

CCXVI.—*The Nature of the Alternating Effect in Carbon Chains. Part XX. The Conditions underlying Vicinal Substitution in o-Substituted Benzenes containing op-Orienting Groups.*

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IN Part V it was shown (Ingold and Ingold, J., 1926, 1310) that whilst acet-*o*-anisidine (I) and aceto-*N*-methyl-*o*-anisidine are nitrated mainly in the 4- and 5-positions, *ON*-diacetyl-*o*-aminophenol (II), in which the disparity between the *op*-orienting powers of the groups is much greater, yields a large proportion of a vicinal nitro-derivative :

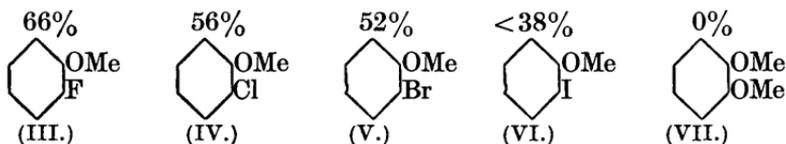


The nitration of *o*-fluoroanisole which was recorded in Part VI (*ibid.*, p. 1328) provided a still more striking example (III) of vicinal substitution in a nucleus *o*-disubstituted with *op*-orienting groups, and in Part VII (*ibid.*, p. 1685) the hypothesis was advanced that, in general, the proportion of *v*-substitution is a function of the disparity between the polar activities of the groups. It was suggested, as a possible explanation, that in an unbalanced system in which the reaction phases are determined almost wholly by one group, the second group may regulate the relative importance of these by controlling the displacement of valency-electrons past the points more directly under its influence.

An opportunity for testing this matter appeared to be provided by the recorded observations on the substitution of the halogen derivatives of benzene. Thus the experiments of Holleman (*Rec. trav. chim.*, 1915, **34**, 204) and Swarts (*ibid.*, **35**, 131) on the nitration of *o*- and *p*-dihalogenobenzenes indicate the sequence  $F < Cl, Br < I$  for the *op*-directive powers of the halogens; and although (owing to the mutual interference of the groups) caution is necessary in generalising from such observations when the directive powers of the groups are close together (as with Cl and Br), the complete sequence  $F < Cl < Br < I$  is indirectly confirmed by the regular gradation of the nuclear reactivity of the monohalogenobenzenes (Olivier, *ibid.*, 1914, **33**, 244; and unpublished observations by Miss F. R. Shaw), and of the dipole moment of comparable mono- and di-halogeno-derivatives (Höjendahl, *Nature*, 1926, **117**, 896; Errera, *Compt. rend.*, 1926, **182**, 1623).

The methoxyl group is more strongly *op*-orienting even than iodine (see below), and hence the above sequence can be expanded to  $F < Cl < Br < I < OMe$ . Therefore, if the circumstances regulating vicinal substitution have been correctly conceived, the successive introduction of these groups into the *o*-position of anisole should produce a series of substances which, taken in order, should show diminishing *v*-substitution. Since the proportion of *v*-nitration of *o*-fluoroanisole has been shown to be 66% (Part VI),\* whilst that of veratrole (VII) is 0%, the other *o*-halogenoanisoles should fall into their places between these limits.

No support for this deduction was forthcoming from the literature. The nitration of *o*-chloroanisole has been investigated successively by Fischli (*Ber.*, 1878, **11**, 1463), Reverdin (*Ber.*, 1896, **29**, 2598), and Reverdin and Eckhard (*Ber.*, 1899, **32**, 2622), all of whom describe the 4-nitro-derivative, but none mentions the formation of any by-product. Reverdin also nitrated *o*-bromoanisole (*loc. cit.*) and *o*-iodoanisole (*ibid.*, p. 997), but in neither case observed the formation of any isomeride of the 4-nitro-compound. We therefore re-investigated the nitration of all these substances, and are able to show that the 6-nitro-compounds also are formed, and that the proportions of vicinal substitution fit into the series as is shown in the following formulæ (IV, V, VI) :



Since the total proportions of the 3- and 5-isomerides oriented by the halogen atoms are only of the order of 2—3% (see experimental portion), the diminishing vicinal substitution in the above series is accompanied by a closely corresponding increase in substitution para to the methoxyl group.

