342. *Aromatic Polyfluoro-compounds. Part X.*[1] *Some Replacement Reactions of Octafluorotoluene.*

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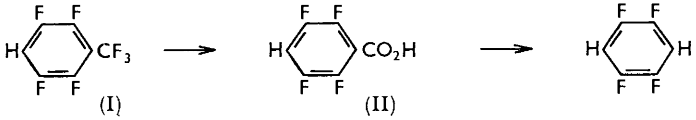
Reactions have been carried out between octafluorotoluene and the following nucleophilic reagents: lithium aluminium hydride, methyl-lithium, potassium thiophenoxide, hydrazine, ammonia, sodium hydrogen sulphide, and sodium ethoxide. In every case, the product was formed by replacement of the fluorine atom *para* to the trifluoromethyl group.

Octafluorotoluene has been made by two methods,[2,3] but only one, the pyrolytic defluorination[2] of perfluoromethylcyclohexane, appears to be of preparative value. We now report some nucleophilic replacement reactions of octafluorotoluene, analogous to those previously described[4-8] for other polyfluoro-aromatic compounds. Under the conditions employed with octafluorotoluene there were formed only mono-replacement products $CF_3{\cdot}C_6F_4X$, where X = H, Me, SPh, NH·NH$_2$, NH$_2$, SH, or OEt, the reagents used being, respectively, lithium aluminium hydride, methyl-lithium, potassium thiophenoxide, hydrazine, ammonia, sodium hydrogen sulphide, and sodium ethoxide. In every case the only isomer detected was the one in which the fluorine atom *para* to the trifluoromethyl group had been replaced. This was demonstrated chemically in three of the cases. First, the heptafluorotoluene (I), from the reaction with lithium aluminium hydride (which reacts as though it were a source of hydride ion) was hydrolysed with concentrated sulphuric acid to a tetrafluorobenzoic acid (II). This was then decarboxylated to the known[9] 1,2,4,5-tetrafluorobenzene:



Mixed isomers of heptafluorotoluene have been prepared before,[10] by hydrogenation of chloroheptafluorotoluene.

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[1] Part IX, Gething, Patrick, and Tatlow, *J.*, 1961, 1574.

[2] Gething, Patrick, Stacey, and Tatlow, *Nature*, 1959, **183**, 588.

[3] McBee, Lindgren, and Ligett, *Ind. Eng. Chem.*, 1947, **39**, 378; Florin, Pummer, and Wall, *J. Res. Nat. Bur. Stand.*, 1959, **62**, 107.

[4] Brooke, Burdon, Stacey, and Tatlow, *J.*, 1960, 1768.

[5] Birchall and Haszeldine, *J.*, 1959, 13.

[6] Robson, Stacey, Stephens, and Tatlow, *J.*, 1960, 4754.

[7] Brooke, Burdon, and Tatlow, *J.*, 1961, 802.

[8] Forbes, Richardson, Stacey, and Tatlow, *J.*, 1959, 2019.

[9] Finger, Reed, Burness, Fort, and Blough, *J. Amer. Chem. Soc.*, 1951, **73**, 145; Infrared Spectral Data, American Petroleum Research Project 44, Serial No. 1018.

[10] Florin, Pummer, and Wall, *J. Res. Nat. Bur. Stand.*, 1959, **62**, 119.

Secondly, the tetrafluorotrifluoromethyltoluene produced in 40% yield by reaction with methyl-lithium was shown to be the 4-trifluoromethyl isomer by fluorination with cobalt trifluoride, since the known[11] perfluoro-1,4-dimethylcyclohexane was formed. Hydrolysis of the tetrafluorotrifluoromethyltoluene with concentrated sulphuric acid gave 2,3,5,6-tetrafluoro-*p*-toluic acid in 12% yield.

Thirdly, the structure of the product (III), formed from the reaction with potassium thiophenoxide, was determined as illustrated. The final product (VI) was identical with the known[6] phenyl 2,3,5,6-tetrafluorophenyl sulphone. The yields in the hydrolysis and decarboxylation steps were low; strict control of the hydrolysis conditions was necessary for even the low yield to be maintained.

