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AROMATIC POLYFLUORO-COMPOUNDS.
PART L.* NUCLEOPHILIC REPLACEMENT REACTIONS OF 2*H*, 2′*H*-OCTAFLUOROBIPHENYL, OCTAFLUOROFLUOREN-9-ONE, AND OCTAFLUORODIBENZOTHIOPHEN AND ITS DIOXIDE

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SUMMARY

Unambiguous syntheses of 2,2′,3,3′,5,5′-hexafluoro-4,4′-dimethoxybiphenyl and 2,2′,4,4′,5,5′-hexafluoro-3,3′-dimethoxybiphenyl show that 2*H*, 2′*H*-octafluorobiphenyl is attacked by sodium methoxide at the 4,4′ positions and not at 5,5′ as claimed in earlier literature, since corrected. It follows from this, in accord with the later report, that octafluorofluoren-9-one is attacked by methoxide at the 3-position and not at the 2, and that octafluorodibenzothiophen and its dioxide are attacked at the 2-position and not at the 3.

INTRODUCTION

We recently studied[2] nucleophilic replacements in decafluorophenanthrene, and found that reaction with sodium methoxide afforded 2,7-dimethoxy-octafluorophenanthrene. For a chemical orientation we wished to relate this dimethoxide to the product from the sodium methoxide attack on 2*H*,2′*H*-octafluorobiphenyl (I). However, Chambers, Cunningham and Spring had reported[3] that (I) reacted with methoxide with replacement of the fluorines at position A (Figure 1), and this seemed incompatible with our results which indicated replacement at

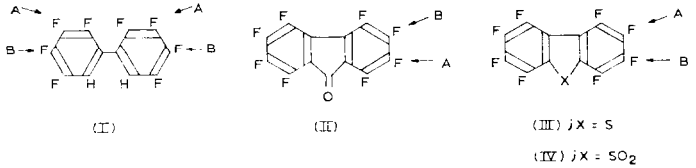


Fig. 1.

* For Part XLIX see ref. 1.

position B. We therefore had an anomaly to resolve. It followed further, that if our expectation of attack at B was correct, there were repercussions on the orientations of nucleophilic replacements with octafluorofluoren-9-one (II) and octafluorodibenzothiophen (III) and its dioxide (IV), since their methoxy derivatives, being related to that from (I), were also thought[3] to arise from attack at position A.

RESULTS

We now report our work on this problem which shows that the dimethoxide made from (I) and sodium methoxide does arise from attack at position B. Hence, the original conclusions[3] were incorrect and not only (I) but (II)–(IV) all react at B. When our experiments were complete we approached Dr. Chambers, and he has recently published[4] the results of a re-investigation of his heterocyclic systems in which he has rigidly orientated one of his products by a new synthesis. His latest results[4], and ours, are now in complete agreement.

Chambers originally[3] proposed attack at A because the ^1H NMR signals of the di-methoxylated products from (I)–(IV) showed that the methoxyls were coupled to two *ortho*-fluorines, thus establishing that attack is at A or at B in all four cases; a comparison of ^{19}F NMR chemical shifts with those of model compounds[3] gave a better fit for attack at A. However, the present results and latest synthesis[4] make it necessary to change these assignments, and an acceptable fit for B-replacement compounds is possible.

Replacement products of (II)–(IV) have been related[3] to replacement products of the biphenyl (I) by the sequences outlined in Figure 2 [N.B. this

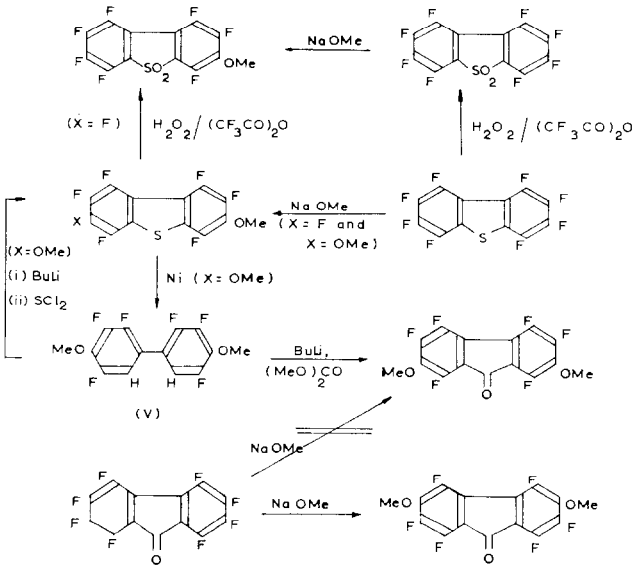


Fig. 2.

