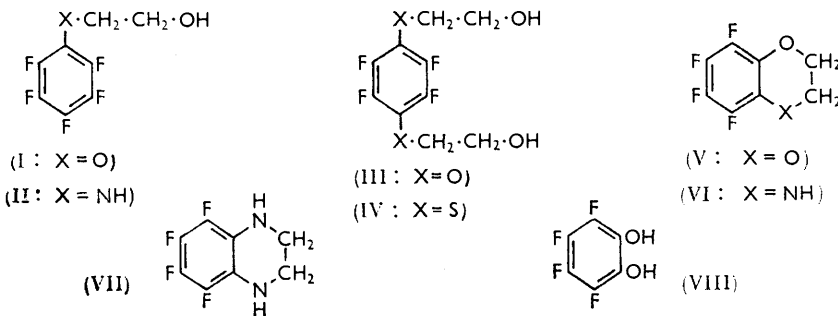**151.** *Polyfluoro-aromatic Compounds. Part XV.[1] The Reaction of Hexafluorobenzene with Bifunctional Nucleophiles.*

By J. BURDON, V. A. DAMODARAN, and J. C. TATLOW.

Hexafluorobenzene reacts with ethylene glycol–sodium hydroxide and with 2-aminoethanol to give the mono-replacement products (I) and (II), which can be cyclised to the heterocycles (V) and (VI). Ethylenediamine reacts to give a cyclic compound (VII) directly. 2-Mercaptoethanol is different in giving a di-replacement product (IV), and we conclude that SR groups activate polyfluoro-aromatic compounds towards nucleophilic attack. The dioxin (V) gives the catechol (VIII) on treatment with aluminium chloride.

UNTIL recently, all the published replacement reactions of polyfluoro-aromatic compounds dealt with monofunctional nucleophiles.[2]   In 1962, Denivelle and Chesneau [3] reported the reaction of hexafluorobenzene with ethylene glycol in the presence of base: they obtained only the di-(2-hydroxyethoxy)-compound (III).   We were investigating similar reactions with various bifunctional nucleophiles, and utilised the bifunctionality by forming cyclic compounds.   This gives a useful route to the 1,2-disubstituted polyfluoro-aromatic compounds which are otherwise difficultly accessible.

While treatment of hexafluorobenzene with an excess of ethylene glycol–sodium hydroxide gave, as reported by Denivelle and Chesneau,[3] the di-replacement compound (III), an equimolecular amount yielded the mono-replacement product (I) in good yield. This compound (I) cyclised on treatment with base to the dioxin (V) which was dealkylated by aluminium chloride to the tetrafluorocatechol (VIII).   On treatment with silver oxide, this last compound appeared to give the red tetrafluoro-*o*-benzoquinone, but we have, as yet, been unable to purify this substance.

(I : X = O)
(II : X = NH)
(III : X = O)
(IV : X = S)
(V : X = O)
(VI : X = NH)
(VII)
(VIII)

Hexafluorobenzene and 2-aminoethanol also gave a mono-replacement product, which from infrared spectral evidence [strong *broad* OH absorption at 3400 cm.$^{-1}$ (in contrast with the *sharp* peaks shown by the NH-containing compounds described in this paper)] and since it formed a nitroso-compound, was the expected *N*-pentafluorophenyl compound (II) and not the isomeric *O*-compound.   Again, treatment with base gave a cyclic compound (VI).

Ethylenediamine gave a cyclic product (VII) only with hexafluorobenzene: non-cyclic material could not be isolated.

2-Mercaptoethanol reacted with hexafluorobenzene in a manner different from the other bifunctional nucleophiles: no mono-replacement product of type (I) or (II) was

[1] Part XIV, Chaudhry and Stephens, *J.*, 1963, 4281.
[2] Tatlow, *Endeavour*, 1962, **22**, 89.
[3] Denivelle and Chesneau, *Compt. rend.*, 1962, **254**, 1646.

formed. Instead, even when only one molecular proportion of 2-mercaptoethanol was used, only the disubstituted product (IV) was isolated—and in good yield. An absence of absorption in the 2600—2550 cm.$^{-1}$ (SH) region and a strong, broad peak at 3400 cm.$^{-1}$ (OH) showed that the compound was (IV) and not the isomeric oxygen-linked substance. Nuclear magnetic resonance showed clearly that the compound was *para*-disubstituted: a single sharp peak indicated only one type of fluorine atom in the molecule.

Since only the disubstituted product was obtained, we must conclude that the 2-hydroxyethylthio-group activates the pentafluorophenyl ring to further nucleophilic attack. Such activation by an SR group was implicit in results previously reported from this Department. Hexafluorobenzene gave [4] only a di-replacement product on treatment with pentafluorothiophenoxide ion and a tetra-replacement product with thiophenoxide. The formation of a polymer,[5] and no bispentafluorophenyl sulphide, from the reaction of an excess of hexafluorobenzene with sodium hydrosulphide is also most plausibly explained by the assumption that polyfluorophenylthio-groups are activating. Miller [6] has also shown that the chlorine in 1-chloro-4-methylthio-2-nitrobenzene is replaced by methoxyl about 22 times faster than the chlorine in 1-chloro-2-nitrobenzene.

