XXXIII.—*The Relative Directive Powers of Groups of the Forms* RO *and* RR′N *in Aromatic Substitution. Part IX. The Nitration of* p-*Cetyloxyanisole and* p-*Benzyloxyanisole.*

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In continuation of Part III (Robinson and Smith, J., 1926, 392) and Part VIII (Clarke, Robinson, and Smith, J., 1927, 2647), the relative directive powers of the cetyloxy- and benzyloxy-groups in the quinol series have been measured. It was thought that low melting points and slow crystallisation would preclude accurate measurements with alkyloxy-groups containing from 5 to 10 carbon atoms. An attempt to analyse the products of nitration of 4-cetyloxyanisole by hydrolysis with alkali of the group ortho- to the nitro-group (compare the hydrolysis of nitroquinol dimethyl ether; Part III, *loc. cit.*) and isolation of 2-nitro-4-methoxyphenol failed owing to the stability of the nitro-ethers. The methods necessarily employed for the nitration of 4-cetyloxyanisole, and the flatness of the curve used for the thermal analysis of the products, made it difficult to obtain accurate values, but the final result (67·9% ortho to $C_{16}H_{33}\cdot O$) probably contains an error of less than 0·6%. This result agrees with the requirements of the theory developed in Part IV (Allan, Oxford, Robinson, and Smith, J., 1926, 401), the alkyloxy-groups in the quinol ethers becoming *more* powerful with increase in the number of methylene groups.

The values of the relative directive powers obtained to date are :

MeO	100	n-BuO	186
EtO	164	$C_{16}H_{33}\cdot O$	212
Pr^{a}O	180	$CH_2Ph\cdot O$...............	107
		p-$NO_2\cdot C_6H_4\cdot CH_2\cdot O$	38

EXPERIMENTAL.

Melting points, unless otherwise stated, were taken in the way described on p. 254, and are 0·5—1·5° lower than m. p.'s taken in capillary tubes.

4-*Cetyloxyanisole*.—Sodium (0·23 g.; 1 mol.) was dissolved in methyl alcohol (10 c.c.), pure cetyl iodide (m. p. 23·3°) (3·52 g.) and pure quinol monomethyl ether (1·24 g.) were added together with acetone (15 c.c.), and the mixture was boiled for 2 hours. After half the solvent had been distilled off, large colourless plates were deposited on cooling. Washed with a little cold methyl alcohol and dried at 30°, these had f. p. 67·7°, m. p. 67·85° (yield, 2·55 g.; 80%). Recrystallisation from methyl alcohol and removal of solvent in a vacuum at 100° gave material of constant f. p. 67·75°, m. p. 67·85° (capillary tube, 68·5°) (Found: C, 79·2, 79·1; H, 11·8, 11·4. $C_{23}H_{40}O_2$ requires C, 79·3; H, 11·6%). Another specimen, prepared from twice the above quantities in ethyl alcohol–acetone as solvent (90% yield) and recrystallised from methyl alcohol–ligroin, had constant f. p. 67·77° and m. p. 67·90°. 4-*Cetyloxyanisole* is easily soluble in hydrocarbon solvents and less easily in alcohols. In the crude reaction product and in the mother-liquors no trace of quinol dimethyl ether could be found.

2-*Nitro*-4-*cetyloxyanisole*.—A solution of potassium methoxide (from 0·39 g. of potassium) in methyl alcohol (15 c.c.) was mixed with 3-nitro-4-methoxyphenol (Part III, *loc. cit.*) (1·69 g.) in acetone (15 c.c.). After addition of cetyl iodide (3·5 g.; 1 mol.) in acetone (15 c.c.), the dark red mixture was boiled for 11 hours; a test portion (then light red) deposited a yellow solid on cooling. The solvent was distilled off, finally in a vacuum at 100°, and the residue extracted with ether. The extract, after being washed twice with 3% potassium hydroxide solution and with water and dried over anhydrous sodium sulphate, yielded 3·85 g. of a yellow oil which soon solidified. Recrystallisation from methyl alcohol (120 c.c.) gave 3·1 g. (80% yield) of light yellow prisms, m. p. 62·40° (capillary tube, 63°). Satisfactory f. p.'s were not obtained, as the substance began to crystallise in prisms with little evolution of heat, then, while the mass was being stirred, a needle form of crystal appeared and the temperature rose to an indefinite value (62·2—63·2°). These crystal forms had definite m. p.'s 62·4° (prisms) and 63·8° (needles), raised by recrystallisation of the substance from methyl alcohol to the final values 62·5° and 63·9° respectively (Found: C, 70·4; H, 10·0. $C_{23}H_{39}O_4N$ requires C, 70·2; H, 10·0%). In a second preparation from entirely different specimens of initial materials and solvents, the product was recrystallised by dissolving it in a little benzene, adding warm methyl alcohol, and cooling the solution; the m. p.'s were 62·5° and 63·9°, unaltered by recrystallisation.

