

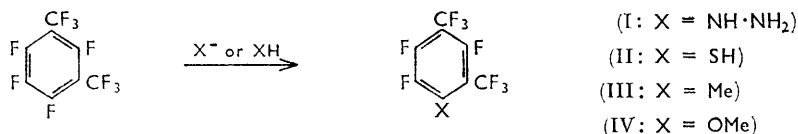
482. Aromatic Polyfluoro-compounds. Part XXIV.¹ Replacement Reactions of Perfluoro-*m*-xylene

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Methyl-lithium, hydrazine, sodium methoxide, and sodium hydrosulphide react with perfluoro-*m*-xylene to replace a fluorine *ortho* to one trifluoromethyl group and *para* to the other.

As part of our programme² on the nucleophilic replacement reactions of aromatic polyfluoro-compounds, we recently described³ the reactions of perfluoro-*o*- and -*p*-xylene. We now report an analogous study on perfluoro-*m*-xylene.

The reactions we have carried out are summarised thus:



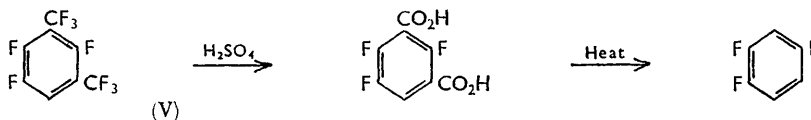
¹ Part XXIII, J. Burdon, C. J. Morton, and D. F. Thomas, *J.*, 1965, 2621.

² J. C. Tatlow, *Endeavour*, 1963, 22, 89.

³ E. V. Aroskar, M. T. Chaudhry, R. Stephens, and J. C. Tatlow, *J.*, 1964, 2975.

These reactions proceeded rapidly and, in order to avoid di-replacement, approximately molar quantities of reactants were used, except with sodium hydrosulphide where polymerisation occurs,⁴ unless an excess of the nucleophile is employed.

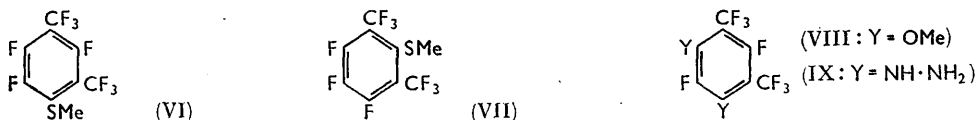
The hydrazine (I) and thiophenol (II) derivatives were converted into the same mono-hydro-isomer (V) by treatment with copper sulphate⁵ and with Raney nickel, respectively. The structure of this compound (V) was established by hydrolysis to the corresponding trifluoroisophthalic acid, followed by decarboxylation of this to the known⁶ 1,2,4-trifluorobenzene.



Drastic fluorination of the methyl-lithium product (III) with cobalt trifluoride gave the same perfluoro(trimethylcyclohexane) as did fluorination of 1,2,4-trimethylbenzene, although in both cases the yields were low.

Proton magnetic resonance spectroscopy indicated⁷ that the methoxy-group in the sodium methoxide product (IV) was adjacent to only one *ortho*-fluorine. With all four nucleophiles, therefore, the same fluorine was replaced.

In only one case was any isomer detected other than the one indicated. When the thiophenol (II) [this showed only a single component on gas-phase chromatography] was methylated, gas-phase chromatography showed two peaks, in the ratio 97:3, in the methylthio-product. The major product (VI) was, of course, derived from the thiophenol (II), and the minor one, although it could not be isolated in a pure state, was probably (VII), since its proton magnetic resonance spectrum indicated that the methylthio-group had no *ortho*-fluorines adjacent to it.



Although the yields in the methyl-lithium, sodium hydrogen sulphide, and sodium methoxide reactions were only fair, this was largely due to difficulties normally attendant on purification of high boiling liquids; no isomers other than those previously mentioned were detected by gas-phase chromatography, or by proton magnetic resonance spectroscopy, in the crude products from any of these reactions.

