L.—*The Relative Directive Powers of Groups of the Forms* RO *and* RR′N *in Aromatic Substitution. Part II. The Nitration of some 2-Benzyloxyanisoles substituted in the Benzyl Group.*

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In this communication the method described in the preceding paper is applied to the determination of the directive powers of the *m*- and *p*-nitrobenzyloxy- and *m*-methoxybenzyloxy-groups.

2-*m* (or *p*)-Nitrobenzyloxyanisole is much more difficult to nitrate than is 2-benzyloxyanisole and it is evident that the introduction of the nitro-group has the effect of depressing the reactivity of the molecule as a whole. This effect is, however, felt to a greater relative extent by the benzyloxy-group than by the methoxyl. In Part I it is shown that the directive power of the benzyloxy-group (MeO, 100) is 113 and we now find that the *m*-nitrobenzyloxy- and *p*-nitrobenzyloxy-groups have, within the limits of experimental error, identical directive powers, namely, 67. Obviously the true value should be smaller still, because a portion of the inhibitory effect of the nitroxyl has been experienced by the methoxyl group. Since the nitro-group exerts its influence to an equal extent from the meta- and para-positions in the benzyl nucleus, it is not an alternating effect but, in all probability, a general polar effect which is under observation. The existence of general electrical effects is widely recognised, but it must be emphasised that, no less than in the case of the alternating effects, a knowledge of the mechanism of the reaction is necessary before a conclusion can be reached as to whether a particular process should be facilitated or hindered. An example will illustrate our meaning. Olivier (*Rec. trav. chim.*, 1922, **41**, 646) has shown that the hydrolysis of *o*-, *m*-, and *p*-nitrobenzyl chlorides in aqueous alcohol is much slower than that of benzyl chloride or any of its chloro-, bromo-, or methyl derivatives and this is another clear case of the general electrical effect of the nitro-group. The fact that the nitrophenols and nitrobenzoic acids, compared with phenol and benzoic acid, respectively, are strong acids shows that the nitro-group increases the affinity for the negative charge, whilst the weak basic nature of the nitroanilines, compared with aniline, shows that the introduction of a nitro-group decreases the affinity for the positive charge. An important exemplification of the latter point is found in the high chemical reactivity of nitro-substituted diazonium salts. Now, under the conditions of Olivier's experiments, the most acceptable view of the mechanism of the hydrolysis is that which postulates partial or complete dissociation of the nitrobenzyl chlorides at some stage and possibly as a result of oxonium salt formation with water or alcohol. Any such process will be inhibited if the affinity of the substituted benzyl group for the positive charge is diminished. Hence, on this mechanism, the theory of the general electrical effect of the nitro-group requires that the hydrolysis of a nitrobenzyl chloride should be slower than that of benzyl chloride. If, however, the benzyl chlorides were hydrolysed through the intermediate formation of a complex anion which subsequently recovered neutrality by ejecting chloridion, then the nitro-group, by increasing the affinity for the negative charge, would facilitate the process.* Conversely, the introduction of nitro-groups into a molecule should retard the formation of complex kations such as those resulting from the attack of an aromatic compound by a diazonium ion, and this is in accordance with experience. It is a short step to the general case of aromatic substitution in which the nucleus is attacked by the positive end of a polarised complex rather than by a positive ion, and the same principles apply. If an aromatic nucleus, A, reacts with a complex, ⊕B–C⊖, then the charge on B is transferred to the nucleus and the bipolar ion, ⊕A–B–C⊖, is produced. Circumstances, such as the introduction of nitroxyl, which reduce the affinity of A for the positive charge must retard the process. In our experiments, the nitro-groups gave rise to no alternating effect whatever, but it should be noted that the system is a complex one summarised as: modifying group—activating centre—point of reaction. That is, the effect of the nitro-groups on the reacting nucleus is only experienced through an oxygen atom, which must be regarded as the effective key-atom. In Olivier's experiments very weak alternating effect (in the expected sense) is superposed on the powerful general effect, whilst Harrison (private communication) has shown that the hydration of 3 : 4′-dinitrotolane yields nothing but 3-nitrophenyl 4-nitrobenzyl ketone, $(m\text{-})NO_2\cdot C_6H_4\cdot CO\cdot CH_2\cdot C_6H_4\cdot NO_2(p\text{-})$, in accordance with the rule of alternate polarities. The general conclusion may be drawn that the alternating polar effect of a nitroxyl group cannot be discerned beyond the limits of the conjugated (crotonoid) system of which it forms a part. We had planned the determination of the directive powers of *m*- and *p*-methoxybenzyloxy-groups, but for reasons explained on p. 391 the latter estimation has not yet been made. The *m*-methoxybenzyloxy-group has the directive power 92 (MeO, 100; $CH_2Ph\cdot O$, 113) and it will suffice to note at this stage that the result is in harmony with the effect which a *m*-methoxy-group has in enhancing the ionisation constants of some substituted benzoic acids (*e.g.*, anisic acid, $K = 3{\cdot}2 \times 10^{-5}$; veratric acid, $K = 3{\cdot}8 \times 10^{-5}$).

