# 959. *Aromatic Polyfluoro-compounds. Part XXV.*[1] *Nucleophilic Replacement Reactions of Pentafluoro-toluene, -anisole, and -phenol*

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

The *meta/para* fluorine replacement ratios in the reactions of pentafluoro-toluene, -anisole, and -phenol with nucleophiles increase with increasing electron-donor capacities of the functional groups (Me < OMe < $O^-$). The reaction rates decrease as these ratios increase. Sodium methoxide, hydrazine, and ammonia react with pentafluorotoluene to replace only the fluorine *para* to the methyl group; both sodium methoxide and methyl-lithium give a *meta/para* replacement ratio of 7 : 12 with pentafluoroanisole; only *meta*-replacement occurs in the pentafluorophenol–potassium hydroxide reaction.

In previous Papers [2,3] we have suggested that the fluorine replacement reactions of $C_6F_5X$ compounds with nucleophiles are governed to some extent by the nature of X; in particular, if X is not powerfully electron-donating or -attracting, then the fluorine *para* to X is replaced. If, however, X is a powerful donor, as exemplified in pentafluoroaniline,[3,4] then *meta*-replacement becomes predominant. The *meta*:*para* replacement ratio should increase with increasing donor power of X, and at the same time the reaction rate should decrease. We have now tested these suggestions in a study of the nucleophilic replacement reactions of, in order of increasing donor capacity of substituent, pentafluoro-toluene, -anisole, and -phenol (the last will presumably react with nucleophiles as $C_6F_5O^-$).

The only products isolated in four reactions of pentafluorotoluene were those in which the fluorine *para* to the methyl group had been replaced. Proton nuclear magnetic resonance ($^1$H n.m.r.) spectroscopy of the crude product from the sodium methoxide reaction indicated that if the *meta*- (II) and *ortho*-methoxy-isomers (III) were formed at all, their total amount was less than 10%. Although the structure of the major, *para*-isomer has not been

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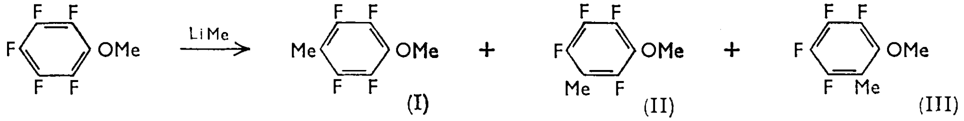
[1] Part XXIV, E. V. Aroskar, J. Burdon, J. G. Campbell, and R. Stephens, *J.*, 1965, 2658.
[2] G. M. Brooke, J. Burdon, and J. C. Tatlow, *J.*, 1961, 802; J. C. Tatlow, *Endeavour*, 1963, **89**, 22; D. J. Alsop, J. Burdon, and J. C. Tatlow, *J.*, 1962, 1801.
[3] G. M. Brooke, J. Burdon, M. Stacey, and J. C. Tatlow, *J.*, 1960, 1768.
[4] J. G. Allen, J. Burdon, and J. C. Tatlow, unpublished work to be submitted as Part XXVII.

identified chemically, its $^1H$ n.m.r. spectrum indicated [5] that both the methyl and the methoxy-group were flanked by two *ortho* fluorines (both showed triplets); $^{19}F$ n.m.r. showed only two magnetically different types of fluorine.

Pentafluorotoluene clearly reacted more slowly with hydrazine than did pentafluorobenzene, which gave [3] about 80% of tetrafluorophenylhydrazine under conditions less drastic than those under which the toluene derivative reacted to the extent of only about 10%. The only product isolated from the latter reaction was the *para*-replacement compound, 2,3,5,6-tetrafluoro-*p*-tolylhydrazine; this structure was determined by $^{19}F$ n.m.r. spectroscopy.