#### EXPERIMENTAL.

*Nitration of o-Chloroanisole.*—A cooled solution of 3.1 g. of nitric acid (*d* 1.5) in acetic anhydride (12 c.c.) was very slowly added to a solution of *o*-chloroanisole (10 g.) in acetic anhydride (40 c.c.), which was cooled in ice and mechanically stirred. When the addition was complete, the solution was allowed to warm to the laboratory temperature and to remain thereat for several hours,

\* A still more extreme case of *v*-substitution can be foreseen in *o*-fluoroacetanilide, which has not yet been investigated, but should yield slightly more than 66% of the 6-nitro-derivative under the conditions used in this investigation and in Part VI.

after which the solvent was removed by distillation under reduced pressure. Distillation of the product yielded 0.8 g. of unchanged *o*-chloroanisole, b. p. about 100°/13 mm. (Found : C, 56.5; H, 4.8. Calc. : C, 56.2; H, 4.9%), and 0.5 g. of undistillable residue, probably dinitro-derivatives, the whole of the remainder being a mixture of mononitro-derivatives (Found : C, 44.9; H, 3.2; N, 7.7. Calc. : C, 44.8; H, 3.2; N, 7.5%) having b. p. 125—165°, which is the b. p. range of an artificial mixture of 4- and 6-nitro-2-chloroanisoles (see below).

The mononitro-derivatives were boiled under reflux with 5% sodium hydroxide for 1 hour, preliminary experiments having shown that the labile isomerides (3- and 5-) are completely decomposed under these conditions and that the reagent is without action on the 4- and 6-nitro-compounds. The latter were extracted with ether, the aqueous solution was acidified with dilute nitric acid, and the nitroguaiacols were extracted with the same solvent. The chloride ion was then estimated either gravimetrically or volumetrically. The values in three separate nitrations were 1.64%, 1.61%, and 1.50%. The yield of mixed nitroguaiacols isolated by extraction with ether from the combined aqueous solutions obtained in the three experiments was equivalent to 1.4% of converted chloronitroanisoles, that is, the yield was 89% on the basis of the chloride estimations. Distillation in steam yielded a yellow solid which when crystallised from water gave a small amount of 3-nitroguaiacol, m. p. 61°, identified by direct comparison; and crystallisation of the original mixture yielded 5-nitroguaiacol, which was similarly identified.

The mixture of 4- and 6-nitro-compounds contained in the ethereal extract from the alkaline solution was analysed by the freezing-point method either directly or after distillation (b. p. as before), preliminary experiments having shown that operations corresponding with those described above do not affect the results obtained.

For the construction of the f. p. diagram, 2-chloro-4-nitroanisole (m. p. 95°) was prepared and purified as described by Reverdin. 2-Chloro-6-nitroanisole was obtained by Holleman (*Rec. trav. chim.*, 1915, **35**, 14) from 2 : 3-dichloronitrobenzene and sodium methoxide, but this method being unsuitable for the preparation of quantities sufficient for our purpose, the following process was evolved. *o*-Chlorophenol was added slowly to mechanically stirred, dilute nitric acid (1 : 3), and the mixture kept over-night at the ordinary temperature. The solid product was then collected, washed with water, and distilled in steam; from the distillate, bright yellow needles of 2-chloro-6-nitrophenol, m. p. 70° (softening at 65°),

separated. This was methylated with a large excess of methyl sulphate and dilute alkali by prolonged mechanical shaking at 40°. The product was collected, washed with sodium or ammonium hydroxide until colourless, and crystallised several times from aqueous alcohol; m. p. 56° (Found: C, 44.9; H, 3.4. Calc.: C, 44.8; H, 3.2%).

The freezing points were taken by the usual method in a double-jacketed tube, provided with arrangements for stirring and seeding, and surrounded by a water-bath, which was also stirred and kept at an approximately constant level well above the substance under examination. The rate at which the temperature was allowed to fall was always close to 0.3° per minute, and the maximal temperatures attained during freezing were accepted as valid readings provided that (a) the rise from the preceding minimum was close to 0.5°, (b) separation of solid with falling temperature but without total solidification did not take place. Temperatures were not corrected, but all were taken under the conditions mentioned on the same thermometer, which was graduated in fifths of a degree and could be read to tenths or less. The following values were obtained for mixtures of 2-chloro-4-nitroanisole and 2-chloro-6-nitroanisole :

2-Chloro-4-nitroanisole.	F. p.	2-Chloro-4-nitroanisole.	F. p.	2-Chloro-4-nitroanisole.	F. p.
100.0%	94.0°	66.3%	72.9°	30.1%	34.8°
91.7	89.3	61.0	71.0	28.9	37.9
86.5	86.6	56.9	67.5	26.2	39.9
82.5	84.0	53.2	64.7	24.0	41.1
78.9	81.9	47.1	58.0	20.0	43.0
76.6	80.0	42.8	52.6	16.5	44.6
73.9	79.0	38.1	47.0	13.0	47.0
72.1	77.5	34.3	42.0	8.3	48.8
68.4	76.0	31.8	38.5	0.0	53.3

These figures lie on a two-branch curve showing a eutectic, f. p. 34.8°, containing 30.1% of the 4-nitro-isomeride.

