1177. *Aromatic Polyfluoro-compounds. Part XXVII.*[1] *Reactions of Pentafluoro-aniline, -N-methylaniline, and -NN-dimethylaniline with Nucleophiles*

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Nucleophilic attack (by ammonia, methylamine, dimethylamine, and sodium methoxide) on pentafluoro-aniline, -*N*-methylaniline, and -*NN*-dimethylaniline replaces the fluorines *meta* and *para* to the amine groups in the approximate ratios (*m*/*p*) 7, 1, and 0·07, respectively. *Ortho*-replacement was <6% with all three substrates. The variation in the *m*/*p* ratio is attributed to steric inhibition of resonance.

ONLY a few isolated reactions of polyfluoroaromatic amines with nucleophiles have been reported. We[2] obtained tetrafluoro-1,3-phenylenediamine from the reaction of pentafluoroaniline with ammonia, tetrafluoro-*NN'*-dimethyl-1,4-phenylenediamine from pentafluoro-*N*-methylaniline and methylamine,[2] and tetrafluoro-*NN'*-diphenyl-1,4-phenylenediamine from pentafluoro-*N*-phenylaniline and sodioaniline.[3] Wall and his co-workers[4] have confirmed the first two reactions, and have also isolated tetrafluoro-*NN*-dimethyl-*p*-phenetidine from the pentafluoro-*NN*-dimethylaniline–sodium ethoxide reaction; they also claimed[4] that dimethylamine reacted with the same substrate to replace the fluorines *ortho, meta*, and *para* to the NMe_2 group in the ratio 4 : 1 : 10. Finally, Holland Moore, and Tamborski[5] have isolated a small amount of 3-aminotetrafluorophenylhydrazine from a reaction between pentafluoroaniline and hydrazine.

We now report a detailed study of the reactions of pentafluoro-aniline, -*N*-methylaniline, and -*NN*-dimethylaniline with ammonia, methylamine, dimethylamine, and sodium methoxide. Our results are summarised in Table 1.

TABLE 1

Reactions of $C_6F_5NH_2$, C_6F_5NHMe, and $C_6F_5NMe_2$ with nucleophiles

		Isomer distribution[a] (%)		
Substrate	Nucleophile	*m*	*p*	*o*[b]
$C_6F_5NH_2$	NH_3[c]	87	13	0
	$MeNH_2$[d]	88	12	0
	Me_2NH[e]	90	10	0
	NaOMe[f]	79	16	5
C_6F_5NHMe	NH_3[c]	40	60	0
	$MeNH_2$[d]	60	40	0
	Me_2NH[e]	52	48	0
	NaOMe[f]	43	52	5
$C_6F_5NMe_2$	NH_3[c]	7	93	0
	$MeNH_2$[d]	6	94	0
	Me_2NH[e]	5	92	3
	NaOMe[f]	2	97	1

[a] These refer to replacement of fluorine *meta, para*, and *ortho* to the amine group. [b] See text. [c] Reactions carried out at 195—225°. [d] At 160—165°. [e] At 110—120°. [f] In refluxing methanol.

In most cases, the isomeric products from the reactions with the amine nucleophiles were not separable by gas–liquid chromatography (g.l.c.), and so all the reaction mixtures were treated with formaldehyde and formic acid (Eschweiler–Clarke methylation[6]),

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[1] Part XXVI, J. Burdon and W. B. Hollyhead, preceding Paper.

[2] G. M. Brooke, J. Burdon, M. Stacey, and J. C. Tatlow, *J.*, 1960, 1768.

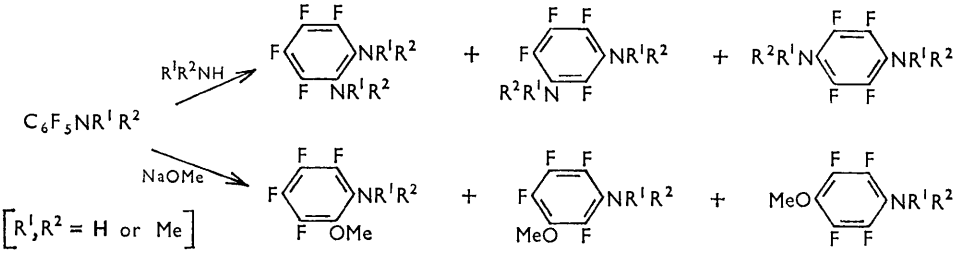
[3] J. Burdon, J. Castaner, and J. C. Tatlow, *J.*, 1964, 5017.