shows the corrected[4] formulae; additional interconversions have since[4] been accomplished]. In our opinion, therefore, the whole pattern of replacement in (II)–(IV) depends critically on whether the biphenyl (I) is attacked at A to give the 2*H*,2′*H*,5,5′-dimethoxy compound (XII), as follows from the original assignment[3] of substitution in octafluorodibenzothiophen (III), or is attacked at B to give the 4,4′-dimethoxy isomer (V). The latter seems more likely, since highly-fluorinated diphenyls are more readily attacked qualitatively by nucleophiles at the 4,4′ positions than is pentafluorobenzene in the 4 position.

Chambers *et al.*[3] also assigned structure (XII) on the basis of NMR spectroscopy. We have repeated their preparation and have obtained a product with a different melting point and with a ^{19}F NMR spectrum whose three signals, whilst having the same chemical shifts as those quoted, do not possess a doublet of doublet of doublet patterns; instead the signals are much more complex and show second-order splitting, which indicates that the expected[5] cross-ring coupling is occurring. We have not tried to analyse the spectrum.

In order, therefore, to establish the structure of the di-replacement product of biphenyl (I) with certainty, we have synthesised both possible dimethoxides, *i.e.* (V) and (XII). The sequence for (V) is shown in Figure 3.

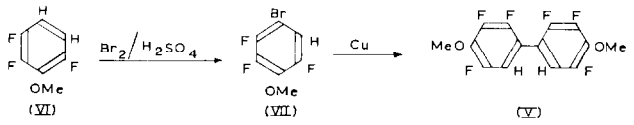


Fig. 3.

The anisole (VI) is a known compound[6], and the only contentious point is its mono-bromination to give (VII). Only one product was formed in this reaction, and we assign structure (VII) to it on two grounds. First, it seems extremely unlikely that, given a choice, methoxyl would direct electrophilic substitution *entirely meta*. Secondly, compound (VII) had been prepared previously[7] in admixture with its isomer (XI). The structure of each was assigned by NMR spectroscopy, the parameters in both cases being in line with literature values. The parameters for compound (VII) prepared according to the scheme outlined in Figure 3 were the same as those previously assigned to this structure in the mixture. For the arguments based on NMR spectra for compounds (VII) and (XI) to be wrong, (in the sense that (VII) is really (XI), and vice-versa), the measured parameters for each would not only have to be out of line with literature values, but out of line in such a way that each would show what was expected of the other! The biphenyl (V), prepared as in Figure 3, was identical with that from the reaction of methoxide with 2*H*, 2′*H*-octafluorobiphenyl.

The product (XII) from reaction of the biphenyl (I) at position A has been prepared as outlined in Figure 4. The position of the methoxyl group in (VIII) was found to be as expected, and was established by NMR spectroscopy, the OMe group being coupled to two *ortho* fluorines[8].

We were surprised and pleased to find that lithiation of (VIII) was so selective. Subsequent carbonation gave (IX) as the only isolated acidic product; this acid was the same as that from the hydrolysis of the known[2] ester (X), thus establishing the position of lithiation. Hydrolysis of the lithio compound gave a mixture of isomers [(XI) ~ 85%; (VII) ~ 15%], whose NMR parameters were the same as those assigned previously[7]. Ullmann coupling of this mixture gave biphenyl (XII) in 40% yield; this compound was different from the product of methoxylation of 2*H*,2′*H*-octafluorobiphenyl.

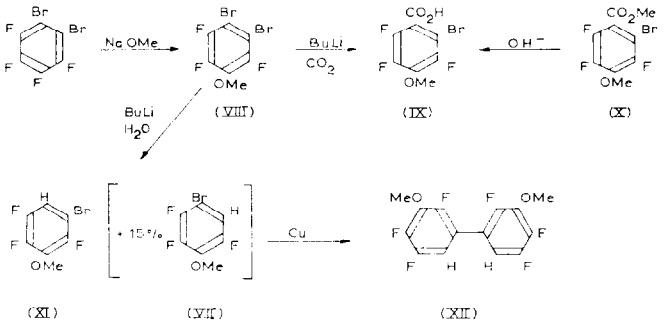


Fig. 4.