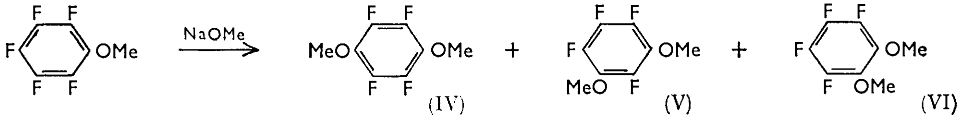


(I) (II) (III)

The toluene gave tetrafluoro-*p*-toluidine with ammonia; this compound was related chemically to the *p*-tolylhydrazine by reductive cleavage of the benzaldehyde *p*-tolylhydrazone to the *N*-acetyl derivative of the toluidine.

In a previous Paper [6] we showed by chemical methods that methyl-lithium also replaced the fluorine *para* to the methyl group in pentafluorotoluene.

We indirectly carried out a replacement reaction of pentafluoroanisole in our first experiments [7] on aromatic polyfluoro-compounds, when we treated hexafluorobenzene with sodium methoxide to give pentafluoroanisole, and, by further reaction, 1,2,4,5-tetrafluoro-3,6-dimethoxybenzene (IV). No other dimethoxy-isomers were isolated, and this has been taken by Wall *et al.*,[8] to imply that none were formed. In fact, the crystalline *para*-compound (IV) obtained amounted to only about 20% of the crude dimethoxy-fraction. We have now found that this *para*-isomer (IV) is indeed the major di-replacement product (52%), but *meta*- (32%) and *ortho*-replacement (16%) also occur to give 1,2,3,5-tetrafluorodimethoxybenzene (V) and 1,2,3,4-tetrafluorodimethoxybenzene (VI), respectively; these relative percentages were determined from the $^{19}F$ n.m.r. spectrum of the crude product.



(IV) (V) (VI)

We have been able to isolate specimens of all three dimethoxy-compounds from the reaction mixture by preparative-scale gas chromatography. The *ortho*- (VI) and *meta*-isomers (V) were identified by synthesis from the known tetrafluoro-catechol [9] and -resorcinol (see later) by methylation with diazomethane.

Some cleavage of the methoxyl group occurred in the methoxide–pentafluoroanisole reaction to give 13% of pentafluorophenol and, presumably, dimethyl ether.

$$C_6F_5OMe + {}^-OMe \longrightarrow C_6F_5O^- + Me_2O$$

No products formed by demethylation of the dimethoxy-compounds were detected and therefore the quoted isomer percentages give a true picture of the pentafluoroanisole–methoxide reaction. Analogous dealkylations are quite common [10] in the polychloro-aromatic field and also with pentafluoroanisole (see later).

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[5] J. Burdon, *Tetrahedron*, 1965, **21**, 1101.

[6] A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens, and J. C. Tatlow, *J.*, 1961, 808.

[7] J. A. Godsell, M. Stacey, and J. C. Tatlow, *Nature*, 1956, **178**, 199.

[8] L. A. Wall, W. J. Pummer, J. E. Fearn, and J. M. Antonucci, *J. Res. Nat. Bur. Stand.*, 1963, **67***A*, 481.

[9] J. Burdon, V. Damodarin, and J. C. Tatlow, *J.*, 1964, 763.

[10] T. de Crauw, *Rec. Trav. chim.*, 1931, **50**, 753; A. F. Holleman, *ibid.*, 1920, **39**, 736; S. M. Shein and V. A. Ignatov, *Zhur. obshchei Khim.*, 1963, **33**, 2645.

Gas chromatography indicated three products from the pentafluoroanisole–methyllithium reaction, but only the major one could be isolated in a pure state; it was the *para*-isomer, 2,3,5,6-tetrafluoro-4-methoxyoluene (I), identical with the product of the pentafluorotoluene–methoxide reaction.