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

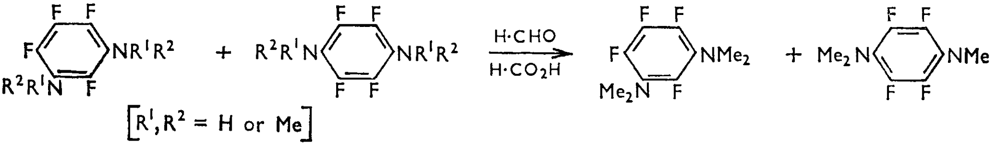
[5] D. G. Holland, G. J. Moore, and C. Tamborski, *J. Org. Chem.*, 1964, **29**, 1562.

[6] H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571; E. C. Wagner, *J. Org. Chem.*, 1954, **19**, 1862.

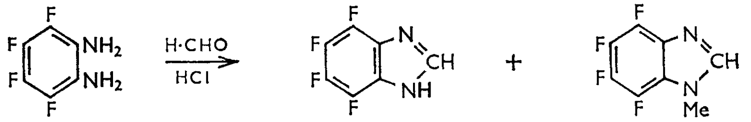
which converted all the >NH groups into >NMe. Since the *o*-, *m*-, and *p*-tetrafluoro-*NNN'N'*-tetramethylphenylenediamines were completely separated by g.l.c., this methylation procedure provided a method of analysis for the reaction products from the amine



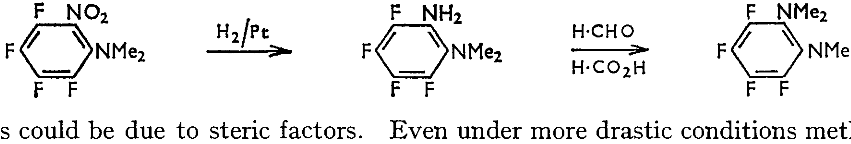
nucleophiles. Authentic specimens of the *meta*- and *para*-*NNN'N*-tetramethyl compounds were provided by methylation of the known [2,7] tetrafluoro-1,3- and -1,4-phenylenediamines; methylation of known mixtures of these two diamines showed that the method of analysis



was reasonably accurate. It was not always possible, however, to determine the amount of *ortho*-replacement by this procedure, since cyclisation reactions might have been occurring instead of simple *N*-methylation. For example, tetrafluoro-1,2-phenylenediamine reacted with formic acid to give 4,5,6,7-tetrafluorobenzimidazole, and with formaldehyde and hydrochloric acid to give the same compound and also its *N*-methyl derivative.



An analogous reaction occurs with *o*-phenylenediamine.[8] It is also clearly possible for cyclisation to a 1,2-dihydrobenzimidazole to occur with an *NN'*-dimethyl-*o*-phenylenediamine. *ortho*-Products could only have been measured, therefore, in those reactions where the products, before methylation, contained an NMe_2 group. Even in such cases, however, *ortho*-products were generally not detected (Table 1). There are two obvious reasons for this. First, the amounts of *ortho*-products in the reactions where they were detectable were very small, and might therefore have been even smaller in the reactions where they were not. Secondly, it was very much more difficult to methylate fully a partially methylated *o*-diamine than its *m*- or *p*-isomer, since in the preparation of tetrafluoro-*NNN'N'*-tetramethyl-1,2-phenylenediamine from the known [9] 2-dimethylamino-3,4,5,6-tetrafluoronitrobenzene, the final methylation proceeded to only a small extent under conditions where analogous *meta*- and *para*-compounds were fully methylated.



This could be due to steric factors. Even under more drastic conditions methylation was still incomplete, and another product, possibly the *NNN'*-trimethyl compound, was

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

[8] O. Fischer and H. Wreszinske, *Ber.*, 1892, **25**, 2711; M. Sprung, *Chem. Rev.*, 1940, **26**, 297.

[9] J. G. Allen, J. Burdon, and J. C. Tatlow, *J.*, 1965, 1045.

formed, besides the fully methylated one. The matter is discussed further in the Experimental section. This incomplete methylation could reduce the observed amount of *ortho*-replacement if one of the slow steps in the reaction were the conversion of the intermediate *N*-CH_2OH [6] or *N*-formyl groups into *N*-methyl, since compounds containing such groups would be expected to have much longer gas-chromatographic retention times than analogues with *N*-methyl groups. A high-boiling compound, possibly pentafluoro-*N*-formyl-*N*-methylaniline from its infrared spectrum, was in fact produced, as well as pentafluoro-*NN*-dimethylaniline, when pentafluoroaniline was treated with formic acid and formaldehyde for a short time.