Further reaction of the methoxy-compound (IV) gave the dimethoxy-compound (VIII), as proton magnetic resonance spectroscopy indicated that the methoxy-groups were identical and were flanked by one *ortho*-fluorine. A dihydrazine has also been obtained and, by analogy, has been assigned the structure (IX).

The trifluoromethyl group is electron-attracting and activates most strongly towards nucleophilic reagents the fluorine substituent *para* to itself,⁸ and next, presumably, those *ortho*. The formation of the major and minor [cf. product (VII)] products of nucleophilic attack on perfluoro-*m*-(and-*o*-³)xylene, and also the di-replacement product (VIII), is consistent with this; such an argument does not, however, take into account any effect of the four fluorines.

⁴ P. Robson, M. Stacey, R. Stephens, and J. C. Tatlow, *J.*, 1962, 4754.

⁵ J. M. Burchall, R. N. Haszeldine, and A. R. Parkinson, *J.*, 1962, 4966.

⁶ G. Schiemann, *J. prakt. Chem.*, 1934, 140, 97.

⁷ J. Burdon, *Tetrahedron*, to be published.

⁸ D. J. Alsop, J. Burdon, and J. C. Tatlow, *J.*, 1962, 1801.

EXPERIMENTAL

2,3,5-Trifluoro-4,6-bis(trifluoromethyl)phenylhydrazine (I).—Perfluoro-*m*-xylene⁹ (12.0 g.), hydrazine hydrate (100%, 2.4 g.), and ethanol (20 ml.) were stirred at room temperature for 3 hr. and then poured into water. Isolation by extraction with methylene chloride gave, after two crystallisations from light petroleum (b. p. 60–80°), **2,3,5-trifluoro-4,6-bis(trifluoromethyl)phenylhydrazine (I)** (10.5 g.), m. p. 72° (Found: C, 32.5; H, 1.0. C₈H₃F₉N₂ requires C, 32.2; H, 1.0%).

With benzaldehyde, in ethanol containing two drops of concentrated sulphuric acid, the compound gave a *benzaldehyde derivative*, m. p. 83° [from light petroleum (b. p. 60–80°)] (Found: C, 46.4; H, 1.8. C₁₅H₇F₉N₂ requires C, 46.5; H, 1.8%).

1,4-Difluoro-2,6-dihydrazino-3,5-bistrifluoromethylbenzene (IX).—Perfluoro-*m*-xylene (1.0 g.), hydrazine hydrate (100%, 0.35 g.), and ethanol (5 ml.) were refluxed for 4 hr. Isolation by extraction with methylene chloride gave **1,4-difluoro-2,6-dihydrazino-3,5-bistrifluoromethylbenzene (IX)** (0.5 g.), m. p. 102–103° [from light petroleum (b. p. 60–80°)] (Found: C, 31.4; H, 2.1. C₈H₆F₈N₄ requires C, 31.0; H, 2.0%).

2,3,5-Trifluoro-4,6-bis(trifluoromethyl)thiophenol (II).—A solution of sodium hydrogen sulphide (2.16 g.) in ethylene glycol (15 ml.) was added, with stirring and at 0°, to a solution of perfluoro-*m*-xylene (4.0 g.) in dry pyridine (15 ml.). After 15 min. at 0°, and then 30 min. at 16°, the mixture was poured into hydrochloric acid (100 ml.; 11*N*) and the product extracted with ether. Most of the ether was removed from the dried (MgSO₄) extracts through a fractionating column (1 ft. × ½ in. bore) packed with glass helices. The product was finally purified (in three portions) by gas chromatography (column 0.5 in. diam. × 6 ft.; packed with silicone gum on Celite; temp. 150°; N₂ flow-rate 2.5 l./hr.) and then distilled *in vacuo* from phosphoric oxide; it was **2,3,5-trifluoro-4,6-bis(trifluoromethyl)thiophenol (II)** (1.3 g.), b. p. 175° (Found: C, 32.4; H, 0.4. C₈HF₉S requires C, 32.0; H, 0.3%).