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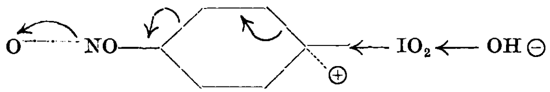
* The hydrolysis of *p*-iodoxynitrobenzene by alkalis (Vorländer and Büchner, *Ber.*, 1925, **58**, 1291) with formation of nitrobenzene and an iodate is a most interesting example of a combined alternating and general effect resulting in the ready production of a complex anion which recovers neutrality by ejecting iodate ion



p-Dinitrobenzene does not undergo a similar reaction and this suggests that an important factor in the situation is the heavy iodine atom, which is doubtless capable of adding electrons to its outer shell.

EXPERIMENTAL.

2-m-*Nitrobenzyloxyanisole*, $OMe{\cdot}C_6H_4{\cdot}O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$.—*m*-Nitrobenzyl bromide, m. p. 59—60°, was obtained in 96% yield by the action of bromine (32 g.) on a mixture of *m*-nitrobenzyl alcohol (31 g.) and red phosphorus (4 g.). A mixture of guaiacol (10 g.), *m*-nitrobenzyl bromide (17 g.), and alcoholic sodium ethoxide (430 c.c. of 0·5*N*) was refluxed for 1·5 hours, and the solid that was precipitated by addition of water was dried and crystallised from alcohol and then twice from light petroleum; it formed small, pale yellow needles, m. p. 47·5—48° (Found: C, 64·8; H, 5·0; N, 5·7. $C_{14}H_{13}O_4N$ requires C, 64·8; H, 5·1; N, 5·4%).

4-*Nitro*-2-m-*nitrobenzyloxyanisole*,

$OMe{\cdot}C_6H_3(NO_2){\cdot}O{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2$.—

The guaiacol carbonate process for the preparation of 5-nitroguaiacol, for some unascertained reason, gave very poor results in this series of experiments and we therefore obtained the substance by the nitration of acetylguaiacol and subsequent hydrolysis (Paul, *Ber.*, 1906, **39**, 2779). The ether of the nitroguaiacol was prepared by the method described for the *m*-nitrobenzylation of guaiacol, except that the reaction mixture was boiled for 2 hours. The substance was crystallised from acetic acid and then twice from alcohol, separating in almost colourless, microscopic plates, m. p. 164·5—165° (Found: C, 55·4; H, 4·3. $C_{14}H_{12}O_6N_2$ requires C, 55·3; H, 4·0%). All the *m*-nitrobenzyloxy-derivatives were more readily soluble in organic solvents than the corresponding *p*-nitrobenzyloxy-compounds.

5-*Nitro*-2-m-*nitrobenzyloxyanisole*.—The potassium salt of 4-nitroguaiacol which separates from the product of hydrolysis of 4-nitroveratrole (Pollecoff and Robinson, J., 1918, **113**, 645) proved to be homogeneous and was brought into reaction with an equivalent quantity of *m*-nitrobenzyl bromide in boiling alcoholic solution (400 c.c. for 12 g. of the salt) during 1·25 hours. The crude product, m. p. 140°, was twice recrystallised from alcohol, separating in colourless, microscopic plates, m. p. 140·5—141·5° (Found: C, 55·5; H, 4·2%).

Method of Determination of Freezing Points.—The material was placed in a thick-walled test-tube (8·5 × 1·5 cm.) provided with a standard Anschütz thermometer (graduated in fifths of a degree, but capable of being read accurately with the aid of a telescope to the nearest 0·05°) and a stirrer of stout silver wire. This vessel was surrounded by an air-jacket and the whole could be heated or cooled in a covered bath of sulphuric acid. The substances to be tested were finely powdered and dried for 10—12 hours at temperatures a few degrees below their m. p. About 1·3 g.

usually sufficed to cover the bulb of the thermometer. The temperature of the outer bath was kept at 20° above the m. p. of the material until this was completely fluid and thereafter at 2° below the f. p., which was ascertained in a rough preliminary experiment or by extrapolation. The liquid in the inner tube was slowly stirred until its temperature was 1·5—2° below the true f. p.; crystallisation was then induced by more vigorous stirring or by scratching; the temperature then rose to a maximum and remained at that temperature, the f. p., for 0·5—3 minutes, slow stirring being continued. In the neighbourhood of the eutectic, the degree of supercooling had a considerable effect on the observed f. p. and, on the other hand, as the mixture approached the eutectic it was less difficult to induce crystallisation. In every case several determinations of each f. p. were made and the mean of the most trustworthy values, the extreme variation not exceeding 0·3°, was calculated. It is not good practice to take the highest value and ignore the remainder, since this high value may have been obtained by some deviation from standard procedure.