Methylation with methyl iodide was considered as a possible solution to the cyclisation difficulties encountered with *o*-diamines. However, as even pentafluoroaniline was incompletely methylated under quite vigorous conditions, the approach was not pursued.

A feature of the pentafluoro-*N*-methylaniline reactions (Table 1) was the large amount of *meta*-replacement. The reaction with methylamine was reported previously [2,4] and the *para*-product—actually not the major one—was the only one isolated (it crystallised from the reaction mixture); this has been taken by Wall [4] to indicate that it was the only one formed.

The reactions of pentafluoro-aniline, -*N*-methylaniline, and -*NN*-dimethylaniline with sodium methoxide differed from the amine reactions in that the *ortho*-replacement products were separable, by g.l.c., from the *meta*- and *para*-isomers. Once again, however, only the fully methylated *meta*- and *para*-isomers were separable, and the same methylation procedure as for the amines was used to analyse the reaction mixtures.

It is clear from Tables 1—3 that the main factors affecting isomer distribution are the nucleophiles and the substrates, with the latter leading to much more variation than the former. Indeed, the differences caused by the nucleophiles alone might actually be even smaller than they appear to be. First, the experimental error covers most of the variation (see Experimental section); secondly, the reactions were carried out in different solvent mixtures, and this has affected isomer ratios in at least one other case.[10] Thirdly, the reactions were carried out at different temperatures for the different nucleophiles; this would almost certainly affect the distributions. It was necessary to vary the temperatures, since ammonia would not react appreciably below 190° with any of the substrates, but above 170° dimethylamine gave di-replacement products, with pentafluoro-*NN*-dimethylaniline at least. Table 2 gives an example of this.

TABLE 2

Reaction of dimethylamine with pentafluoro-*NN*-dimethylaniline

Temp.	% *m*	% *p*	% *o*	% Di-replacement
120°	5	92	3	0
170	5	88	3	4
230	3	65	13	19

The other substrates behaved similarly (Table 3). Wall [4] treated pentafluoro-*NN*-dimethylaniline with aqueous dimethylamine at 235° and found that the *o* : *m* : *p* ratio was 4 : 1 : 10, but, surprisingly, in view of our results, he reported no di-replacement. Because of the large amount of di-replacement at 230°, reactions with dimethylamine at this temperature would seem to have little bearing on the orientation problem in $C_6F_5NR^1R^2$ compounds.

In view of the small amount of *ortho*-replacement, we do not think that it would be worthwhile to discuss its significance at this stage in our investigations. We suggest that the currently significant feature in all these reactions is the trend in the *meta* : *para* replacement ratio with increasing *N*-methylation of the substrates. This ratio is approximately 7 with pentafluoroaniline, 1 with pentafluoro-*N*-methylaniline, and 0·07 with pentafluoro-*NN*-dimethylaniline. For the reasons given above, variations in these ratios for the

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

different nucleophiles will not be discussed. Although they might be real, they are much less than the variations between substrates. Another significant factor is the relative reactivity of the substrates. By treating each of them with dimethylamine for a time insufficient to give complete reaction, and then comparing the product : starting material ratios, the order of decreasing reactivity was found to be $C_6F_5NMe_2 > C_6F_5NHMe > C_6F_5NH_2$. All this is most easily attributed to steric inhibition of resonance. With pentafluoro-*NN*-dimethylaniline, the *N*-methyl/*ortho*-fluorine interaction bends or twists the NMe_2 group out of the ring plane, and thus reduces any effect of the nitrogen lone-pair on the ring. The NMe_2 group therefore behaves largely as an inert substituent and this leads, as is observed, to relatively rapid replacement mainly of the fluorine *para* to the NMe_2 group. This is analogous to other C_6F_5X compounds, where the fluorine *para* to X is the main one replaced providing X is not a strong electron donor.[11,12] At the other extreme, the lone-pair in pentafluoroaniline can exert a much greater effect, and, if it can interact with the π-electron system of the ring, by any mechanism it would be expected to deactivate the *ortho*- and *para*-positions more than the *meta*-position towards nucleophilic attack. Thus, the observed, slow, *meta*-replacement is reasonable. With the *N*-methyl compound an intermediate situation would be expected.

The ultraviolet spectra of these polyfluoroaromatic amines support the suggestion of steric inhibition of resonance. In cyclohexane, pentafluoroaniline had $\lambda_{max.}$ at 215 mμ (ε 18,000), pentafluoro-*N*-methylaniline at 225 and 217 mμ (ε 16,800), and pentafluoro-*NN*-dimethylaniline at 217 mμ (ε 10,000). The decreasing extinction coefficients imply a decreasing conjugation of the nitrogen lone-pair with the ring. In the non-fluorinated analogues, the extinction coefficients increase in the same order ($C_6H_5NH_2 < C_6H_5NHMe < C_6H_5NMe_2$).