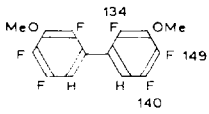
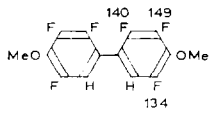
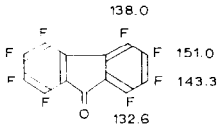
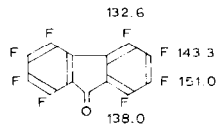
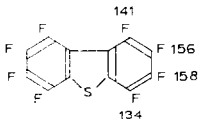
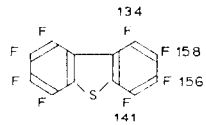
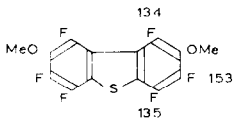
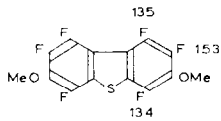
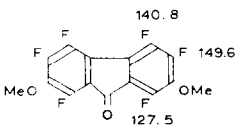
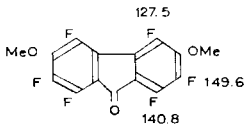
The completion of these two syntheses shows, beyond reasonable doubt, that compounds (I)–(IV) react at position B and not position A. All that remains is for the original ^{19}F NMR chemical shift assignments[3] to be amended to fit attack at B. The more important of these amendments are shown in Table 1. From the point of view of NMR spectroscopy the main difference is the interchange of the assignments of fluorines 1 and 4. The assignments for fluorines 2 and 3 in compounds (II) and (III) have also been exchanged, a move which is certainly open to argument, but does not affect our structures. Although the fit is not quite as good as that based on attack at A, it is quite acceptable. In their later work, Chambers and Spring[4] have re-examined the NMR assignments for all their systems in the light of their new chemical evidence, and their re-allocation of the data agrees with that which we now present. These authors have also outlined the shortcomings of the model compound approach for deducing NMR assignments in these systems.

The replacement of the fluorines at position B in compounds (I)–(III) is expected. DePasquale and Tamborski[9] have shown that decafluorobiphenyl is about 10^3-times more reactive towards sodium pentafluorophenate than pentafluorobenzene (both compounds react *para* to the non-fluorine substituent). Thus, reaction at position B in biphenyl (I) is reasonable.

Attack at position B in compound (II), and at position A in compounds (III) and (IV), is similar to an attack *para* to a group XPh, where X = CO, S, or SO_2. Attack at position A in (II), and at position B in (III) and (IV), is similar to an attack *para* to a polyfluorophenyl group. This is illustrated in Figure 5.

TABLE 1

STRUCTURES AND ^{19}F NMR CHEMICAL SHIFTS [a]

Reference 3	This paper and ref. 4
	
	
	
	
	

[a] In ppm upfield from $CFCl_3$ (changed from C_6F_6 reference where necessary by addition of 162.9)

The following Hammett σ^- values can be applied to nucleophilic replacement in compounds (II)–(IV) to quantify this approximation (all values derived from nucleophilic aromatic substitution data): Ph–C=O, 0.88[10]; PhS, ~0.4*; $PhSO_2$,

* N. J. DALY, G. KRUGER AND J. MILLER, *Austral. J. Chem., 11* (1958) 290 give the σ^- value for SMe as 0.343. The σ^- value for SPh is not available, but, by comparison with other data, it would not be expected to be much different from that for SMe—perhaps a little higher.

1.12[10]; C_6F_5, ~0.55*. Attack at position B in the fluorenone (II) and in the thiophen (III) is entirely reasonable on the basis of these figures. However, attack at B on the dioxide (IV) is not; perhaps the value of 1.12 should not be applied to (IV) because in this case the SO_2 group is forced into an orientation which may not be the same as that to which this figure applies. Again, these conclusions agree with the discussion of some relative reactivity measurements on these systems[4].

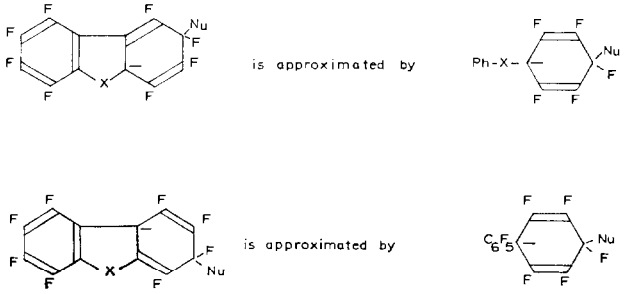


Fig. 5.