The reactions described in this paper could be extended to carbanion-type nucleophiles and this offers the prospect of the synthesis of many polyfluoro-heterocyclic compounds.

EXPERIMENTAL

Reaction of Hexafluorobenzene with Ethylene Glycol.—Hexafluorobenzene (21·0 g.), sodium hydroxide (5·20 g., 1·15 mol.), and ethylene glycol (50 ml.) were refluxed for 3 hr., with occasional shaking, and then poured into water (200 ml.). The aqueous mixture was acidified, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with dilute aqueous sodium hydroxide (to remove traces of pentafluorophenol) and then water, and dried (MgSO$_4$). Distillation *in vacuo* gave three fractions: (i) b. p. 90—110°/15 mm. (2·3 g.) (this was slightly impure 2-pentafluorophenoxyethanol); (ii) *2-pentafluorophenoxyethanol* (I) (14·3 g.), b. p. 110°/15 mm. (Found: C, 41·8; H, 2·3. C$_8$H$_5$F$_5$O$_2$ requires C, 42·1; H, 2·2%); (iii) b. p. 180—210°/15 mm. (2·8 g.) [infrared spectroscopy showed this to be mainly tetrafluoro-1,4-di-(2-hydroxyethoxy)benzene]. Fraction (ii) gave a *phenylurethane derivative*, m. p. 91—92° (from carbon tetrachloride) (Found: C, 52·1; H, 2·7. C$_{15}$H$_{10}$F$_5$NO$_3$ requires C, 51·9; H, 2·9%).

When sodium metal was used instead of sodium hydroxide, the yield of 2-pentafluorophenoxy ethanol was 33%.

Cyclisation of 2-Pentafluorophenoxyethanol (I).—2-Pentafluorophenoxyethanol (14·5 g.), anhydrous potassium carbonate (5·8 g.), and dimethylformamide (200 ml.) were refluxed for 20 hr. and then poured into ice–water (1 l.). Acidification and then filtration yielded a solid which was crystallised from aqueous ethanol to give *5,6,7,8-tetrafluoro-2,3-dihydro-1,4-benzodioxin* (V) (5·50 g.), m. p. 78—79° (Found: C, 46·5; H, 1·9. C$_8$H$_4$F$_4$O$_2$ requires C, 46·2; H, 1·9%).

3,4,5,6-Tetrafluorocatechol (VIII).—The benzodioxin (V) (0·60 g.) and anhydrous aluminium chloride (2·4 g.) were refluxed in dry benzene (25 ml.) for 6 hr., and the mixture was then poured on to ice. The product (0·55 g.) was isolated as a viscous liquid by acidification followed by ether-extraction. Two sublimations at 60—80°/15 mm. gave the hygroscopic *3,4,5,6-tetrafluorocatechol* (VIII) (0·30 g.), m. p. 67·5—69° (sealed tube) (Found: C, 39·3; H, 1·0. C$_6$H$_2$F$_4$O$_2$ requires C, 39·6; H, 1·1%).

The catechol gave a blue colour with aqueous ferric chloride and, on treatment with toluene-*p*-sulphonyl chloride in pyridine, a *ditoluene-p-sulphonate*, m. p. 118—120° (from ethanol) (Found: C, 48·8; H, 2·8. C$_{20}$H$_{14}$F$_4$O$_6$S$_2$ requires C, 49·0; H, 2·9%).

Reaction of Hexafluorobenzene with 2-Aminoethanol.—Hexafluorobenzene (15·0 g.), 2-aminoethanol (37·5 g., 7·62 mol.), ethanol (105 ml.), and water (22 ml.) were heated at 110° for 22 hr.

[4] Robson, Smith, Stephens, and Tatlow, *J.*, 1963, 3692.
[5] Robson, Stacey, Stephens, and Tatlow, *J.*, 1960, 4754.
[6] Daly, Kniger, and Miller, *Austral. J. Chem.*, 1958, **11**, 290.

Most of the ethanol was removed by distillation *in vacuo*, and the remaining liquid was poured into water (200 ml.). Separation of the organic layer, followed by extraction of the aqueous layer with methylene chloride and then distillation of the combined and dried (MgSO₄) organic phases, gave slightly impure 2-*pentafluoroanilinoethanol* (II) (9·60 g.), b. p. 115—118°/7—10 mm. Redistillation gave the pure compound (6·30 g.), b. p. 118°/8 mm. (Found: C, 42·4; H, 2·6. C₈H₆F₅NO requires C, 42·3; H, 2·7%).