1,2,4-Trifluoro-6-methylthio-3,5-bistrifluoromethylbenzene (VI).—The thiophenol (9.0 g.) was added at 0° to ethereal diazomethane (60 ml.; *ca.* 0.6*N*) and the mixture kept at room temperature for 2 days. Most of the ether was removed by distillation through a 1 ft. column packed with glass helices. Gas chromatography showed that the residue (8.0 g.) contained, besides a small amount of ether, two components whose peak areas were in the ratio 3 : 97. Preparative gas chromatography (column 35 mm. dia. × 4.8 m.; packed with silicone gum on Celite; temp. 140°; N₂ flow-rate 12 l./hr.) on 5 g. of the mixture gave (i) ether, (ii) a mixture (*ca.* 1 : 1) of the two product components (0.4 g.), and (iii) **1,2,4-trifluoro-6-methylthio-3,5-bistrifluoromethylbenzene (VI)** (3.3 g.) b. p. 197° (Found: C, 34.6; H, 1.0. C₉H₅F₉S requires C, 34.4; H, 1.0%). The proton magnetic resonance spectrum of this compound in carbon tetrachloride showed a doublet (*J* = 2.1 c./sec.) at 2.55 p.p.m. The spectrum of the second fraction showed the same doublet and a sharp, single peak at 2.43 p.p.m., of approximately equal intensity.

1,2,4-Trifluoro-3,5-bistrifluoromethylbenzene.—(a) *From 2,3,5-trifluoro-4,6-bistrifluoromethylphenylhydrazine (I).* Aqueous copper sulphate (25 g. of pentahydrate in 100 ml. water) was added, with stirring, to a suspension of the hydrazine (I) (10.0 g.) in water (50 ml.) at 80°. The reaction mixture was then refluxed for 45 min. and the product steam-distilled from it. Distillation *in vacuo* from phosphoric oxide gave **1,2,4-trifluoro-3,5-bistrifluoromethylbenzene** (4.8 g.), b. p. 123° (Found: C, 36.2; H, 0.6. C₈HF₉ requires C, 35.8; H, 0.4%).

(b) *From 2,3,5-trifluoro-4,6-bis(trifluoromethyl)thiophenol (II).* The thiophenol (II) (1.0 g.), Raney nickel (*ca.* 10 g.), and ethylene glycol (10 ml.) were heated at 145° for 8 hr. and then poured into water. Extraction with ether, removal of the ether through a fractionating column (1 ft. × ½ in. bore) packed with glass helices, and separation of the residue by gas chromatography (35 mm. diam. column; temp. 100°; N₂ flow-rate 17 l./hr.) gave ether and **1,2,4-trifluoro-3,5-bistrifluoromethylbenzene** (0.4 g.), identified by comparison of its infrared spectrum with the compound prepared in (a).

2,4,5-Trifluoroisophthalic Acid.—**1,2,4-Trifluoro-3,5-bistrifluoromethylbenzene** (4.8 g.) and sulphuric acid (*d* 1.84; 20 ml.) were heated in a sealed tube at 155° for 17.5 hr. The reaction mixture was poured on to ice and the product extracted with ether (2 × 50 ml.). The ether layer was washed with aqueous sodium hydrogen carbonate (10%, 150 ml.) and rejected. Acidification of the alkaline layer, followed by ether extraction gave **2,4,5-trifluoroisophthalic**

⁹ P. Robson, J. Roylance, R. Stephens, J. C. Tatlow, and R. E. Worthington, *J.*, 1964, 5748.

acid (2.3 g.), m. p. 199° (from benzene-ethanol) (Found: C, 43.6; H, 1.6. $C_8H_3F_3O_4$ requires C, 43.7; H, 1.4%).

In water, the acid gave a *di*-(*S*-benzylthiuronium) salt dihydrate, m. p. 163.5° (from aqueous ethanol) (Found: C, 49.1; H, 4.4. $C_{24}H_{23}F_3N_4O_4S_2 \cdot 2H_2O$ requires C, 49.0; H, 4.6%).