Mixtures of 4-*Nitro*-2-m-*nitrobenzyloxyanisole and* 5-*Nitro*-2-m-*nitrobenzyloxyanisole.*

% 5-nitro-isomeride.	F. p.	% 5-nitro-isomeride.	F. p.
0·0	165·3°	50·2	137·0°
11·47	160·35	55·0	130·9
20·56	156·0	60·1	128·7
29·77	151·4	65·5	129·1 (?)
34·85	148·45	70·3	127·5
39·59	145·1	80·7	133·5
45·47	140·55	92·0	139·1
50·19	136·7	100·0	142·65
54·44	132·2		
Obtained by adding the 5-nitro-isomeride to the 4-nitro-isomeride.		Obtained by adding the 4-nitro-isomeride to the 5-nitro-isomeride.	

Nitration of 2-m-*Nitrobenzyloxyanisole.*—The ether (2·170 g.) dissolved in pure acetic acid (25 c.c.) was nitrated by the addition of boiled nitric acid (10 c.c.; *d* 1·42) in one portion, the mixture being mechanically stirred and efficiently cooled by water at 14°. Subsequent operations were exactly the same as those described below in the case of the *p*-nitrobenzyloxy-isomeride. The yield was 98·4% of that theoretically possible and in this case the correction applied to the f. p. was + 0·1°. The corrected f. p. of the nitration product (A) was 145·1° and from the graph this is found to correspond to 39·6% of the 5-nitro-isomeride (Lagrange interpolation formula—39·7%). The corrected f. p. of a mixture (B) of 1·2372 g. of (A) and 0·2520 g. of the 4-nitro-isomeride was 149·65°. From the graph this corresponds to 32·7% of the 5-nitro-isomeride (L.I.F.—32·9%) and hence (A) contained 39·4% (39·6%) of the

5-nitro-isomeride. The best value for the % of 5-nitro-2-*m*-nitrobenzyloxyanisole in the nitration product appears to be 39·6. Hence the directive power of the *m*-nitrobenzyloxy-group is 67. This was confirmed by taking 0·9579 g. of (B) and adding 0·2808 g. of the 5-nitro-isomeride, thus bringing the % of the latter to 48·1. From the graph, the f. p. should be 138·4° (Found : 138·2°).

Mixtures of 4-*Nitro*-2-p-*nitrobenzyloxyanisole and* 5-*Nitro*-2-p-*nitrobenzyloxyanisole.*—The compounds were obtained exactly like the isomerides and in excellent yields. They were crystallised thrice from benzene and obtained in pale yellow, flat needles, sparingly soluble in most organic solvents. The 4-nitro-isomeride has m. p. 167—168° (Found : C, 55·5; H, 4·0. $C_{14}H_{12}O_6N_2$ requires C, 55·3; H, 4·0%) and the 5-nitro-isomeride has m. p. 163·5—164·5° (Found : C, 55·3; H, 4·1%).

% 5-nitro-isomeride.	F. p.
0·0	168·3°
6·00	165·6
18·76	159·25
27·86	154·55
40·48	146·9
49·60	139·5

Obtained by adding the 5-nitro-isomeride to the 4-nitro-isomeride.

% 5-nitro-isomeride.	F. p.
49·4	139·3°
55·0	138·4
58·9	140·8
63·2	144·2
71·7	150·05
76·3	152·8
83·8	157·0
89·5	160·0
100·0	165·0

Obtained by adding the 4-nitro-isomeride to the 5-nitro-isomeride.