EXPERIMENTAL

Pentafluoro-NN-*dimethylaniline.*—(*a*) *From hexafluorobenzene.* Hexafluorobenzene (5·0 g.), dimethylamine (5 ml.), and ethanol (15 ml.) were heated at 75° in a sealed tube for 12 hr. The mixture was poured into water and the product isolated by extraction with ether; it was pentafluoro-*NN*-dimethylaniline (3·8 g.), b. p. 160—162° (lit.,[4] 88°/1 mm.) (Found: C, 45·4; H, 2·8. Calc. for $C_8H_6F_5N$: C, 45·5; H, 2·9%).

(*b*) *From pentafluoroaniline.* The aniline (3·0 g.), aqueous formic acid (90% w/w; 30 ml.), and aqueous formaldehyde (40% w/v; 3 ml.) were heated under reflux for 18 hr. and then poured into water. Neutralisation with sodium hydrogen carbonate, followed by extraction with ether, gave pentafluoro-*NN*-dimethylaniline (2·8 g.), b. p. 161—163°, identified by infrared (i.r.) spectroscopy.

When this reaction was repeated, but heating for only 6 hr., pentafluoro-*NN*-dimethylaniline (1·95 g.) and a colourless solid (0·8 g.), b. p. 155°/18 mm., were produced. The solid had a strong i.r. absorption at 1700 cm.$^{-1}$ and was transparent at 3500 cm.$^{-1}$ (NH).

When pentafluoroaniline (3·0 g.) was heated with methyl iodide (2 ml.) at 140° for 12 hr. in a sealed tube, g.l.c. indicated that the product (2·1 g.) was a mixture of comparable amounts of pentafluoro-aniline, -*N*-methylaniline, and -*NN*-dimethylaniline.

2,3,5,6-*Tetrafluoro*-NNN′N′-*tetramethyl*-1,4-*phenylenediamine.*—(*a*) *From* 2,3,5,6-*tetrafluoro*-1,4-*phenylenediamine.* The diamine[7] (0·82 g.), 90% formic acid (20 ml.), and 40% formalin (2 ml.) were heated under reflux for 18 hr. Isolation as in (*b*) above gave crude 2,3,5,6-tetrafluoro-*NNN′N′*-tetramethyl-1,4-phenylenediamine (0·6 g.), m. p. 30—33°; sublimation *in vacuo* gave the pure compound (0·2 g.), m. p. 38·5° (Found: C, 50·6; H, 5·1. Calc. for $C_{10}H_{12}F_4N_2$: C, 50·8; H, 5·1%). Wall[4] obtained this compound as a liquid, b. p. 140—148°/1 mm.

(*b*) *From hexafluorobenzene.* Hexafluorobenzene (8·0 g.) was heated at 110° for 18 hr. with dimethylamine and ethanol in a sealed tube. Isolation as in (*a*) of the previous experiment gave a crude solid (7·2 g.), m. p. 29—33°, which was distilled *in vacuo* to give 2,3,5,6-tetrafluoro-*NNN′N′*-tetramethyl-1,4-phenylenediamine (3·8 g.), m. p. and mixed m. p. 38°.

Reaction of Pentafluoro-NN-*dimethylaniline and Dimethylamine at* 230°.—The aniline (10 g.)

[11] J. C. Tatlow, *Endeavour*, 1963, **22**, 89.

[12] J. Burdon, W. B. Hollyhead, J. C. Tatlow, *J.*, 1965, 5152.

and dimethylamine (10 ml.) were heated at 230° in a sealed tube for 18 hr. Separation of the products (after washing with water) by g.l.c. (6 m. × 35 mm. diam. column, packed with silicone gum on Celite, 160°, N_2 flow-rate 20 l./hr.) gave (i), pentafluoro-*NN*-dimethylaniline (trace) (i.r.); (ii), 3,4,5,6-*tetrafluoro*-NNN'N'-*tetramethyl*-1,2-*phenylenediamine* (0·3 g.), b. p. 88°/13 mm. (Found: C, 51·4; H, 5·4%). The ^{1}H n.m.r. spectrum showed a doublet (J = 0·9 c./sec.) at 2·83, and the ^{19}F spectrum two multiplets of equal intensity at 73·9 and 88·8. Peak (iii) was 2,4,5,6-tetrafluoro-*NNN'N'*-1,3-phenylenediamine (<0·05 g.) (i.r.); (iv) was a solid (2·4 g.) which crystallised from ether to give 2,3,5,6-tetrafluoro-*NNN'N'*-tetramethyl-1,4-phenylenediamine (1·6 g.), m. p. and mixed m. p. 38—39°; and (v) was 1,2,4-*trisdimethylamino*-3,5,6-*trifluorobenzene* (0·8 g.), b. p. 126°/0·1 mm. (Found: C, 55·1; H, 7·0. $C_{12}H_{18}F_3N_3$ requires C, 55·2; H, 6·9%); the ^{19}F n.m.r. spectrum showed two multiplets, in intensity ratio 1 : 2, at 60·1 and 79·4; the ^{1}H spectrum was a broad, incompletely resolved, band at 2·75.

