CLXX.—*The Nature of the Alternating Effect in Carbon Chains. Part VI. A Study of the Relative Directive Efficiencies of Oxygen and Fluorine in Aromatic Substitution.*

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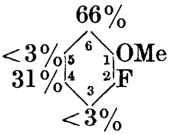
IN continuation of the work, described in the preceding part, on the establishment of the sequence N>O>F for the *op*-directive powers of these atoms in the neutral state and directly attached to the benzene ring, the method previously used for comparing the relative directive efficiencies of nitrogen and oxygen atoms has now been applied to the comparison of oxygen with fluorine. *o*-Fluoroanisole has been nitrated with the results indicated in the following formula :



The methods by which these figures have been determined are fully described in the experimental portion, and it need only be stated here that the 3- and 5-nitro-derivatives were estimated together (2·7%) by taking advantage of the lability of their fluorine towards alkaline reagents, and that the 4-nitro-compound was estimated colorimetrically after reduction, utilising the fact that *p*-anisidine gives a violet coloration with ferric chloride, whilst the *o*-compound does not. The 4-nitro-derivative was isolated as such from the nitration mixture and identified by synthesis, whilst the 6-nitro-compound, which was also synthesised and was a liquid at the ordinary temperature, was reduced with elimination of fluorine and identified as *o*-anisidine hydrochloride.

From the data given, it is clear that whether we disregard the large amount of *o*-substitution as an effect to which special influences contribute and consider only substitution in positions 4 and 5, or whether we accept the total *op*-direction by each group as the better measure of its directive power, the oxygen atom is the more effective directing agent. So great is the difference that although only one case has been investigated it appears reasonable to infer that the conclusion drawn will hold generally amongst derivatives of *o*-fluorophenol.

The sequence $N > O > F$ is thus established; and this is the expected sequence, since the electronic grouping of fluorine most closely approaches the internally satisfied condition exemplified in neon (preceding paper).

EXPERIMENTAL.

Preparation of o-*Fluoroanisole.*—Some difficulty was experienced in obtaining this substance, but it was ultimately prepared by the action of hydrofluoric acid on the *diazopiperidide* obtained from *o*-anisidine. A solution of 25 g. of *o*-anisidine in 60 c.c. of hydrochloric acid was diazotised below 0° by a solution of 15 g. of sodium nitrite in 50 c.c. of water, the mixture being mechanically stirred. On pouring the product into a solution of potassium hydroxide (30 g.) and piperidine (17 g.) in 150 c.c. of water, an oil was precipitated which rapidly solidified (yield 35—37 g.) and on crystallisation from methyl alcohol yielded lemon-yellow prisms, m. p. 30° (Found: C, 65·0; * H, 7.6. $C_{12}H_{17}ON_3$ requires C, 65·8; H, 7·8%).

This diazopiperidide (35 g.) was heated for 1 hour on the steam-bath with 150 c.c. of concentrated aqueous hydrofluoric acid. Ice was then added and the mixture poured into an excess of 30% aqueous sodium hydroxide, care being taken to avoid over-heating, since the fluoroanisole is very volatile with steam. The *fluoroanisole* was isolated by distillation in steam and separated from the piperidine contained in the steam-distillate by extraction with ether after acidification. It is a colourless, mobile liquid, b. p. 154—155° (Found: C, 66·6; H, 5·6. C_7H_7OF requires C, 66·7; H, 5·6%). The average yield was 6% of the theoretical.

Dinitration.—In a preliminary experiment in which 1 g. of *o*-fluoroanisole was run through a fine capillary tube into 2 c.c. of

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* A better analysis is, unfortunately, not available; difficulty was experienced in burning the substance owing to the rapidity with which it decomposed.

nitric acid (*d* 1·5) at —10°, and the product mixed with crushed ice, a solid dinitro-compound was obtained which on crystallisation from ethyl alcohol formed pale yellow needles, m. p. 86—87°. Judging from the results of mononitration (below), we believe this to be 4 : 6-*dinitro-2-fluoroanisole,* although no special proof of its constitution is here offered (Found : C, 38·7 ; H, 2·2. $C_7H_5O_5N_2F$ requires C, 38·9 ; H, 2·3%).

