° (Found: C, 46·5; H, 2·4. $C_9H_5F_4NO_2$ requires C, 46·0; H, 2·1%). The ^{1}H n.m.r. spectrum of an acetone solution showed a single peak at 5·10 and a doublet (J = 1·3 c./sec.) at 3·17, in intensity ratio 2 : 3.

The 4-(methylamino)-acid did not react when treated in the same way with formaldehyde.

Pentafluorobenzoic Acid and Dimethylamine.—The acid (4·30 g.) and 33% w/w ethanolic dimethylamine (10 ml.) were heated in a sealed tube at 100° for 20 hr. The mixture was poured into water and the neutral and the acidic products separated as in the methylamine reaction.

Gas-phase chromatography of the neutral products (1·68 g.), b. p. 163—164° (at 130° through silicone gum on Celite) showed two peaks whose areas were in the ratio 4 : 1. The ^{1}H n.m.r. spectrum of the neat liquid showed, in the Me_2N region [8] (2·7—3·1), a triplet (J = 2·2 c./sec.) at 2·92 and a doublet (J = 1·2 c./sec.) at 2·81, in intensity ratio 4 : 1; and also a triplet (J = 7·0 c./sec.) of triplets (J = 10·0 c./sec.), centred at 6·48, of $\frac{1}{6}$th the intensity of the methylamino-triplet.

The ^{1}H n.m.r. spectrum of the acidic products (1·37 g.) indicated the presence of 2- and 4-(dimethylamino)tetrafluorobenzoic acids (57%; 43%). Separation of these acids by chromatography on silica gel as before, but with 5% acetone in light petroleum (b. p. 40—60°) as eluent, gave 2-(*dimethylamino*)-3,4,5,6-*tetrafluorobenzoic acid* (IV) (0·70 g.), m. p. 114—115° (80% recovery from toluene) (Found: C, 45·8; H, 3·0. $C_9H_7F_4NO_2$ requires C, 45·6; H, 3·0%), and 4-(*dimethylamino*)-2,3,5,6-*tetrafluorobenzoic acid* (VI) (0·48 g.), m. p. 165—166° (80% recovery from toluene) (Found: C, 45·9; H, 2·8%). Repetition on pentafluorobenzoic acid (1·0 g.) at 70° gave neutral products (0·3 g.) (not investigated) and acidic products (0·65 g.); ^{1}H n.m.r. showed the acidic products to be 2- and 4-(dimethylamino)tetrafluorobenzoic acids (45%; 55%).

The 2-(dimethylamino)-acid gave an S-*benzylthiuronium salt*, m. p. 186—187° (from aqueous ethanol (Found: C, 50·0; H, 4·4. $C_{17}H_{17}F_4N_3O_2S$ requires C, 50·6; H, 4·2%). The 4-(dimethylamino)-acid also gave an S-*benzylthiuronium salt*, m. p. 191—192° (from aqueous ethanol) (Found: C, 50·8; H, 4·3%).

2,3,5,6-*Tetrafluoro*-NN-*dimethylaniline* (IX).—Pentafluorobenzene (4·0 g.) and 33% w/w ethanolic dimethylamine (5·0 ml.) were heated in a sealed tube at 75° for 20 hr. The mixture was poured into water, and the product isolated by ether extraction; it was 2,3,5,6-*tetrafluoro*-NN-*dimethylaniline* (IX) (3·1 g.), b. p. 163—164° (Found: C, 49·5; H, 3·5. $C_8H_7F_4N$ requires C, 49·8; H, 3·7%). Gas–liquid chromatography of this compound showed a minor (~5%) and a major peak, whose retention times were the same as those of the minor and the major components, respectively, of the neutral product from the pentafluorobenzoic acid–dimethylamine reaction. The i.r. spectrum of the compound was also very similar to that of the same neutral product.

Decarboxylation of Amino-acids.—(*a*) *Dimethylaminotetrafluorobenzoic acids*. A mixture of the 2- and 4-(dimethylamino)-acids [(IV) and (VI)] (0·50 g.; 0·47 g.), ethanol (3 ml.) and 33% w/w ethanolic dimethylamine (0·55 ml.) was heated at 100° in a sealed tube for 20 hr. Isolation as in previous experiments gave an acidic solid (0·63 g.), which ^{1}H n.m.r. spectroscopy indicated was a mixture of the 2-(39%) and the 4-(dimethylamino)-acids (61%), and a neutral liquid (0·18 g.) which, by gas chromatography peak-area measurements, was a 4 : 1 mixture of 2,3,4,5- and 2,3,5,6-tetrafluoro-*NN*-dimethylaniline, respectively. ^{1}H N.m.r. spectroscopy indicated a 4 : 1 mixture of the same components.

(*b*) *Tetrafluoro(methylamino)benzoic acids.* A mixture of tetrafluoro-4- and -6-(methylamino)benzoic acids [(III) and (V)] (0·50 g.; 0·40 g.), ethanol (3·0 ml.), and 33% w/w ethanolic methylamine (0·5 ml.) was heated at 100° in a sealed tube for 16 hr. Isolation as in (*a*) gave an acidic product (0·75 g.), which had the same composition (^{1}H n.m.r.) as the starting mixture, and no ($<$0·05 g.) neutral products.

Pentafluorobenzoic Acid and Ammonia.—The acid (3·2 g.) and aqueous ammonia (5 ml.; *d* 0·88) were heated at 120° overnight in a sealed tube. The reaction mixture was poured into water (20 ml.), and the lower organic layer (2·2 g.) separated and distilled; it was pentafluorobenzene (1·8 g.), b. p. 84°, identified by i.r. spectroscopy. Acidification of the remaining aqueous solution, followed by ether extraction, gave no acidic products.