2,4,5,6-*Tetrafluoro*-NNN'N'-*tetramethyl*-1,3-*phenylenediamine*.—2,4,5,6-*Tetrafluoro*-1,3-phenylenediamine [2] (3·0 g.) was heated under reflux with 90% formic acid (40 ml.) and 40% formalin (6 ml.) for 18 hr. Isolation as in the first experiment gave the liquid 2,4,5,6-*tetrafluoro*-NNN'N'-*tetramethyl*-1,3-*phenylenediamine* (1·8 g.), b. p. 110°/18 mm. (Found: C, 50·6; H, 5·2%).

Reactions of 3,4,5,6-*Tetrafluoro*-1,2-*phenylenediamine*.—(*a*) *With formic acid*. The diamine [7] (0·8 g.) was heated under reflux with 90% formic acid (8 ml.) for 15 hr., and the mixture then poured into water. Neutralisation with sodium hydrogen carbonate followed by ether extraction gave 4,5,6,7-*tetrafluorobenzimidazole* (0·52 g.), m. p. 232° (from acetone–benzene) (Found: C, 44·3; H, 1·3. $C_7H_2F_4N_2$ requires C, 44·2; H, 1·1%), $\nu_{max.}$ at 2800 cm.$^{-1}$ (acidic NH), $\lambda_{max.}$ (EtOH) at 240 (ε 5000) and 227 mμ (ε 5200), and $\lambda_{infl.}$ at 265 mμ (ε 2000). The ^{1}H n.m.r. spectrum showed a singlet at 8·22 (aromatic C–H).

(*b*) *With formaldehyde*. The diamine (1·7 g.) was heated under reflux with 5N-hydrochloric acid (40 ml.) and 40% formalin (4 ml.) for 15 hr. Isolation as in (*a*) left a residue which was extracted with refluxing benzene (10 ml.). The insoluble material (0·58 g.) was crystallised from benzene–acetone to give 4,5,6,7-tetrafluorobenzimidazole (0·25 g.), m. p. and mixed m. p. 231°.

Evaporation of the benzene extracts, followed by sublimation (90°/0·05 mm.) of the residue gave a colourless solid (0·18 g.), which was crystallised from light petroleum (b. p. 80—100°)–benzene to give 4,5,6,7-*tetrafluoro*-N-*methylbenzimidazole* (0·08 g.), m. p. 115—115·5° (Found: C, 46·9; H, 2·2. $C_8H_4F_4N_2$ requires C, 47·1; H, 2·0%). The compound was transparent in the i.r. region at 2600—3000 cm.$^{-1}$, and had $\lambda_{max.}$ (EtOH) at 245 (ε 5000) and 230 (ε 4800), and $\lambda_{infl.}$ at 267 mμ (ε 2000). The ^{1}H n.m.r. spectrum, in acetone, showed a singlet at 8·22, and a doublet (J = 1·4 c./sec., N–Me protons coupling to the *ortho*-fluorine [13]) at 4·05, in intensity ratio 1 : 3.

3,4,5,6-*Tetrafluoro*-NNN'N'-*tetramethyl*-1,2-*phenylenediamine from the Methylation of Tetrafluoro*-NN-*dimethyl*-1,2-*phenylenediamine*.—2-Dimethylamino-3,4,5,6-tetrafluoronitrobenzene [9] (2·4 g.) was hydrogenated in ethanol (50 ml.) at atmospheric pressure and room temperature over Adams platinum catalyst. Filtration and evaporation left a colourless liquid (2·0 g.), presumably tetrafluoro-*NN*-dimethyl-1,2-phenylenediamine, which rapidly became purple in air and which showed only a single peak on g.l.c. This liquid was heated under reflux for 72 hr. with 90% formic acid (20 ml.) and formalin (2 ml.), and the product (0·8 g.) isolated as before; g.l.c. showed two incompletely resolved peaks. Chromatography on alumina (1 ft. × 1½ in. diam. column) with light petroleum (b. p. 40—60°) as eluent gave three fractions, the last two of which contained both g.l.c. product peaks. The first fraction (0·02 g.) gave a single peak on g.l.c., which corresponded to the shortest-retained of the two original peaks; this fraction was also identical (i.r.) with 3,4,5,6-tetrafluoro-*NNN'N'*-1,2-phenylenediamine prepared earlier.