Mononitration.—*o*-Fluoroanisole (6·5 g.), mixed with acetic anhydride (25 g.), was treated at 0° with a mixture of fuming nitric acid (2·20 c.c.) and acetic anhydride (9 c.c.). The nitration proceeded smoothly with evolution of heat, and the mixture was kept at the ordinary temperature for 3—4 hours and then poured into water. The oil which separated was collected and diluted with ether, the aqueous solution was extracted with ether, and the combined ethereal solutions were dried and evaporated. The residue, after drying for a short time over potassium hydroxide, was distilled, practically the whole boiling at 114—116°/2 mm. (Found : C, 49·2 ; H, 3·4. $C_7H_6O_3NF$ requires C, 49·1 ; H, 3·5%).

3-*Nitro- and* 5-*Nitro-*o-*fluoroanisole.*—These were estimated together by taking advantage of the lability of their fluorine in the presence of boiling 0·5*N*-aqueous sodium carbonate, or dilute methyl-alcoholic sodium methoxide prepared from 2 g. of sodium and 200 c.c. of methyl alcohol. With the first of these reagents at its boiling point, and with the second at 60°, a quantity of fluoride ion corresponding with the decomposition of about 2·5—3·0% of nitrofluoroanisole was liberated rapidly, whilst prolonged treatment produced very little further action. After 3 hours' treatment with boiling sodium carbonate, the liberation of fluoride ion corresponded to 2·7% of decomposed nitrofluoroanisole (average of three concordant determinations) and almost the same figure, 2·8%, was obtained on using sodium methoxide. To ascertain if any correction was needed for the possible decomposition of the 4- and 6-nitro-derivatives, these two substances (see below) were treated for the same period under the same conditions. With 4-nitrofluoroanisole and sodium carbonate, the decomposition was zero (two determinations), and the same result was obtained with sodium ethoxide. Only a small quantity of 6-nitrofluoroanisole was available, but a single determination by the sodium carbonate method indicated the decomposition of 0·2%. From these results it is evident that the 4- and 6-nitro-derivatives do not decompose appreciably under the conditions used. On the other hand, 4-nitrofluoroanisole is decomposed at a measurable velocity at 85° by sodium methoxide of the dilution stated above, and, in this connexion, reference may be made to Holleman and Beekman's experiment on the alcoholysis of *m*-nitrofluorobenzene (*Rec. trav. chim.*, 1904, **23**, 235). The mixed 3- and 5-nitroguaiacols were isolated from the above decompositions with sodium, but the quantity was too small for the estimation of their relative proportions by the steam distillation method employed by Ingold and Ingold (preceding paper). A small quantity of pure 5-nitroguaiacol was isolated by taking advantage of the sparing solubility of its potassium salt in 4*N*-aqueous potassium hydroxide.

4-*Nitro*-o-*fluoroanisole*.—The nitrofluoroanisoles recovered after decomposition of the 3- and 5-derivatives with sodium carbonate formed a mixture which was liquid at the ordinary temperature but, on cooling in an efficient freezing mixture, set to a paste of crystals. These were collected below −20°, and when freed from adhering oil, had m. p. 47—49°. By crystallisation from ligroin pale yellow prisms were obtained, m. p. 52—52·5°, which were identified by direct comparison and a mixed m. p. determination with a specimen synthesised as described below. The yield accounted for about 10% of the nitration product.

Synthesis of 4-*Nitro*-o-*fluoroanisole*.—4-Nitro-*o*-anisidine (25 g.) prepared from 2 : 4-dinitrochlorobenzene, *via* 2 : 4-dinitroanisole, was dissolved in 50 c.c. of boiling 20% hydrochloric acid, and the solution cooled with rapid stirring to ensure fine division of the solid. Diazotisation was effected in the usual way with 11 g. of sodium nitrite, and the mixture poured into a solution of 30 g. of potassium hydroxide and 13 g. of piperidine in 150 c.c. of water with the addition of sufficient ice to maintain the temperature at 0°. The oily precipitate soon solidified (yield, 35 g.), and crystallisation from ethyl alcohol gave buff needles, m. p. 95—96° (Found : C, 54·5; H, 6·0. $C_{12}H_{16}O_3N_4$ requires C, 54·2; H, 5·9%). This *diazopiperidide* (35 g.) was warmed on the steam-bath for 1 hour with 175 c.c. of concentrated hydrofluoric acid, the mixture being rapidly stirred at the commencement of the process. After the addition of ice the mixture was poured into 1·5 l. of 30% sodium hydroxide kept at 0°, and after complete neutralisation the mixture, which contained a brown precipitate of unknown constitution, was distilled in a current of steam. The nitrofluoroanisole crystallised in the receiver. but it was found convenient to extract it with ether. It melted at 45—49° in the crude condition and at 52—53° after crystallisation from ligroin (Found : C, 49·3; H, 3·5. $C_7H_6O_3NF$ requires C, 49·1; H, 3·5%). The yield was 1·3 g., that is, 7% of the theoretical.