Nitration of 2-p-*Nitrobenzyloxyanisole.*—The *p*-nitrobenzyl ether of guaiacol was obtained like the *m*-nitrobenzyl ether and crystallised from alcohol in pale yellow, glistening leaflets, m. p. 63·5° (Found : C, 64·9; H, 5·0. $C_{14}H_{13}O_4N$ requires C, 64·8; H, 5·1%). The substance is readily soluble in ether, benzene, chloroform, or acetic acid, sparingly soluble in cold methyl or ethyl alcohol and in hot light petroleum. Lyman and Reid (*J. Amer. Chem. Soc.*, 1920, **42**, 615) quote the m. p. (63·6°) of the substance but give no further details. A solution of the ether (3·4 g.) in acetic acid (30 c.c.) was mechanically stirred, cooled in ice, and boiled nitric acid (3 c.c.; *d* 1·42) mixed with acetic acid (3 c.c.) was gradually introduced. After 2 hours, unchanged substance was recovered, whereas 2-benzyloxyanisole was readily nitrated under similar conditions. Next, the theoretical amount of nitric acid was added to an approximately 10% solution of the ether in acetic acid, and the mixture heated on the steam-bath to 90° without a colour change. One drop of nitric acid was then added and in a minute the liquid suddenly became red and in a short time a considerable amount of a yellow solid crystallised. The addition of a second molecular proportion of nitric acid produced no effect and the temperature was then raised to 100° for 15 minutes, giving a clear solution. Water was added and the product collected, washed, and dried in the air and at 120° for 2 hours (Found : C, 55·2; H, 4·0. Calc. : C, 55·4; H, 4·0%). On analysis (f. p. 145·95°) this material was found to contain 42% of the 5-nitro-isomeride, and this conclusion was confirmed by addition of the 4-nitro-isomeride and the determination of the f. p. of the mixture.

Nitration at 14°. Boiled nitric acid (10 c.c.; *d* 1·42) was added to a stirred solution of the ether (2·422 g.) in acetic acid (30 c.c.) cooled by water at 14°. In about a minute crystallisation occurred without a change in the colour of the liquid, and after 15 minutes water was added and the product collected, washed, and dried at 80—100° for 10 hours. The yield was 99·1% of that theoretically possible. The f. p. of the crude product was 147·0° and in order to apply a correction for traces of impurities the following procedure was adopted. The finely powdered product (1·5 g.) was heated with pure methyl alcohol (10 c.c.) until the latter boiled; the mixture was then cooled, finally in water at 10°. The solid was collected, 10 c.c. of methyl alcohol being employed for washing the flask and an equal volume for washing on the filter. The material dried at 100° for 1 hour lost very little weight and had f. p. 147·2°. A repetition of the process gave a mixture, f. p. 147·0°. Hence the corrected f. p. of the nitration product is 147·4°. From the graph we find that the corresponding % of the 5-nitro-isomeride is 39·8 (L.I.F.—39·8). The corrected f. p. of a mixture of the nitration product (1·1706 g.) and the 4-nitro-isomeride (0·2419 g.) is 152·0° Using the interpolation formula, this corresponds to 32·5% of the 5-nitro-isomeride or 39·2% of the 5-nitro-isomeride in the nitration product. The best value for the composition of the mixture obtained by nitration of 2-*p*-nitrobenzyloxyanisole is 4-nitro-2-*p*-nitrobenzyloxyanisole 60·5% and 5-nitro-2-*p*-nitrobenzyloxyanisole 39·5%, whence the directive power of the *p*-nitrobenzyloxy-group is 67. On this assumption, the f. p. of a mixture of the nitration product (0·3842 g.) and the 5-nitro-isomeride (0·7388 g.) should be 154·5° on a branch of the curve not previously employed (Found : 154·25°). An artificial mixture of the two isomerides containing 39·5% of the 5-nitro-isomeride had f. p. 147·25° [Found : Nitration product, f. p. 147·0°; f. p. (corr.) 147·4°].

2-m-*Methoxybenzyloxyanisole.*—Guaiacol (4·9 g.) and *m*-methoxybenzyl bromide (8 g.) (Lapworth and Shoesmith, J., 1922, **121**, 1392) were added to a solution of sodium ethoxide (from 0·9 g. of sodium) in 95% alcohol (300 c.c.), and the mixture heated in the steam-bath for 10 minutes. The product was isolated by extraction with ether after addition of water, and 4·0 g., b. p. 220°/22 mm., m. p. 28—31°, were obtained. By crystallisation from light petroleum the m. p. was raised to 31·5° (Found : C, 74·0; H, 6·5. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%).

4-*Nitro*-2-m-*methoxybenzyloxyanisole*, crystallising from alcohol in short, pale yellow, glistening needles, m. p. 116—117° (Found : C, 62·2; H, 5·4. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2%), and 5-*nitro*-2-m-*methoxybenzyloxyanisole*, crystallising from alcohol in very pale yellow, slender needles, m. p. 98·5—99·5° (Found : C, 61·8; H, 5·5%), were prepared by methods closely resembling those employed for the nitrobenzyl ethers of 5- and 4-nitroguaiacols. The yields were good.