(III) (IV) (V) (VI)

Reaction of octafluorotoluene with hydrazine gave 2,3,5,6-tetrafluoro-4-trifluoromethylphenylhydrazine in 36% yield. This structure was established by removal of the hydrazino-group with Fehling's solution,[4] to give 4*H*-heptafluorotoluene (I), identical with that obtained from the reaction with lithium aluminium hydride.

Treatment of octafluorotoluene with aqueous ammonia at 135° gave 2,3,5,6-tetrafluoro-4-trifluoromethylaniline in 82% yield. When aqueous-ethanolic ammonia[4] was employed an impure product was obtained: the impurity may have been the analogous ethoxy-compound, since other[7] ammoniations in aqueous ethanol have given small amounts of ethoxy-compounds. When the benzylidene derivative of 2,3,5,6-tetrafluoro-4-trifluoromethylphenylhydrazine was reduced with zinc dust in acetic acid[12] the same aniline was obtained, thus proving that it was the tetrafluoro-4-trifluoromethyl isomer. Attempts to hydrolyse this aniline to 4-aminotetrafluorobenzoic acid with concentrated sulphuric acid, phosphoric acid, 48% hydrobromic acid or 2N-sodium hydroxide all failed: the compound was either recovered or converted into a tar.

A thiophenol was prepared in 52% yield by treatment of octafluorotoluene with sodium hydrogen sulphide in pyridine–ethylene glycol.[6] Surprisingly, desulphurisation with Raney nickel failed with both this thiophenol and the phenyl sulphide (III), though the method works well for other sulphur-containing polyfluoro-aromatic compounds.[6] This thiophenol was destroyed, and the sulphide was unaffected. Nuclear magnetic resonance spectroscopy showed that the thiophenol was the 4-trifluoromethyl isomer: only three magnetically different types of fluorine atom were present in the molecule.

Attempts to prepare the phenol from octafluorotoluene failed. Direct methods, such as treatment with potassium hydroxide in t-butyl alcohol[5] or in pyridine–ethylene glycol, apparently gave mixtures of polyphenols. Although sodium ethoxide gave 1-ethoxy-2,3,5,6-tetrafluoro-4-trifluoromethylbenzene (structure determined by nuclear magnetic resonance spectroscopy) in 90% yield, the ether linkage could not be split without affecting the rest of the molecule. Treatment with aluminium chloride introduced chlorine, hydrazine brought about complete decomposition, and hydriodic acid hydrolysed the trifluoromethyl group to give 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid. The ethoxy-compound was unaffected by lithium aluminium hydride, boron trichloride, or boron trifluoride etherate. When octafluorotoluene was treated with sodium benzyl oxide in benzyl alcohol, and the resulting mixture was hydrogenated over platinum oxide in an attempt to cleave the intermediate benzyl ether to the phenol, most of the fluorine atoms in the rest of the molecule were replaced by hydrogen.

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[11] Fowler, Hamilton, Kasper, Weber, Burford, and Anderson, *Ind. Eng. Chem.*, 1947, **39**, 375.

[12] Franzen, *Ber.*, 1905, **38**, 1415; *J. prakt. Chem.*, 1905, **72**, 211.

In an earlier paper [7] we argued that compounds of the type C_6F_5X would undergo nucleophilic replacement predominately in the position *para* to X, unless X were very strongly electron-attracting or -repelling. Electron-attracting groups should also enhance the reactivity of the compound towards nucleophiles. Although the trifluoromethyl group is electron-attracting, it is very much less activating in nucleophilic replacement [13,14] than is the nitro-group. The latter is the only electron-attracting substituent discovered [7] so far which upsets the *para*-directing effect of the fluorine atoms in the pentafluorophenyl group: pentafluoronitrobenzene reacted very quickly with ammonia to give [7] the *o*- and the *p*-nitroaniline in a ratio of about 7 : 3. Slight activation caused by the trifluoromethyl group should be at the already activated *para*-position, since activation by the trifluoromethyl group of the replacement of *ortho*-substituents has been observed [14] in other cases to be abnormally low. This was attributed [14] to repulsion between the fluorine atoms and the reagent, although the size of the group must have some effect. It is not surprising, then, that the fluorine *para* to the trifluoromethyl group is the one replaced first in octafluorotoluene, and at a rate qualitatively little different from that of a comparable elimination from pentafluorobenzene.