The $^1H$ n.m.r. spectrum of the crude product showed two triplets in the methoxyl region in intensity ratio 12 : 7, attibutable to the *para*- (I) and *meta*-isomer (II), respectively. Such a composition was also consistent with the appearance of the gas chromatogram, which further indicated that the fastest-moving component, presumably the *ortho*-isomer (III), comprised about 10% of the total product. This isomer distribution is almost the same as that determined for the methoxide reaction, but too much significance should not be read into the result, as the reactions were carried out at different temperatures and in different solvents, which could lead to different distributions.[11] We feel that the important point is that the trend is the same for each reaction, *i.e.*, increased *meta*-replacement.

Further studies of the nucleophilic replacement reactions of pentafluoroanisole were prevented, since methoxyl cleavage was the only detectable reaction with nitrogen bases and with lithium aluminium hydride. The reactions with hydrazine (to give hydrazinium pentafluorophenate) [12] and with ammonia [8] were reported previously, and we now find that dimethylamine gives a high yield of dimethylammonium pentafluorophenate, and that pentafluorophenol is the only isolable product from the lithium aluminium hydride reaction. Wall *et al.*,[8] however, isolated tetrafluoro-*p*-anisidine from reaction with sodamide in liquid ammonia, but the yield was too low (14%) for the reaction to be necessarily of any orientational significance.

Pummer and Wall have already reported [13] the isolation of tetrafluororesorcinol from the reaction of aqueous potassium hydroxide with hexafluorobenzene. We have effectively repeated this reaction by treating pentafluorophenol with potassium hydroxide in t-butyl alcohol. The resorcinol appeared to be the only (>90%) product, as the $^{19}F$ n.m.r. spectrum of the crude products, after methylation, showed only tetrafluororesorcinol dimethyl ether. The structure of the parent resorcinol followed from the same spectrum, which showed three groups of multiplets in intensity ratio 1 : 2 : 1; the resorcinol also differed in melting point from the known tetrafluoro-catechol [9] and -hydroquinone.[14]

No other reactions of pentafluorophenol have been carried out; no reaction took place on refluxing for a week with sodium methoxide in methanol, which clearly indicates the great deactivating power of the $O^-$-substituent; even pentafluoroaniline reacts under these conditions.[4] Dimethylamine did not react below temperatures which caused extensive tar formation.

The qualitative reactivity order [$C_6F_5H > C_6F_5Me > C_6F_5OMe > C_6F_5O^-$] towards nucleophiles is in line with our previous suggestions, as is the increasing amount of *meta*-replacement in the same order. It would seem that the methyl group is not a sufficiently powerful electron donor to overcome the *para*-directing effect of the five fluorine atoms, although it does slow the rate of reaction significantly. However, the much more powerful donor $O^-$ overcomes the *para*-effect completely and is, moreover, the most exclusively *meta*-directing and the most deactivating group we have yet found in the polyfluoro-aromatic field.

## EXPERIMENTAL

*Nuclear Magnetic Resonance Spectra.*—The $^1H$ spectra were measured on a Varian A-60 spectrometer; line positions are in p.p.m. downfield from tetramethylsilane as internal reference.

The $^{19}F$ spectra were measured on either a Mullard SL 44 Mark 2 instrument at 30·1 Mc./sec. or a Varian HR100 at 94·1 Mc./sec.; line positions are in p.p.m. upfield from trifluoroacetic acid as internal reference.

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

[12] E. J. Forbes, R. D. Richardson, M. Stacey, and J. C. Tatlow, *J.*, 1959, 2019.

[13] W. J. Pummer and L. A. Wall, *J. Res. Nat. Bur. Stand.*, 1964, **68***A*, 277.

[14] E. Nield and J. C. Tatlow, *Tetrahedron*, 1960, **8**, 38.

2,3,5,6-*Tetrafluoro*-4-*methoxytoluene* (I).—Pentafluorotoluene [6,15] (8·5 g.) and sodium methoxide in methanol (110 ml.; 0·6M) were refluxed for 72 hr. and then poured into water. The crude product (7·0 g.) was isolated by ether extraction and distilled from phosphoric oxide to give 2,3,5,6-*tetrafluoro*-4-*methoxytoluene* (I) (5·0 g.), b. p. 171—172° (Found: C, 49·7; H, 3·2. $C_8H_6F_4O$ requires C, 49·5; H, 3·1%).