Nucleophilic attack on octafluorodibenzofuran was correctly shown[3] by Chambers *et al.* to take place at the 3 position, as would be expected[11] from a σ^- value for PhO of −0.32.

EXPERIMENTAL

Bromination of 2,3,6-trifluoroanisole (VI)

A mixture of bromine (3.0 g) and fuming (60% SO_3) sulphuric acid (20 ml) was added over a period of 5 min to the stirred anisole[6] (3.0 g) at 0°. After further stirring for 3 h the reaction mixture was poured into water, and the product was isolated by ether extraction. It was 1-bromo-2,3,5-trifluoro-4-methoxybenzene (VII) (nc) (2.5 g, 56%), b.p. 195°, (Found: C, 34.7; H, 1.7. $C_7H_4BrF_3O$ requires C, 34.9; H, 1.8%). ^{19}F NMR spectroscopy showed that <5% of the isomeric 1-bromo-2,4,5-trifluoro-3-methoxybenzene (XI) was present.

2,2',3,3'5,5'-Hexafluoro-4,4'-dimethoxybiphenyl (V)

(a) From 1-bromo-2,3,5-trifluoro-4-dimethoxybiphenyl (VII)

The anisole (VII) (1.0 g) was heated with activated copper bronze (3 g) in a sealed glass tube at 230° for 2 days. The title compound (0.65 g, 97%) was extracted from the reaction mixture with ether and recrystallised from light petroleum (b.p. 60–80°); it had m.p. 126° (first reported[3] as 147°; later work[4] 125–126°) (Calc. for $C_{14}H_8F_6O_2$: C, 52.2; H, 2.5. Found: C, 52.1; H, 2.7%). The ^{19}F NMR spectrum showed signals of equal intensity at 133.5, 141.5, and

* Ref. 9 gives σ value for C_6F_5 as 0.4. Re-plotting of the same data, but with σ^- values and not σ values, gives σ^- for C_6F_5 as ~ 0.55.

150.3 ppm (upfield from internal $CFCl_3$). Each was a complex multiplet not at all like the doublet of doublet of doublet patterns described by Chambers *et al.* in their first paper[3]; the spectrum is clearly second-order, indicative in this case of cross-ring coupling. Dr. Chambers has informed us that his authentic specimen[4] and this one have identical IR and NMR spectra.

(b) From 2H, 2′H-octafluorobiphenyl (I)

The biphenyl (I)[12] (1.5 g) was heated under reflux with 0.41 *M* sodium methoxide in methanol (24.4 ml) for 48 h. The reaction mixture was evaporated, the residue extracted with ether, and the extracts dried and evaporated to leave a residue (1.5 g) which TLC (silica gel) showed contained three components; only the second was present in any significant quantity. This component (0.8 g, 62%) was separated (from 1.2 g of residue) by chromatography on silica gel with benzene–light petroleum (b.p. 40–60°) (1:1) as eluent. Further purification by sublimation and recrystallisation gave 2,2′,3,3′,5,5′-hexafluoro-4,4′-dimethoxybiphenyl (V), m.p. and mixed m.p. with the compound prepared as in method (a) 126° (the compounds also had identical IR and NMR spectra), (Found: C, 52.3; H, 2.6%).

1,2-Dibromo-3,4,6-trifluoro-5-methoxybenzene (VIII) [with G. M. Pearl]

1,2-Dibromotetrafluorobenzene[13] (12.0 g) was heated under reflux with 0.82 *M* sodium methoxide in methanol (48 ml) for 24 h. The reaction mixture was poured into water and the product isolated by ether extraction. The methoxy compound (nc) (VIII) (8.5 g, 68%) had b.p. 94°/1 mm Hg (Found: C, 26.4; H, 0.8; Br, 49.7. $C_7H_3Br_2F_3O$ requires C, 26.3; H, 0.9; Br, 50.0%). The ^1H NMR spectrum showed a triplet (*J* 1.5 Hz) at 4.1 τ (OMe).

Reaction of 1,2-dibromo-3,4,6-trifluoro-5-methoxybenzene (VIII) with butyl-lithium

A 2.25 *M* solution of butyl-lithium in hexane (8.3 ml) was added drop-wise over 15 min, with stirring and under nitrogen, to a cooled (−78°) mixture of the anisole (VIII) (6.0 g) and ether (30 ml). Water (10 ml) and 4 *M* hydrochloric acid (10 ml) were then added. The reaction mixture was allowed to warm to room temperature and the ether layer was separated, dried ($MgSO_4$), and distilled to give 1-bromo-2,4,5-trifluoro-3-methoxybenzene (XI) containing *ca.* 15% of 1-bromo-2,3,5-trifluoro-4-methoxybenzene (VII) (3.1 g, 69%), b.p. 194° (analysis by ^{19}F NMR spectroscopy) (Found: C, 35.0; H, 1.8%).