When the methylation was carried out for 15 hr., ^{1}H n.m.r. spectroscopy showed that the product was mainly (>70%) starting material.

3,4,5,6-*Tetrafluoro*-o-*anisidine*.—2,3,4,5-Tetrafluoro-6-nitroanisole [9] (0·98 g.) was hydrogenated in ethanol over Adams catalyst at room temperature and atmospheric pressure. Filtration and evaporation left a tar (0·4 g.) which was distilled *in vacuo* to give 3,4,5,6-*tetrafluoro*-o-*anisidine* (0·25 g.), b. p. 130° (bath)/10 mm. (Found: C, 43·7; H, 2·7. $C_7H_5F_4NO$ requires C, 43·1; H, 2·6%).

3,4,5,6-*Tetrafluoro*-NN-*dimethyl*-o-*anisidine*.—The tetrafluoro-*o*-anisidine (0·7 g.) was heated under reflux with 90% formic acid (10 ml.) and 40% formalin (1 ml.) for 18 hr. Isolation as in previous experiments gave a tar (0·4 g.) which was distilled *in vacuo* to give 3,4,5,6-*tetrafluoro*-NN-*dimethyl*-o-*anisidine* (0·12 g.), b. p. 60° (bath)/0·1 mm. (Found: C, 48·7; H, 3·9. $C_9H_9F_4NO$ requires C, 48·5; H, 4·1%). The ^1H n.m.r. spectrum showed two doublets, in intensity ratio 1 : 2, at 3·83 (J = 2·0 c./sec.) (OMe) and 2·83 (1·2 c./sec.) (NMe_2).[13]

2,3,5,6-*Tetrafluoro*-NN-*dimethyl*-p-*anisidine*.—2,3,5,6-Tetrafluoro-*p*-anisidine [14] (0·49 g.) was methylated as in the previous experiment to give 2,3,5,6-*tetrafluoro*-NN-*dimethyl*-p-*anisidine* (0·30 g.), b. p. 98°/16·5 mm. (Found: C, 48·6; H, 4·1%). The ^1H n.m.r. spectrum showed two triplets, in intensity ratio 1 : 2, at 3·88 (J = 1·0 c./sec.) (OMe) and 2·85 (J = 1·7 c./sec.) (NMe_2).[13]

*Reactions of Pentafluoro-aniline, -*N*-methylaniline, and -*NN*-dimethylaniline with Amines*.—The anilines were heated at the tabulated temperatures with the amines, in most cases in the presence of water and ethanol, in sealed tubes for 18 hr. The reaction mixtures were poured into water, and the crude products isolated by extraction with ether. Methylation of these products with 90% formic acid (*ca.* 5 ml. per N–H bond expected in the products per g. of starting aniline) and 40% formalin (*ca.* 0·5 ml./NH/g.) were carried out as described previously. The composition of the final product was determined by relative peak area measurements on gas–liquid chromatograms (column 2 m. × 3 mm. diam.; packed with silicone gum on Celite; 150—156°; N_2 flow-rate 4 l./hr.). Each quoted isomer ratio is the mean of the ratios from four g.l.c. runs; no run differed by more than 3% from its mean. When a figure is quoted for *ortho*-product, it was derived from the combined areas of the two partially resolved peaks referred to in the experiment describing the methylation of tetrafluoro-*NN*-dimethyl-1,2-phenylenediamine. All three product peaks (counting the *ortho*-doublet as one) were completely resolved by g.l.c.; their retention order was o-$C_6F_4(NMe_2)_2$ < m-$C_6F_4(NMe_2)_2$ < p-$C_6F_4(NMe_2)_2$. The methylation procedure was omitted for the pentafluoro-*NN*-dimethylaniline–dimethylamine reactions; in these reactions, the *ortho*-product showed as a single peak. The results are given in Table 3.