The $^1H$ n.m.r. spectrum of the crude product showed only (>90%) a triplet ($J$ = 2·15 c./sec.) at 2·14 (Me) and a triplet ($J$ = 1·2 c./sec.) at 3·97 (OMe). The $^{19}F$ n.m.r. spectrum showed two multiplets of equal intensity centred at 72·0 and 85·3.

2,3,5,6-*Tetrafluoro*-p-*tolylhydrazine*.—Pentafluorotoluene (2·65 g.), hydrazine hydrate (10 ml.; 100%), and sufficient ethanol to render the mixture homogeneous were refluxed for 6 days. The mixture was poured into water and a white solid (0·80 g.) precipitated. Further product (0·70 g.) was obtained by ether extraction of the aqueous filtrate. The combined products were crystallised from light petroleum (b. p. 80—100°) to give 2,3,5,6-*tetrafluoro*-p-*tolylhydrazine* (1·1 g.), m. p. 82—83° (Found: C, 43·2; H, 3·0. $C_7H_6F_4N_2$ requires C, 43·3; H, 3·1%).

When the reaction was carried out for only 12 hr., the product was mainly unchanged pentafluorotoluene.

The $^{19}F$ n.m.r. spectrum of a 3M-solution in acetone showed two multiplets of equal intensity centred at 69·4 and 79·4.

Heating the hydrazine with benzaldehyde gave the *benzaldehyde derivative* (65%), m. p. 114—116° (from aqueous ethanol) (Found: C, 59·5; H, 3·6. $C_{14}H_{10}F_4N_2$ requires C, 59·6; H, 3·6%).

2,3,5,6-*Tetrafluoro*-p-*toluidine*.—Pentafluorotoluene (1·5 g.), aqueous ammonia (*d* 0·88; 3 ml.), and ethanol (10 ml.) were heated at 200° in a sealed tube for 65 hr. The mixture was poured into water and the product isolated by ether extraction; sublimation at 60°/12 mm. gave 2,3,5,6-*tetrafluoro*-p-*toluidine* (0·9 g.), m. p. 63—64° (Found: C, 46·8; H, 3·1. $C_7H_5F_4N$ requires C, 46·9; H, 2·8%).

Acetylation gave an N-*acetyl derivative*, m. p. 156·5—157° (from aqueous ethanol) (Found: C, 49·0; H, 3·4. $C_9H_7F_4NO$ requires C, 48·9; H, 3·2%).

Benzaldehyde tetrafluoro-*p*-tolylhydrazone (6·7 g.), zinc dust (145 g.), and glacial acetic acid (700 ml.) were refluxed for 22 hr. The mixture was diluted with 5N-sulphuric acid (1 l.), and extracted with ether, to yield *N*-acetyl-2,3,5,6-tetrafluoro-*p*-toluidine (1·95 g.), m. p. and mixed m. p. 154—156°.