Mixtures of 4-*Nitro*-2-m-*methoxybenzyloxyanisole and* 5-*Nitro*-2-m-*methoxybenzyloxyanisole.*—The following freezing points were observed, the first number of each pair indicating the percentage of the 5-nitro-isomeride in the mixture : 0·0, 114·85° (1); 11·78, 109·8° (2); 18·57, 106·8° (3); 21·52, 105·3° (4); 31·00, 100·35° (5); 34·20, 98·3° (6); 41·55, 93·1° (7); 50·20, 85·6° (8); 53·91, 82·5° (9); 62·23, 75·2° (10). In applying the Lagrange interpolation formula, the values (1), (2), and (3) were ignored, because in these cases supercooling to the extent of 3° or 4° was necessary. A smooth curve can be drawn through points corresponding to the values (1) to (9) inclusive, and (10) is probably on the other side of the eutectic.

Nitration of 2-m-*Methoxybenzyloxyanisole.*—The nitration was carried out like that of 2-*p*-nitrobenzyloxyanisole, except that the temperature was 0° and the flask was kept over-night in melting ice. The yield from 1·9642 g. of the ether was 2·3020 g. (99·0%) and the pale yellow, dry product had m. p. 78—94° (Found : C, 62·4; H, 5·3; N, 5·3. Calc. : C, 62·3; H, 5·2; N, 4·8%). The f. p. of the nitration product was 87·05°, whilst mixtures of the nitration product (1·6128 g.) with 0·2398 g. and 0·3608 g. of the 4-nitro-isomeride froze at 92·85° and 95·4°, respectively. Careful examination of these figures by graphical and algebraic methods, taking into consideration the fact that the f. p. 92·85° is close to a determined point (7) 93·1°, shows that the best value for the composition of the nitration mixture is 48·0% of 5-nitro-2-*m*-methoxybenzyloxyanisole and 52% of 4-nitro-2-*m*-methoxybenzyloxyanisole. The directive power of the *m*-methoxybenzyloxy-group is accordingly 92.

2-p-*Methoxybenzyloxyanisole.*—A solution of anisyl alcohol (5 c.c.) in benzene (30 c.c.) was saturated with hydrogen chloride. The reaction was very rapid. The solution decanted from the aqueous layer was dried by calcium chloride and, the excess of hydrogen chloride having been removed in a current of dry air, added to a boiling solution of sodium ethoxide (from 1·0 g. of sodium) and guaiacol (6·5 g.) in absolute alcohol (300 c.c.); the mixture was then refluxed for 1·5 hours. The neutral ether, isolated in the usual manner, crystallised from light petroleum in rosettes of white needles, m. p. 94—96° (Found : C, 73·4; H, 6·5. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%). Despite repeated efforts, satisfactory conditions for the nitration of this compound could not be established. It has not, therefore, been possible to make use of the data recorded below.

4-*Nitro*-2-p-*methoxybenzyloxyanisole*.—This substance, prepared like the 5-nitro-isomeride described below, was crystallised from alcohol and then repeatedly from light petroleum, separating in very pale yellow, glistening needles, m. p. 129—130° (Found: N, 4·9. $C_{15}H_{15}O_5N$ requires N, 4·8%).

5-*Nitro*-2-p-*methoxybenzyloxyanisole*.—The *p*-methoxybenzylation of 4-nitroguaiacol was carried out in the usual manner, with *p*-methoxybenzyl bromide, but the yield was poor. After crystallisation from aqueous alcohol the substance melted at 108° with softening at 100°. Better results were obtained by the following method. Anisyl alcohol (4 c.c.) was converted into chloride in benzene solution as described above, and the liquid decanted from the aqueous layer shaken vigorously for one hour with a solution of the potassium salt (10 g.) of 4-nitroguaiacol in dilute aqueous sodium hydroxide (300 c.c.). The neutral product was extracted with ether, isolated, and crystallised from alcohol and then from light petroleum, separating in pale yellowish-brown, short needles, m. p. 109° with slight softening at 100° (Found : C, 62·2; H, 5·4. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2%).

Mixtures of the 4- and 5-nitro-2-*p*-methoxybenzyloxyanisoles had the following f. p., the first number of each pair indicating the percentage of the 4-nitro-isomeride : 0·0, 107·8°; 7·01, 103·7°; 19·14, 96·0°; 21·97, 93·4°; 23·20, 91·05°; 29·32, 85·75°; 38·11, 82·2°; 43·64, 91·05°. In this case, it was necessary to resort to seeding, as otherwise the degree of supercooling required was 3° or more.

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