Decarboxylation of 2,4,5-Trifluoroisophthalic Acid.—The acid (0.5 g.) was heated at 350° in a sealed tube for 44 hr. The product was distilled from the tube *in vacuo* and then redistilled from phosphoric oxide *in vacuo* to give 1,2,4-trifluorobenzene (0.3 g.) with a correct infrared spectrum.

2,3,5-Trifluoro-4,6-bistrifluoromethyltoluene (III).—Methyl-lithium in ether (30 ml.; 0.7N) was added, with stirring and at room temperature, to perfluoro-*m*-xylene (6.0 g.) in ether (30 ml.) at such a rate that the ether refluxed gently. After being stirred for a further 30 min. the mixture was washed with water, dried ($MgSO_4$), and most of the ether removed by distillation through a 1 ft. column packed with glass helices. The residue was separated by gas chromatography (35 mm. diam. column; temp. 100°; N_2 flow-rate 10 l./hr.) into ether and 2,3,5-trifluoro-4,6-bistrifluoromethyltoluene (III) (2.4 g.), b. p. 149–150° (Found: C, 38.4; H, 1.0. $C_9H_3F_9$ requires C, 38.3; H, 1.1%).

Perfluoro-(1,2,4-trimethylcyclohexane).—2,3,5-Trifluoro-4,6-bistrifluoromethyltoluene (III) (3.0 g.) was fluorinated in a small cobalt trifluoride reactor¹⁰ at 300°. The product (3.8 g.) was separated by gas chromatography (35 mm. \times 4.8 m. column; packed with dinonyl phthalate on Celite; temp. 100°; N_2 flow-rate 15 l./hr.) and the shortest retained, major, product was collected and distilled from phosphoric oxide *in vacuo*; it was perfluoro(1,2,4-trimethylcyclohexane (0.5 g.), b. p. 125° (lit.,⁹ 123–125°) (Found: C, 24.1. Calc. for C_9F_{18} : C, 24.0%) identical (infrared) with a specimen (12% yield) prepared by fluorination of 1,2,4-trimethylbenzene.¹¹

*Reaction of Perfluoro-*m*-xylene with Methoxide.*—Perfluoro-*m*-xylene (6.0 g.) and sodium methoxide in methanol (20 ml.; 1N) were refluxed for 5 min. and then poured into water. The crude product was isolated by ether extraction and purified by gas chromatography (35 mm. column; silicone gum packing; temp. 100°; N_2 flow-rate 10 l./hr.) to give 1,2,4-trifluoro-6-methoxy-3,5-bistrifluoromethylbenzene (IV) (1.6 g.) b. p. 165° (Found: C, 36.5; H, 1.3. $C_9H_3F_9O$ requires C, 36.3; H, 1.0%).

The above reaction was repeated on perfluoro-*m*-xylene (4.0 g.) and sodium methoxide in methanol (16 ml.; 1.9N) to give 1,4-difluoro-2,6-dimethoxy-3,5-bistrifluoromethylbenzene (VIII) (2.5 g.), b. p. 207° (Found: C, 38.9; H, 1.9. $C_{10}H_6F_8O_2$ requires C, 38.7; H, 2.0%).

The proton magnetic resonance spectrum of the monomethoxy-compound (IV) as a pure liquid showed a doublet ($J = 3.4$ c./sec.) at 4.21 p.p.m.; the dimethoxy-compound (VIII), in acetone, also showed a doublet ($J = 2.9$ c./sec.) at 4.11 p.p.m.

Nuclear Magnetic Resonance Spectra.—Nuclear magnetic resonance spectra were measured on a Varian A60 instrument at 60 Mc./sec. The chemical shifts are in p.p.m. downfield from tetramethylsilane as internal reference.

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¹⁰ J. Burdon, T. M. Hodgins, R. Stephens, and J. C. Tatlow, *J.*, 1965, 2382.

¹¹ R. N. Haszeldine and F. Smith, *J.*, 1950, 3617.