TABLE 3

Substrate (Wt. in g.)		Nucleophile [a] (Vol. in ml.)	Ethanol (ml.)	Water (ml.)	Temp.	*m*/*p* ratio [b]	*o*/*p* ratio [c]
$C_6F_5NH_2$	(5·0)	1 (6)	15	—	225°	6·60	0
,,	(1·3)	1 (1·5)	4	—	225	6·60	0
,,	(1·1)	2 (3)	—	1	165 [d]	7·05	0
,,	(2·0)	4 (4)	10	4	115 [e]	9·50	0
,,	(2·0)	4 (4)	10	4	220 [e,]	5·49	0
,,	(1·0)	4 (2)	5	2	180	6·10	0
C_6F_5NHMe	(1·2)	1 (3)	5	—	195	0·66	0
,,	(1·6)	2 (8)	—	4	165	1·44	0
,,	(6·0)	2 (13)	7	5	165	1·55	0
,,	(1·5)	3 (8)	—	4	110	1·08	0
,,	(0·3)	3 (8)	—	1	160	1·12	0·33
$C_6F_5NMe_2$	(2·0)	1 (5)	5	—	205	0·075	0
,,	(1·5)	2 (8)	—	4	160	0·069	0
,,	(2·0)	2 (10)	—	5	205	0·053	0·010
,,	(1·0)	3 (6)	—	3	120	0·054	0·033
,,	(0·5)	4 (2)	10	2	170 [g]	0·057	0·034
,,	(10)	4 (10)	—	—	230 [h]	0·046	0·020

[a] 1 = aqueous ammonia (*d* 0·88); 2 = 33% w/w ethanolic methylamine; 3 = 33% w/w ethanolic dimethylamine; 4 = dimethylamine. [b] *m*/*p* ratio = ratio of area of 2,4,5,6-tetrafluoro-*NN*-dimethyl-1,3-phenylenediamine peak to 2,3,5,6-tetrafluoro-*NN*-dimethyl-1,4-phenylenediamine peak. [c] Analogous to *b*. [d] This reaction was repeated on pentafluoroaniline (4 g.) at 200° and the products (2·1 g.) (before methylation) were distilled [130°(bath)/18 mm.] and analysed (Found: C, 43·1; H, 3·0. Calc. for $C_7H_5F_4N_2$: C, 43·3; H, 3·1%). [e] Products separated (g.l.c.) and identified (i.r.). [f] *ca.* 0·5% Tri-replacement compound indicated by g.l.c. [g] 4% Tri-replacement. [h] 19% Tri-replacement.

Three mixtures of tetrafluoro-1,3-phenylenediamine and -1,4-phenylenediamine, containing 51, 42, and 24% of the 1,4-isomer, were subjected to the methylation and g.l.c. analysis procedure. The measured amounts of 1,4-isomer were 52, 41, and 23%, respectively. This implies that the figures in Table 1 are accurate to ±1%; we suggest ±4% as a more realistic figure.

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

[14] J. Burdon, C. J. Morton, and D. F. Thomas, *J.*, 1965, 2621.

In order to test whether preferential decomposition of one isomer was occurring in the amination, hexafluorobenzene (8·0 g.) was heated at 155° in a sealed tube with 33% w/w ethanolic methylamine (30 ml.) and water (10 ml.) for 15 hr. Isolation as before, and separation by g.l.c. (silicone gum on Celite-packed column at 150°) gave pentafluoro-*N*-methylaniline (5·9 g.) (i.r.) and mixed di-replacement products (2·0 g.). The latter were divided into two portions, one of which was re-treated with methylamine at 175° for 13 hr. The product from this reaction, and the other portion, were methylated in the usual way and the *m*/*p* ratio [see footnote (*b*), Table 3] determined for each; for the re-treated portion, the ratio was 1·71, and for the other 1·76, thus showing that neither isomer was decomposed selectively at 175°.

Reaction of Pentafluoroaniline with Sodium Methoxide.—The aniline (12·0 g.) was heated under reflux with sodium methoxide in methanol (2N; 150 ml.) for 3 days. The mixture was poured into water and the product (14·1 g.) isolated by ether extraction. Methylation as usual with formic acid and formaldehyde for 18 hr. gave a product (13·5 g.) which contained five components (g.l.c.). Separation by g.l.c. (35 mm. diam. column, packed with silicone gum on Celite, 160°) gave (i), ether (trace); (ii), pentafluoro-*NN*-dimethylaniline (3·0 g.) (i.r.); (iii), 2,3,4,5-tetrafluoro-*NN*-dimethyl-*o*-anisidine (0·27 g.) (i.r.); (iv), 2,4,5,6-*tetrafluoro*-NN-*dimethyl*-m-*anisidine* (2·6 g.), b. p. 92°/16·5 mm. (Found: C, 48·1; H, 4·5%); the ^{19}F n.m.r. spectrum showed four multiplets of equal intensity at 66·7, 73·9, 82·7, and 88·8, and the ^{1}H spectrum two triplets at 2·82 ($J = 1·7$ c./sec.) (NMe_2) and 3·85 ($J = 0·9$ c./sec.) (OMe);[13] and (v), a mixture (2·4 g.) of component (iv) and a component with the same retention time as 2,3,5,6-tetrafluoro-*NN*-dimethyl-*p*-anisidine.