Pentafluorobenzoic Acid and Hydrazine.—The acid (2·87 g.), ethanol (10 ml.), water (10 ml.), and 100% hydrazine hydrate (3 ml.) were heated under reflux for 20 hr. The mixture was poured into water, and a black solid, insoluble in organic solvents, precipitated. Acidification of the aqueous mixture followed by ether extraction yielded a solid (1·1 g.) which was crystallised from toluene to give impure 2,3,5,6-tetrafluoro-4-hydrazinobenzoic acid (XII) (0·7 g.), m. p. 110—120° (decomp.). Repeated crystallisations from toluene or aqueous ethanol did not yield a pure product; ^{19}F n.m.r. indicated that pentafluorobenzoic acid was the main impurity. No ether-soluble neutral products were formed.

The crude hydrazino-acid gave a *benzaldehyde derivative*, m. p. 235° [from light petroleum (b. p. 100—120°)] (Found: C, 53·0; H, 2·4. $C_{14}H_8F_4N_2O_2$ requires C, 53·8; H, 2·6%).

4-*Amino*-2,3,5,6-*tetrafluorobenzoic Acid* (XI).—The above benzaldehyde hydrazone (0·6 g.), glacial acetic acid (10 ml.), and zinc powder (0·5 g.) were heated under reflux overnight, and then poured into water (100 ml.). The product (0·24 g.) was isolated by ether extraction and then crystallised from toluene; it was 4-*amino*-2,3,5,6-*tetrafluorobenzoic acid* (XI) (0·17 g.), m. p. 178—180° (Found: C, 40·4; H, 1·4. $C_7H_3F_4NO_2$ requires C, 40·2; H, 1·5%).

Methylation of Aminotetrafluorobenzoic Acids.—(*a*) 4-*Amino*-2,3,5,6-*tetrafluorobenzoic acid* (XI). The acid (0·1 g.), 40% formalin (0·5 ml.), and 90% formic acid (5·0 ml.) were heated on a steam-bath for 16 hr., and then poured into water (100 ml.). The pH of this solution was adjusted to 4 with solid sodium hydrogen carbonate and the product (0·08 g.) extracted with ether. Crystallisation from toluene gave 4-(dimethylamino)-2,3,5,6-tetrafluorobenzoic acid (VI) (0·04 g.), m. p. and mixed m. p. 163—164°.

(*b*) 2,3,5,6-*Tetrafluoro*-4-(*methylamino*)*benzoic acid* (V). The acid (0·54 g.), 40% formalin (1·0 ml.), and 90% formic acid (10 ml.) were heated under reflux for 16 hr. Concentrated sulphuric acid (*ca.* 10 ml.) was added to the mixture (to destroy formic acid) and the resulting solution was diluted with water (100 ml.) and then extracted with ether. Evaporation of the dried ($MgSO_4$) extracts and crystallisation of the residue (0·10 g.) from toluene gave 4-(dimethylamino)-2,3,5,6-tetrafluorobenzoic acid (VI) (0·06 g.), m. p. and mixed m. p. 163—165°.

(*c*) 2,3,4,5-*Tetrafluoro*-6-(*methylamino*)*benzoic acid* (III). This acid (0·51 g.) was treated as in (*b*) to give 2-(dimethylamino)-3,4,5,6-tetrafluorobenzoic acid (IV) (0·1 g. crude; 0·07 g. pure), m. p. and mixed m. p. 113°.

2,3,5,6-*Tetrafluorobenzoic Acid.*—Aqueous copper sulphate (1·25 g. in 5 ml.) was added slowly, with stirring, to a heated (80°) mixture of crude 2,3,5,6-tetrafluoro-4-hydrazinobenzoic acid (XII) (0·53 g.) and water (5 ml.). Vigorous evolution of gas occurred, and the reaction mixture was heated under reflux for 30 min. The product (0·20 g.) was isolated by ether extraction, and crystallised from toluene–light petroleum (b. p. 40—60°) to give 2,3,5,6-tetrafluorobenzoic acid (0·15 g.), m. p. and mixed m. p. 152—153° (lit.,[10] 154°).

Nuclear Magnetic Resonance Measurements.—The ^{1}H spectra were measured in acetone solution on a Varian A 60 instrument at 60 Mc./sec.; the chemical shifts in Table 2 and elsewhere are quoted in p.p.m. downfield from tetramethylsilane as internal reference. The ^{19}F spectra were also measured in acetone, on a Varian HR100 instrument at 94·1 Mc./sec.; the chemical shifts are in p.p.m. upfield from trifluoroacetic acid as internal reference.

TABLE 2

N.m.r. spectral data

	^{1}H Spectrum		^{19}F Spectrum
Compound	δ [a]	J (c./sec.) [b]	δ [c]
(I)	4·15	1·8t	64·5, 82·7
(II)	2·65	1·2t	58·1, 64·3
(III)	3·07	6·5d	58·0, 75·5, 83·3, 98·9
(IV)	2·90	2·6d	63·4, 64·8, 75·5, 81·1
(V)	3·15	3·0t	66·2, 86·0
(VI)	3·03	1·7t	65·6, 75·5
(VIII)	3·05	2·5t	66·2, 87·1
(IX)	2·93	2·2t	64·5, 74·9

[a] Methyl protons only. [b] d = doublet; t = triplet. [c] Centres of multiplets, all of equal intensity.

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