The f. p.'s of samples of mixed 4- and 6-nitro-compounds obtained in independent nitrations were 53.9° and 51.2°, which correspond with 43.2 and 41.3%, respectively, of the 4-nitro-derivative, since in each case the addition of small amounts of this compound raised the f. p. Another sample, f. p. 54.2°, corresponding with 43.8% of the 4-nitro-compound, on treatment with 22, 34, and 49% of its weight of the 6-nitro-derivative, had f. p.'s 44.7°, 40.8°, and 36.8°, respectively, which agree closely with the curve.

The most probable values of the proportions of the isomerides to the nearest unit % are therefore: 4-nitro, 42%; 6-nitro, 56%; 3- plus 5-nitro-, 2%.

The value for the 4-nitro-compound was confirmed by separation after the destruction of the 3- and 5-nitro-derivatives. The mixture

of the 4- and 6-nitro-compounds (10.00 g.) was fractionally crystallised from dilute alcohol, 32% of the pure 4-derivative being obtained. The combined residues had f. p.  $46^{\circ}$  on the branch of the f. p. curve in which the solid phase is the 6-nitro-isomeride. It follows that both isomerides can be qualitatively separated by crystallisation from dilute alcohol, followed by partial solidification of the fused residues. The above f. p. corresponds with 15% of the 4-nitro-compound, so that the quantity originally present was  $32 + (0.15 \times 68) = 42.2\%$  of the binary mixture, that is, 41.6% of the original nitration product.

*Nitration of o-Bromoanisole.*—These experiments were so similar to the preceding series that only the more important differences need be mentioned.

Boiling with alkali for 4 hours was carried out to ensure complete destruction of the 3- and 5-nitro-compounds.

2-Bromo-6-nitrophenol, m. p.  $65^{\circ}$ , which was prepared in the same way as its chloro-analogue, could not be methylated conveniently with methyl sulphate, and was therefore converted into its silver salt, which was heated under reflux with a large excess of methyl iodide dissolved in benzene. Final purification was effected as in the case of the chloro-compound. M. p.  $66^{\circ}$ .

The whole of the f. p. curve of the 4- and 6-nitro-compounds was not plotted, but only a portion containing the f. p. of the nitration mixture on each branch and the eutectic. It was found convenient to allow a slightly higher rise of temperature on freezing, and  $1.0^{\circ}$  was the standard taken.

The results were as follows: The products from two independent nitrations yielded bromide ion corresponding with 2.70 and 2.67%, respectively, of the 3- plus 5-isomerides, and the yield of mixed nitroguaiacols was 85% calculated on this basis. The f. p. curve used for analysis of the mixture of the 4- and 6-nitro-compounds was based on the following f. p. observations:

2-Bromo-4-nitroanisole.	F. p.	2-Bromo-4-nitroanisole.	F. p.	2-Bromo-4-nitroanisole.	F. p.
0.0%	64.3°	23.7%	49.4°	36.9%	52.0°
7.1	59.6	25.2	47.1	42.2	56.2
13.3	55.7	27.3	46.8	43.4	57.5
17.7	52.8	29.7	46.8	45.8	60.0
20.2	50.9	32.2	48.3	50.5	65.0

The curve contains two rectilinear branches intersecting at 29% of the 4-nitro-compound, the corresponding f. p. being  $45.5^{\circ}$ . The binary mixtures obtained from two nitration experiments had f. p.'s  $60.0^{\circ}$  and  $61.8^{\circ}$ , indicating, respectively, 46.0 and 47.5% of the 4-nitro-derivative, since additions of small amounts of this isomeride to the first sample showed the f. p. to be on the corresponding

branch of the curve. The second sample was mixed with the exact quantity of the 6-nitro-isomeride calculated to change the composition to that of the eutectic. The f. p. was then  $45.0^{\circ}$  and the addition of further small quantities of the 6-nitro-compound raised this.

The most probable values of the proportions of the isomerides to the nearest unit % are therefore : 4-nitro-, 45%; 6-nitro-, 52%; 3- plus 5-nitro-, 3%.

*Nitration of o-Iodoanisole.*—*o*-Iodoanisole was nitrated in acetic anhydride solution (a) under the conditions used for the analogous chloro- and bromo-compounds, (b) at greater dilutions, (c) at a lower temperature,  $-10^{\circ}$  to  $-5^{\circ}$ . In each case, a small amount of iodine was liberated which afterwards became reabsorbed. For this reason, and also because it was not found possible selectively to destroy the 3- and 5-nitro-compounds by alkalis or bases (despite numerous exploratory experiments with *o*-iodonitrobenzene), we were unable to study the nitration product quantitatively. Reverdin (*loc. cit.*) isolated 60% of the 4-nitro-compound from his nitration product, and we therefore endeavoured to isolate as much as possible of this isomeride by his method. From the products of two independent nitrations we obtained 62% and 58%, respectively, of this isomeride, but the residues could not be separated.

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