This experiment was repeated on 9.2 g of the anisole, but instead of adding water the reaction mixture was poured on to a slurry of solid carbon dioxide and ether. This mixture was allowed to warm to room temperature and was then shaken with 4 *M* sodium hydroxide. The ether layer was discarded, the aqueous layer acidified and the acidic product (5.3 g) extracted from it with ether. Recrystallisation from aqueous methanol gave 2-bromo-3,5,6-trifluoro-4-methoxybenzoic acid (IX) (4.1 g, 50%), m.p. and mixed m.p. with the specimen described below, 110°.

2-Bromo-3,5,6-trifluoro-4-methoxybenzoic acid (IX)

The methyl ester (X)[2] of the title acid (1.1 g) was heated under reflux for 1 h with potassium hydroxide (12 g) in methanol (12 ml). The reaction mixture was acidified and extracted with ether to yield the acid (IX) (nc) (0.75 g, 71%), m.p. 111° (aqueous methanol) (Found: C, 34.2; H, 1.6. $C_8H_4BrF_3O_3$ requires C, 33.7; H, 1.4%).

2,2',4,4',5,5'-Hexafluoro-3,3'-dimethoxybiphenyl (XII)

Crude 1-bromo-2,4,5-trifluoro-3-methoxybenzene (XI) (1.5 g) (see above) was heated at 210° for 2 days in a sealed glass tube with activated copper bronze (3 g). The reaction mixture was extracted with ether and the extracts were evaporated to leave a residue (0.75 g) which was sublimed at 140° *in vacuo*, and then twice recrystallised from aqueous methanol to give 2,2',4,4',5,5'-hexafluoro-3,3'-dimethoxybiphenyl (XII) (nc) (0.4 g, 40%), m.p. 96°, depressed on admixture with its isomer (V) (Found: C, 52.1; H, 2.7%). The compound showed signals of equal intensity in its ^{19}F NMR spectrum at 134.7, 141.2 and 150.9 ppm (upfield from internal $CFCl_3$). These signals, although in very similar places to those shown by the isomer (V), had different fine splitting. The IR spectrum of this compound was also similar to, but different from, that of its isomer.

ACKNOWLEDGEMENTS

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REFERENCES

1 Part XLIX. J. BURDON, AND W. T. WESTWOOD, *J. Chem. Soc. (C)*, (1970) 1271.
2 J. BURDON, B. L. KANE and J. C. TATLOW, *J. Chem. Soc. (C)*, (1971) 1601.
3 R. D. CHAMBERS, J. A. CUNNINGHAM AND D. J. SPRING, *Tetrahedron, 24* (1968) 3997; R. D. CHAMBERS AND D. J. SPRING, *Tetrahedron, 25* (1969) 565; *idem*, *Chem. Comm.*, (1968) 713; R. D. CHAMBERS, J. A. CUNNINGHAM, AND D. J. SPRING, *J. Chem. Soc. (C)*, (1968) 1560.
4 R. D. CHAMBERS, AND D. J. SPRING, *Tetrahedron, 27* (1971) 669.
5 D. E. FENTON AND A. G. MASSEY, *Tetrahedron, 21* (1965) 2719.
6 J. BURDON AND W. B. HOLLYHEAD, *J. Chem. Soc.*, (1965) 6326.
7 J. BURDON, D. R. KING, AND J. C. TATLOW, *Tetrahedron, 22* (1966) 2541.
8 J. BURDON, *Tetrahedron, 21* (1965) 1101.
9 R. J. DEPASQUALE AND C. TAMBORSKI, *J. Org. Chem., 32* (1967) 3163.
10 J. MILLER, *Austral. J. Chem., 9* (1956) 61.
11 C. D. RICHIE AND W. F. SAGER, *Prog. Phys. Org. Chem., 2* (1964) 323.
12 L. J. BELF, M. W. BUXTON, AND J. F. TILNEY-BASSET, *Tetrahedron, 23* (1967) 4719.
13 E. NIELD, R. STEPHENS, AND J. C. TATLOW, *J. Chem. Soc.*, (1960) 3800.