*Reaction of Pentafluoroanisole with Sodium Methoxide*.—Pentafluoroanisole [7,12] (8·3 g.) was refluxed with sodium methoxide in methanol (60 ml.; 0·9M) for 64 hr. The mixture was poured into water, extracted with ether, and the ethereal solution dried ($MgSO_4$) and evaporated to leave a semi-solid residue (6·8 g.). Crystallisation of 6·20 g. from aqueous ethanol gave 1,2,4,5-tetrafluoro-3,6-dimethoxybenzene (IV) (2·10 g.), m. p. 54° (lit.,[7] 51·5—52·5°). Evaporation of the mother liquors from this crystallisation left a residue which was distilled [b. p. 170—190° (bath)] from phosphoric oxide to give the mixed tetrafluorodimethoxybenzenes (4·00 g.) as a liquid (Found: C, 45·5; H, 2·7. Calc. for $C_8H_6F_4O_2$: C, 45·7; H, 2·9%). A gas chromatogram of this liquid showed three components, but only the fastest-moving was completely separated. Preparative gas–liquid chromatography (g.l.c.) (column 4·8 m. × 35 mm. diam.; packed with silicone gum on Celite; temperature 140°; $N_2$ flow-rate 15 l./hr.) on the same mixture (1·8 g.) gave (i) 1,2,3,4-tetrafluorodimethoxybenzene (VI) (0·2 g.), identified from its infrared (i.r.) spectrum; (ii) 1,2,3,5-tetrafluorodimethoxybenzene (V) (0·2 g.) (*ca.* 90% pure by i.r.); (iii) a mixture of fractions (ii) and (iv) (0·4 g.); and (iv) 1,2,4,5-tetrafluorodimethoxybenzene (0·4 g.), m. p. 48° (i.r.).

The $^{19}F$ n.m.r. spectrum of the original mixed (semi-solid) dimethoxy-compounds showed three groups of multiplets centred at about 76·5, 84, and 90; the fine structures of these showed the features of all three isomers and nothing else [the *para*-isomer (IV) alone gives a single peak at 83·3; the *ortho* (VI) shows a typical $A_2X_2$ spectrum centred at 83·3 and 89·9; and the *meta* (V) three multiplets of intensity ratio 1 : 2 : 1 centred at 76·5, 84·0, and 90·2, respectively]. From this spectrum, the relative isomer percentages were calculated to be $o : m : p = 16 : 32 : 52$ (±5%).

The original aqueous solution (after the ether extraction of the dimethoxy-compounds) was acidified and extracted with ether to yield a phenolic liquid (1·0 g.) which was methylated

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[15] J. M. Birchall and R. N. Haszeldine, *J.*, 1961, 3719.

with diazomethane to give pentafluoroanisole (0·6 g.) (i.r.) which, according to gas chromatography, contained no (<5%) dimethoxy-products.

1,2,3,4-*Tetrafluoro*-5,6-*dimethoxybenzene* (VI).—A solution of diazomethane in ether (*ca.* 2M) was added dropwise to a solution of tetrafluorocatechol [9] (1·5 g.) in ether (20 ml.) until a yellow colour persisted. Evaporation of the ether and distillation of the residue at 85—90°/13 mm. gave 1,2,3,4-*tetrafluoro*-5,6-*dimethoxybenzene* (1·1 g.), b. p. 185° (Found: C, 46·0; H, 2·8. $C_8H_6F_4O_2$ requires C, 45·7; H, 2·9%).

*Pentafluoroanisole and Methyl-lithium.*—Methyl-lithium in ether (65 ml.; 0·5M) was added to pentafluoroanisole (5·00 g.), the mixture refluxed for 1 hr., and poured into water, with stirring. The ether layer was dried ($MgSO_4$) and evaporated to leave a brown liquid (4·80 g.). G.l.c. indicated three, partially resolved, components. Part (2·50 g.) of the product was separated by g.l.c. (as in the methoxide experiment) into (i) a mixture of ether and pentafluoroanisole (<0·1 g.), and (ii) mixed tetrafluoromethoxytoluenes (2·0 g.), b. p. 170—180° (bath) (Found: C, 49·7; H, 3·0. Calc. for $C_8H_6F_4O$: C, 49·5; H, 3·1%). The $^1H$ n.m.r. spectrum of this mixture showed, in the 3·7—4·3 range (methoxyl), triplets at 3·90 ($J$ = 1·0 c./sec.) and 3·96 ($J$ = 1·2 c./sec.) in intensity ratio 7 : 12, respectively. Only the low-field triplet increased in intensity when authentic 2,3,5,6-tetrafluoro-4-methoxytoluene (I) was added to the mixture.