The compound gave a positive Liebermann nitroso-reaction (secondary amine), and in the infrared region it had a broad, strong peak at *ca.* 3400 cm.⁻¹ (OH) and a sharp medium peak at 1675 cm.⁻¹ (NH). The compound gave a 3,5-*dinitrobenzoate*, m. p. 78—79° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 42·6; H, 1·9. C₁₅H₈F₅N₃O₆ requires C, 42·8; H, 1·9%). This derivative gave a positive Liebermann reaction and its infrared spectrum had sharp, medium peaks at *ca.* 3400 and 1670 cm.⁻¹ (both NH).

Cyclisation of 2-*Pentafluoroanilinoethanol* (II).—The ethanol (1·59 g.), anhydrous potassium carbonate (1·36 g.), and dimethylformamide (75 ml.) were refluxed for 16 hr. and then poured into ice–water (600 ml.). The aqueous solution was extracted with methylene chloride, and the dried (MgSO₄) extracts were evaporated (the dimethylformamide *in vacuo*) to leave a viscous liquid which solidified on treatment with a small amount of ice–water. This solid (0·70 g.) was purified by passage through a column (15 cm. × 1 cm.) of alumina (benzene eluent) to give, after recrystallisation from light petroleum (b. p. 60—80°), 5,6,7,8-*tetrafluoro-2,3-dihydro-1,4-benzoxazine* (VI) (0·31 g.), m. p. 72—73° (Found: C, 46·6; H, 2·4. C₈H₅F₄NO requires C, 46·4; H, 2·4%).

This compound had sharp, strong peaks in the infrared spectrum at *ca.* 3400 and 1670 cm.⁻¹. It gave a *toluene*-p-*sulphonate salt*, m. p. 194° (from acetone) (Found: C, 47·8; H, 3·2. C₁₅H₁₃F₄NO₄S requires C, 47·5; H, 3·5%) on mixing acetone solutions of the compound and toluene-*p*-sulphonic acid.

Reaction of Hexafluorobenzene with Ethylenediamine.—Hexafluorobenzene (10·0 g.), ethylenediamine (40 ml., 11·1 mol.), ethanol (210 ml.), and water (45 ml.) were heated at 110° for 43 hr. The solvents and excess of ethylenediamine were removed *in vacuo* and the semi-solid residue was purified by passage through a column (15 cm. × 3·5 cm.) of alumina (ether eluent) to give, after recrystallisation from benzene, 5,6,7,8-*tetrafluoro-1,2,3,4-tetrahydroquinoxaline* (VII) (4·14 g.), m. p. 148—150° (Found: C, 46·8; H, 2·9. C₈H₆F₄N₂ requires C, 46·6; H, 2·9%).

This compound had sharp, strong peaks in the infrared spectrum at *ca.* 3400 and 1670 cm.⁻¹. It gave a *ditoluene*-p-*sulphonate salt*, m. p. 220° (from acetone) (Found: C, 47·9; H, 4·0. C₂₂H₂₂F₄N₂O₆S₂ requires C, 48·0; H, 4·0%), and a *dinitroso-derivative*, m. p. 95—97° (decomp.) (from aqueous ethanol) (Found: C, 36·0; H, 1·8. C₈H₄F₄N₄O₂ requires C, 36·4; H, 1·5%).

Reaction of Hexafluorobenzene with 2-*Mercaptoethanol.*—Hexafluorobenzene (5·00 g.), 2-mercaptoethanol (4·20 g., 2·0 mol.), anhydrous potassium carbonate (4·0 g.), and dioxan (25 ml.) were refluxed for 14 hr. and then poured into ice–water. The aqueous mixture was acidified with concentrated hydrochloric acid, and the precipitate (5·2 g.), m. p. 91—92°, was filtered off and recrystallised from ethanol to give 1,2,4,5-*tetrafluoro-3,5-bis-2-hydroxyethylthio-benzene* (IV) (3·50 g.), m. p. 99—100° (Found: C, 39·6; H, 2·9. C₁₀H₁₀F₄O₂S₂ requires C, 39·7; H, 3·3%).

When the experiment was repeated on hexafluorobenzene (10·0 g.) and 2-mercaptoethanol (4·00 g., 0·95 mol.), the yield of pure (IV) was 3·60 g.

The nuclear magnetic resonance spectrum [Mullard SL mark 2 instrument; 30·107 Mc/sec. frequency] of a saturated solution of the tetrafluoro-compound (IV) in dimethylformamide consisted of a single peak at 56·7 p.p.m. upfield from trifluoroacetic acid as external reference. The compound gave a *bisphenylurethane derivative*, m. p. 167—168° (from acetone–carbon tetrachloride) (Found: C, 53·2; H, 3·8. C₂₉H₂₀F₄N₂O₄S₂ requires C, 53·3; H, 3·7%).