3-*Nitro*-4-*cetyloxyanisole*.—Solutions of potassium methoxide (1·17 g., 3 mols., of potassium in 70 c.c.) and 2-nitro-4-methoxyphenol (5·07 g., 3 mols., in 50 c.c.) in methyl alcohol were mixed and boiled together with cetyl iodide (3·52 g., 1 mol.) for 25 hours. The solid obtained on cooling was washed with methyl alcohol and with water and dried in the air. It was a greyish-yellow powder, not easily wetted by water, sparingly soluble in hot methyl or ethyl alcohol, and easily soluble in warm benzene. Recrystallisation from methyl alcohol (170 c.c.) gave 2·51 g. of very light yellow crystals, m. p. (capillary) 50·5° (yield, 63%). Evaporation of the mother-liquor to 40 c.c. did not give a second crop. After removal of solvent in a vacuum at 120°, the substance had f. p. 49·1° and m. p. 49·4°. Recrystallisation of 2·50 g. from methyl alcohol (65 c.c.) gave 2·37 g., f. p. 49·28°, m. p. 49·47°. A third recrystallisation (from benzene–methyl alcohol) changed these values only to 49·28° and 49·50° respectively (Found: C, 70·2; H, 9·8. $C_{23}H_{39}O_4N$ requires C, 70·2; H, 10·0%). From the reaction mixture, unchanged 2-nitro-4-methoxyphenol (3·8 g., 2·2 mols.) was recovered. In a second preparation, the same quantities being used, the yield obtained after 48 hours' boiling was 2·90 g. (75%). Repeated crystallisation raised the m. p. and f. p. to the constant values 49·3° and 49·45° respectively, but this specimen continued to have a relatively slow rate of crystallisation.

Action of alkalis. At 230° a mixture of 2- and 3-nitro-4-cetyloxyanisoles was unattacked by 10% aqueous potassium hydroxide after 4 hours. Addition of *n*-propyl alcohol and reheating at 140° for 4 hours caused slow hydrolysis : a trace of 2-nitro-4-methoxyphenol (m. p. 79°) was isolated.

Mixtures of 2- *and* 3-*Nitro*-4-*cetyloxyanisoles*.—As the slope of the f. p. curve was very small near the composition of the nitration product, it was thought advisable to plot the mean of the f. p. and the m. p. The f. p. and the m. p. themselves were each the average of 3—6 determinations. The same thermometer, apparatus, and procedure were used in working with the nitration product as with the synthetic mixtures. For the f. p.'s the temperature of the bath (apparatus of the Beckmann type) was 0·5° below that of the freezing liquid; for the m. p.'s, 2·0° above that of the melting solid. The curve was drawn from the following values.

3-Nitro-cmpd., %.	Mean f. p. (*a*).	Mean m. p. (*b*).	Mean of *a* and *b*.	3-Nitro-cmpd., %.	Mean f. p. (*a*).	Mean m. p. (*b*).	Mean of *a* and *b*.
69·85	41·7°*	42·15°	41·92°	59·3	43·05°	43·3°	43·17°
67·95	42·15	42·50	42·32	54·65	43·20	43·37	43·28
67·7	42·15	42·55	42·35	51·9	43·35	43·6	43·47
65·4	42·35	42·7	42·52	46·7	43·25	43·45	43·35
63·0	42·65	43·0	42·82				

* For thermometer corrections, see the footnote on p. 257.

The binary system is a complex one and is being further investigated.