Complete separation of the three products was not possible by gas chromatography; with the same column and conditions as above, the mixture (ii) (2·0 g.) gave (a) a mixture of all three methoxy-compounds (0·7 g.) and (b) 2,3,5,6-tetrafluoro-4-methoxytoluene (0·2 g.) (i.r.).

*Pentafluoroanisole and Dimethylamine.*—The anisole (4·00 g.) and ethanolic dimethylamine (10 ml.; 33% w/w) were heated at 110° in a sealed tube for 12 hr. A crystalline solid (4·10 g.), m. p. 228° (subl.) (the m. p. varied considerably with the rate of heating for all specimens of this salt), separated. Recrystallisation from water gave *dimethylammonium pentafluorophenate* (3·08 g.), m. p. 219° (subl.) (Found: C, 41·9; H, 3·6. $C_8H_8F_5NO$ requires C, 41·9; H, 3·5%).

When ethanolic dimethylamine was added to a solution of hydrazinium pentafluorophenate [12] (0·4 g.) in water (10 ml.), a precipitate of dimethylammonium pentafluorophenate (0·2 g.), m. p. 234° (subl.), formed (i.r.).

*Pentafluoroanisole and Lithium Aluminium Hydride.* (With G. M. BROOKE).—The anisole (1·2 g.) and lithium aluminium hydride (0·05 g.) in ether (10 ml.) were refluxed for 68 hr. Sulphuric acid (20 ml.; 2N) was added to the cooled reaction mixture, the ether layer was separated and the aqueous layer extracted with more ether. The combined ether solutions were shaken with aqueous potassium hydroxide (0·5 g. in 3 ml.); potassium pentafluorophenate dihydrate (0·36 g.), m. p. 235° (decomp.) (lit.,[12] 245°) precipitated. Evaporation of the dried ($MgSO_4$) ether layer left pentafluoroanisole (0·4 g.); both products were identified by i.r. spectroscopy.

*Pentafluorophenol and Potassium Hydroxide.*—The phenol (2·2 g.), potassium hydroxide (5 g.), and t-butyl alcohol (15 ml.) were heated at 170° in an autoclave for 30 hr. The reaction mixture was poured into water, acidified, and extracted with ether to give a dark semi-solid product (2·5 g.). This quantity was insufficient to separate the unreacted phenol from the tetrafluororesorcinol by distillation (cf. ref. 13) although repeated crystallisation from benzene gave a small amount of material m. p. 74—75° (lit.,[13] m. p. 72—75° for a hydrate of tetrafluororesorcinol). Instead, the reaction mixture was methylated with diazomethane (as for tetrafluorocatechol), and the product (2·5 g.) separated as before, by g.l.c., to give (i) pentafluoroanisole (0·5 g.), and (ii) 1,2,3,5-*tetrafluoro*-4,6-*dimethoxybenzene* (1·5 g.), b. p. 184° (Found: C, 45·9; H, 2·8. $C_8H_6F_4O_2$ requires C, 45·7; H, 2·9%).

The $^{19}F$ n.m.r. spectrum showed a doublet ($J$ = 6 c./sec.) at 76·5 (5-fluorine), a doublet ($J$ = 21 c./sec.) at 84·0 (1- and 3-fluorines), and a triplet ($J$ = 21 c./sec.) of doublets ($J$ = 6 c./sec.) at 90·2 (2-fluorine), in intensity ratio 1 : 2 : 1; this gives $J_{12} = J_{23} = 21$ c./sec; $J_{25} = 6$ c./sec.; and $J_{15} = J_{35} \sim 0$ c./sec. Both the line positions and the coupling constants are in accordance with results [16] obtained on other aromatic polyfluoro-compounds.

CHEMISTRY DEPARTMENT, UNIVERSITY OF BIRMINGHAM,
EDGBASTON, BIRMINGHAM 15.

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[16] L. F. Thomas, unpublished work.