Repetition on pentafluoroaniline (2·1 g.) gave, before methylation, a product which showed four peaks on g.l.c. (3 mm. diam. column, packed with silicone gum on Celite, 135°) whose retention times corresponded to (i), ether; (ii), pentafluoroaniline; (iii), tetrafluoro-*o*-anisidine; and (iv), a mixture of tetrafluoro-*m*- and -*p*-anisidine. The ratio of the areas of peaks (iii) and (iv) was 1 : 23·5. After methylation, g.l.c. showed five peaks; the relative areas of the peaks corresponding to tetrafluoro-*NN*-dimethyl-*o*-, -*m*-, and -*p*-anisidine were 1 : 13·2 : 4·0, respectively. Further repetition gave 1 : 12·4 : 3·2 for these ratios. The ^{1}H n.m.r. spectra of the products, both before and after methylation, showed two overlapping triplets, in approximate intensity ratio 5 : 1, in the methoxyl region (3·7—4·3).[13]

Reaction of Pentafluoro-N-*methylaniline with Sodium Methoxide.*—The aniline[2] (1·82 g.) was heated under reflux with sodium methoxide in methanol (2N; 25 ml.) for 24 hr. Isolation as in the previous experiment gave a product which showed four g.l.c. peaks. The area ratio of the last two [presumably *o*-$C_6F_4(OMe)NHMe$ and a mixture of its *m* and *p*-isomers, respectively] was 1 : 18·5. Methylation gave another product, which showed five g.l.c. peaks; the area ratios of the last three [*o*-, *m*-, and *p*-$C_6F_4(OMe)NMe_2$, respectively] were 1 : 8·4 : 11·9. Repetition gave 1 : 5·8 : 10·0 for these ratios; the ^{1}H n.m.r. spectra of both mixtures showed two overlapping triplets of approximately equal intensity in the methoxyl region.

Reactions of Pentafluoro-NN-*dimethylaniline with Sodium Methoxide.*—The aniline (8·1 g.) was heated under reflux with 1·06N sodium methoxide in methanol (50 ml.) for 24 hr. Isolation as before gave a product which showed only one peak on g.l.c. This peak was split into shorter- and longer-retained fractions by g.l.c. (35 mm. diam. column, packed with silicone gum on Celite, 145°); the first fraction (0·16 g.) showed three peaks on analytical g.l.c., corresponding to the *o*-, *m*-, and *p*-$C_6F_4(OMe)NMe_2$ isomers, whose areas were in the ratio 1 : 3·5 : 4·5. The second fraction (2·85 g.) was 2,3,5,6-tetrafluoro-*NN*-dimethyl-*p*-anisidine (i.r.). The procedure probably underestimates the amounts of the *o*- and *m*-$C_6F_4(OMe)NMe_2$ isomers, as the second g.l.c. fraction may still have contained small amounts of them.

Calibration of the Gas Chromatograph for the Methoxide Reactions.—Various mixtures of *m*- and *p*-$C_6F_4(OMe)NMe_2$ were chromatographed in the same way as in the three previous experiments, and the peak area ratios measured. This Table has been used to correct the ratios

m/*p* (Wt. ratio)	0·27	0·86	1·41	2·46	3·00	4·04
m/*p* (G.l.c. peak-area ratio)	0·22	0·76	1·00	1·95	2·20	2·90

found in the three previous experiments, and the corrected figures are given as percentages in Table 1. In view of this, and also because the *m*- and *p*-$C_6F_4(OMe)NMe_2$ peaks are not completely resolved, the figures in Table 1 for these isomers are accurate to about ±8%.

A mixture of 36·5% tetrafluoro-*o*-anisidine and 63·5% tetrafluoro-*p*-anisidine was methylated, and the products analysed by g.l.c. in the usual way. Peak-area measurements gave

o-$C_6F_4(OMe)NMe_2$ as 33%. In view of the small percentage of *ortho*-replacement in all three reactions, this difference is insignificant.

Nuclear Magnetic Resonance Spectra.—The ^1H spectra were measured on a Varian A60 instrument at 60 Mc./sec. and chemical shifts are quoted in p.p.m. downfield from tetramethylsilane as internal reference. The ^{19}F spectra were measured on a Varian HR 100 at 94·1 Mc./sec. and chemical shifts are in p.p.m. upfield from trifluoroacetic acid as internal reference.

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