EXPERIMENTAL

Reaction of Octafluorotoluene with Lithium Aluminium Hydride.—Octafluorotoluene [2] (3·00 g., 1 mol.) was refluxed in dry diethyl ether (10 ml.) with lithium aluminium hydride (0·12 g., 0·25 mol.) for 85 hr. After decomposition of the excess of lithium aluminium hydride with dilute sulphuric acid, the ethereal layer was dried (Na_2SO_4) and most of the ether was removed by fractional distillation through a 3 in. Vigreux column. Separation of the residual mixture on a preparative-scale vapour-phase chromatography column (16 ft. long × 3 in. diam., packed with dinonyl phthalate on kieselguhr, 1 : 4. Nitrogen flow-rate, 55 l./hr.) at 100° yielded ether (2·5 g.), octafluorotoluene (0·2 g.), and 4H-*heptafluorotoluene* (I) (1·4 g.), b. p. 111—112° (Found: C, 38·6; H, 0·4. C_7HF_7 requires C, 38·5; H, 0·5%).

Hydrolysis of 4H-*Heptafluorotoluene* (I).—The toluene (I) (2·15 g.) was heated with sulphuric acid (*d* 1·84; 5 ml.) in a sealed tube at 150° for 18 hr. The mixture was poured on ice, and the product was extracted with ether. The extracts were washed with aqueous sodium hydrogen carbonate, and these washings were acidified with hydrochloric acid and then extracted with ether. Evaporation of these dried (Na_2SO_4) extracts left a brown crystalline residue (1·31 g.) which was recrystallised from toluene to give 2,3,5,6-*tetrafluorobenzoic acid* (II) (0·62 g.), m. p. 154° (Found: C, 43·8; H, 1·1. $C_7H_2F_4O_2$ requires C, 43·3; H, 1·0%).

The acid gave an S-*benzylthiouronium salt*, m. p. 173° (from water) (Found: C, 50·1; H, 3·4. $C_{15}H_{12}F_4N_2O_2S$ requires C, 50·0; H, 3·4%).

Decarboxylation of 2,3,5,6-*Tetrafluorobenzoic Acid* (II).—The acid (0·21 g.) was heated with soda-lime (0·43 g.), a brown liquid (0·12 g.) distilling from the mixture. Redistillation of the liquid from phosphoric oxide gave pure 1,2,4,5-tetrafluorobenzene (0·10 g.), identified by infrared spectroscopy.[9]

Reaction of Octafluorotoluene with Methyl-lithium.—A solution of methyl-lithium in diethyl ether (0·023 g./ml.; 60 ml.) was added to a solution of octafluorotoluene (10·2 g.) in dry ether (25 ml.) at such a rate that the ether refluxed gently. The mixture was then refluxed for 4 hr., washed with water to remove lithium salts, and dried (Na_2SO_4). Most of the ether was removed by fractional distillation through a 6 in. column packed with Dixon gauzes. Separation of the residual mixture on a preparative-scale vapour-phase chromatography column (16 ft. long × 3 in. diam., packed with silicone gum on keiselguhr, 1 : 4. Nitrogen flow-rate 56 l./hr.) at 120° yielded ether and octafluorotoluene (together *ca.* 0·2 g.) and 2,3,5,6-*tetrafluoro*-4-*trifluoromethyltoluene* (4·0 g.), b. p. 143—145° (Found: C, 41·7; H, 1·2. $C_8H_3F_7$ requires C, 41·4; H, 1·3%).

Fluorination of 2,3,5,6-*Tetrafluoro*-4-*trifluoromethyltoluene.*—The toluene (2·0 g.) was run into a small unstirred reactor [15] filled with cobalt trifluoride and initially at 335°. After 15 min., nitrogen was passed through the reactor for 15 min. and the product was collected in a glass

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[13] Bolto, Liveris, and Miller, *J.*, 1956, 750.

[14] Heppolette, Miller, and Williams, *J.*, 1955, 2929.

[15] Evans, Godsell, Stephens, Tatlow, and Wiseman, *Tetrahedron*, 1958, **2**, 183.

trap cooled in liquid air. It was washed with aqueous sodium hydrogen carbonate and distilled *in vacuo*, from phosphoric oxide, to give perfluoro-1,4-dimethylcyclohexane (0·5 g.), identified by its infrared spectrum.