On reduction by boiling for 15 minutes with stannous chloride and hydrochloric acid it was converted smoothly into *p*-anisidine, the elimination of fluorine being quantitative. The anisidine thus obtained melted at 56—57°, alone and when mixed with a genuine specimen (Found: C, 68·8; H, 7·5. Calc.: C, 68·9; H, 7·4%.

Calc. for C_7H_8ONF : C, 59·6; H, 5·7%). An application of this reaction is described below.

Synthesis of 6-*Nitro*-o-*fluoroanisole*.—The silver salt of 2 : 6-dinitrophenol was boiled with a benzene solution of methyl iodide, and the dinitroanisole so obtained was reduced by hydrogen sulphide in methyl-alcoholic ammonia solution to 6-nitro-*o*-anisidine (yield 35%). The *hydrochloride* of this base separated from hydrochloric acid in clusters of pale yellow needles, m. p. 198°.

The base was converted into its *diazopiperidide* by the method described in the preceding paragraph. The diazopiperidide, after draining on porous porcelain, but without further purification, was decomposed with hydrofluoric acid, and the 6-*nitro*-o-*fluoroanisole* isolated by distillation in steam. After redistillation it was obtained as a pale yellow oil, b. p. 110°/1 mm. (Found : C, 49·6; H, 3·7. $C_7H_8O_3NF$ requires C, 49·1; H, 3·5%).

On reduction by stannous chloride and hydrochloric acid *o*-anisidine was obtained unaccompanied by any fluoro-base.

Estimation of the Proportions of 4- *and* 6-*Nitro*-o-*fluoroanisoles obtained by Nitration*.—The mixture of 4- and 6-nitrofluoroanisoles obtained after decomposition of the 3- and 5-nitro-isomerides by sodium carbonate was reduced with stannous chloride as described above. The yield of distilled bases was 90% of the theoretical, and analysis showed that the whole of the fluorine had been eliminated (Found : C, 69·1; H, 7·2%).

A weighed portion of these mixed bases was treated with hydrochloric acid; *o*-anisidine hydrochloride (m. p. 225°, alone and mixed with an authentic specimen; a mixture with *p*-anisidine hydrochloride, m. p. 215°, melted at 170—180°) was thus obtained. The yield corresponded with 48% of 6-nitrofluoroanisole in the original mixture.

In order to estimate the relative proportions of *o*- and *p*-anisidine in the mixture of these bases, a series of artificial mixtures, in the proportions 20 : 80, 40 : 60, 60 : 40, and 80 : 20, was prepared in the form of 1% solutions in ethyl alcohol. Each of these was tested in turn against a 1% solution of the experimental mixture, equal volumes of the solutions under comparison being added to equal portions of a solution of ferric chloride in similar colorimeter tubes. By comparing the colours, it was found that the proportion of *p*-isomeride in the experimental mixture lay between 20% and 40%. The process was repeated with three more standards, containing 25%, 30%, and 35%, respectively, of *p*-compound. As these tests indicated that the proportion of *p*-isomeride lay between 30% and 35%, an additional standard, containing 32·5% of *p*-anisidine and 67·5% of *o*-anisidine, was made. This agreed as exactly as could be ascertained with the experimental mixture, both as regards rate of development of the colour and its maximum intensity. The conditions being so adjusted that about 2—4 minutes were required for the colour to reach its maximum intensity, it was found that the rate of development of colour was more sensitive than maximum intensity to changes of composition and served as a better means of comparison. In the final experiments, therefore, all solutions were immersed in the same bath before mixing, and to avoid differences of temperature during the readings the two tubes were surrounded by a metal screen and symmetrically illuminated. The results are believed to be correct to 2%.

On acetylation of the experimental mixture of bases, a mixture of acetyl derivatives was obtained which set at 59°, and admixture with small amounts of either aceto-*o*-anisidide or aceto-*p*-anisidide raised this setting point, whence it appears that the proportion in which the two substances were present in the acetylation product corresponds approximately with the eutectic composition. The following approximate setting points of mixtures of aceto-*o*-anisidide and aceto-*p*-anisidide indicate that the eutectic contains about 31% of the *p*-compound and sets at 60°, and this supplies confirmation of the figure obtained colorimetrically :

Proportion of para- ...	17·3%	21·4%	24·4%	30·6%	35·0%	39·1%
Setting point	71°	67·5°	64°	60°	63·5°	67°

These values were determined by the cooling curve method.

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