Hydrolysis of 2,3,5,6-*Tetrafluoro*-4-*trifluoromethyltoluene*.—The toluene (2·90 g.) was heated with sulphuric acid (*d* 1·84; 7 ml.) in a sealed tube at 158° for 18 hr. The mixture was poured on ice, and the product was extracted with ether. The extracts were washed with aqueous sodium hydrogen carbonate, and these washings were acidified with hydrochloric acid. The precipitate (0·48 g.) was filtered off, and the rest of the product (0·21 g.) was isolated from the filtrate by ether-extraction. Two recrystallisations of the combined products from water gave 2,3,5,6-*tetrafluoro*-4-*toluic acid* (0·31 g.), m. p. 174° (Found: C, 45·9; H, 2·1. $C_8H_4F_4O_2$ requires C, 46·2; H, 1·9%).

The acid gave an S-*benzylthiouronium salt*, m. p. 204° (from water) (Found: C, 51·0; H, 3·8. $C_{16}H_{14}F_4N_2O_2S$ requires C, 51·3; H, 3·8%).

Phenyl 2,3,5,6-*Tetrafluoro*-4-*trifluoromethylphenyl Sulphide* (III).—A hot solution of potassium thiophenoxide (1·26 g., 1 mol.) in pyridine (50 ml.) was added quickly to octafluorotoluene (2·0 g., 1 mol.) in pyridine (15 ml.), and the mixture was refluxed for 5 min. It was then poured on ice, acidified with hydrochloric acid and the product was isolated by ether-extraction. It was the *sulphide* (III) (1·26 g.), b. p. 92°/0·2 mm. (Found: C, 48·1; H, 1·6. $C_{13}H_5F_7S$ requires C, 47·9; H, 1·5%).

Phenyl 2,3,5,6-*Tetrafluoro*-4-*trifluoromethylphenyl Sulphone* (IV).—A mixture of the sulphide (III) (4·0 g.), glacial acetic acid (40 ml.) and 30% w/v hydrogen peroxide (4 ml.) was kept at 100° for 1 hr. and then poured into water (200 ml.). The white precipitate recrystallised from ethanol, to give the *sulphone* (IV) (3·3 g.), m. p. 139·5° (Found: C, 43·8; H, 1·5. $C_{13}H_5F_7O_2S$ requires C, 43·6; H, 1·4%).

Hydrolysis of the Sulphone (IV).—The sulphone (2·92 g.) was heated with sulphuric acid (*d* 1·84; 10 ml.) at 160° for 14 hr. The mixture was poured on ice, and the product was extracted with ether. The extracts were washed with aqueous sodium hydrogen carbonate, and these washings were acidified and the acid product isolated by ether-extraction. It was 4-*benzenesulphonyl*-2,3,5,6-*tetrafluorobenzoic acid hydrate* (V) (0·28 g.), m. p. 158° (from water) (Found: C, 44·5; H, 2·5. $C_{13}H_6F_4O_4S,H_2O$ requires C, 44·3; H, 2·3%). Unchanged sulphone (IV) (1·58 g.) was obtained on evaporation of the first ether extracts.

The action of sulphuric acid at 135° for 14 hr. or at 165° for 42 hr. gave no acid product, only recovered sulphone (71% and 9% respectively) and tar.

Decarboxylation of 4-*Benzenesulphonyl*-2,3,5,6-*tetrafluorobenzoic Acid* (V).—The acid (V) (0·10 g.) was heated strongly with sodium hydrogen carbonate (0·40 g.). The sublimate (0·01 g.), m. p. 146°, had an infrared spectrum identical with that of phenyl 2,3,5,6-tetrafluorophenyl sulphone [6] (VI) (lit.,[6] m. p. 164°).

2,3,5,6-*Tetrafluoro*-4-*trifluoromethylphenylhydrazine*.—Octafluorotoluene (5·00 g.), 100% w/w hydrazine hydrate (1·5 g.), and ethanol (15 ml.) were refluxed for 6 hr. and the mixture was poured into water (50 ml.). The brown precipitate (4·42 g.), m. p. 77°, recrystallised from aqueous ethanol to yield the *hydrazine* (1·9 g.), m. p. 84° (Found: C, 33·9; H, 1·3. $C_7H_3F_7N_2$ requires C, 33·9; H, 1·2%).

Treatment of the hydrazine with benzaldehyde in sulphuric acid–ethanol gave the *hydrazone* (80%), m. p. 178·5° (from aqueous ethanol) (Found: C, 50·4; H, 2·0. $C_{14}H_7F_7N_2$ requires C, 50·0; H, 2·1%).

Removal of Hydrazine from 2,3,5,6-*Tetrafluoro*-4-*trifluoromethylphenylhydrazine*.—A mixture of the phenylhydrazine (3·86 g.) and Fehling's solution [a mixture of solution " A " (300 ml.) and " B " (300 ml.)] was distilled. The distillate separated into two layers, the lower of which was redistilled from phosphoric oxide, to give 4*H*-heptafluorotoluene (I) (0·95 g.), b. p. 111—112°, identified by its infrared spectrum (see above).

2,3,5,6-*Tetrafluoro*-4-*trifluoromethylaniline*.—(a) *From octafluorotoluene*. Octafluorotoluene (4·07 g.) was heated with aqueous ammonia (*d* 0·88; 4 ml.) in a sealed tube at 132° for 22 hr. The mixture was poured into water (50 ml.) and isolation by ether-extraction gave the *aniline* (3·30 g.), b. p. 186° (Found: C, 36·5; H, 1·0. $C_7H_2F_7N$ requires C, 36·1; H, 0·9%).

Refluxing of the aniline with trifluoroacetic anhydride for 30 min. gave the *trifluoroacetyl derivative* (71%), m. p. 151° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 33·0; H, 0·2. $C_9HF_{10}NO$ requires C, 32·9; H, 0·3%).

(b) *From benzaldehyde* 2,3,5,6-*tetrafluoro*-4-*trifluoromethylphenylhydrazone*. The hydrazone

(2·10 g.) was refluxed with zinc powder (4·00 g.) in glacial acetic acid (20 ml.) for 3 hr. The mixture was poured into water (200 ml.), and the product (0·65 g.) was isolated by ether-extraction. Infrared spectroscopy showed it to be identical with the aniline described in (a).

2,3,5,6-*Tetrafluoro*-4-*trifluoromethylthiophenol*.—Hydrogen sulphide was passed into a solution of sodium hydroxide (5·0 g.) in ethylene glycol (16 ml.) at 180—185° for 3 hr. The green viscous mixture was quickly added to octafluorotoluene (4·0 g.) in pyridine (15 ml.). After the mixture had been kept at 0° for 30 min. and at 70° for 45 min., it was acidified with hydrochloric acid and extracted with ether. Distillation of the dried (Na_2SO_4) extracts gave the *thiophenol* (2·2 g.), b. p. 169° (Found: C, 33·6; H, 0·7. C_7HF_7S requires C, 33·6; H, 0·4%).

1-*Ethoxy*-2,3,5,6-*tetrafluoro*-4-*trifluoromethylbenzene*.—Octafluorotoluene (5·00 g.) was refluxed with ethanolic sodium ethoxide (0·13 g./ml.; 11·1 ml., 1·00 mol.) for 30 min. and the mixture was poured into water (200 ml.). Distillation of the lower layer from phosphoric oxide afforded 1-*ethoxy*-2,3,5,6-*tetrafluoro*-4-*trifluoromethylbenzene* (5·00 g.), b. p. 174—176° (Found: C, 41·3; H, 2·0. $C_9H_5F_7O$ requires C, 41·2; H, 1·9%).

Reaction of Hydriodic Acid with 1-*Ethoxy*-2,3,5,6-*tetrafluoro*-4-*trifluoromethylbenzene*.—The ethoxy-compound (4·91 g.) was refluxed with 57% hydriodic acid (22 ml.) for 48 hr. After dilution with water, the mixture was steam-distilled. The distillate was neutralised with sodium hydrogen carbonate and again steam-distilled to remove ethyl iodide and starting material. The residual solution from the second steam-distillation was acidified with hydrochloric acid and extracted with ether. Evaporation of the dried (Na_2SO_4) extracts left a crystalline solid (1·30 g.) which recrystallised from benzene, to give 2,3,5,6-*tetrafluoro*-4-*hydroxybenzoic acid hydrate* (1·17 g.), m. p. 157° (Found: C, 36·5; H, 1·8%; equiv., 108. $C_7H_2F_4O_3,H_2O$ requires C, 36·9; H, 1·8%; equiv., 114).

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