Nitration of 4-*Cetyloxyanisole*.—The results are summarised in the following table :

Nitration.	Temp.	Yield, %.	F. p., mean.	M. p., mean.	Mean.	% 3-Nitro-isomeride indicated.	Corrected %.
1	25°	97	42·25°	42·55°	42·40°	67·1	67·6
2	25	98	—	42·44	—	67·8	68·0
							67·8 (mean)
3	0	—	42·18	42·50	42·34	67·5	67·5
4	0	98·5	42·05	42·36	42·20	68·6	68·0
5	0	98	42·18	42·45	42·32	67·7	68·15
							67·9 (mean)

(1) A solution and suspension of 4-cetyloxyanisole (0·87 g.) in acetic acid (f. p. 16·4°; 25 c.c.) at 25° was shaken in a thermostat, and a mixture of nitric acid (colourless 70%, 0·45 c.c., 3 mols.) and acetic acid (5 c.c.) at 25° was added in one lot. Gradually the colour became light yellow and after 5 minutes the plates of the ether were replaced by needles of the nitro-compounds. The reaction mixture was kept at 25° for 10 minutes longer, and then warmed

to 30° to obtain a clear solution. After 2 minutes the solution was cooled (crystals separated), and ice-water (100 c.c.) added. The solid, collected after some minutes, was washed with water, sodium carbonate solution, and again with water. After being dried over solid potassium hydroxide for 36 hours in a vacuum (finally at 120°), it weighed 0·952 g. (yield, 97%), although a trace was lost in transference. As the sodium carbonate wash-liquor showed no sign of red colour, and the acetic–nitric acid filtrate remained yellow on basification, the nitration had not been accompanied by hydrolysis. The product was clear yellow, its rate of crystallisation high, and the difference between f. p. and m. p. slightly less than normal. It was apparently a binary mixture, but in the absence of evidence from the eutectic temperature the purity was tested by adding to the mixture (0·9519 g.) pure 2-nitro-4-cetyloxyanisole (0·1033 g.). The new mixture had f. p. 42·92° and m. p. 43·05°; mean 42·98°, corresponding to 61·0% of the 3-nitro-isomeride. The nitration product therefore contained 67·6% of this isomeride. The difference (0·5%) between this and the original value (67·1%) is smaller than the error due to the flatness of the curve.

(2) The second nitration was carried out at 25° as in (1), except that a mixture of nitric acid (4 c.c., 21 mols.) and acetic acid (12 c.c.) at 25° was added in one lot, and the flask shaken for 30 minutes at 25°. Before the product was dissolved by warming, powdered anhydrous sodium acetate (6 g.) was added cautiously. Although the m. p. of the product was sharp, the crystallisation was sluggish and the f. p. indefinite (41·6—42·1°). The product, added to a synthetical mixture of identical m. p., caused no change in the melting point. The figures given in the table (columns 7 and 8) are the compositions indicated (*a*) by the m. p., (*b*) from the usual mean f. p.–m. p. corresponding to the observed m. p.

(3) For comparison with previous work on the quinol ethers it was desirable to nitrate 4-cetyloxyanisole at 0°. (The effect of temperature seems to be much greater than that of concentration of nitric acid, as is indicated by the results of the nitration of 4-benzyloxyanisole; p. 257.)

A mixture of nitric acid (*d* 1·42) (1 c.c.) and acetic acid (f. p. 16°) (7 c.c.) freezes at about 2°. The following procedure was therefore adopted. 4-Cetyloxyanisole (0·87 g.) was dissolved in acetic acid (6 c.c.) in a stoppered flask and cooled for ½ hour in ice-water. A mixture of acetic acid (6 c.c.) and nitric acid (2 c.c.) was cooled to 1° and added to the soft solid in the flask (0—1°). After vigorous shaking in the ice-bath, the acetic acid melted and nitration began (finished in about 20 minutes). The mixture was kept for 2 hours at 0°, acetic acid (13 c.c.) and then anhydrous sodium acetate were added, the temperature was raised to 30°, and the product isolated in the usual way. It had a light green colour, but crystallised rapidly.

(4) The nitration was done as in (3). The purity of the product was tested by addition of a synthetic mixture (0·4 g., mean f. p.–m. p. 42·18°; 68·6% of 3-nitro-isomeride) to 0·5 g.: a rise of 0·04° in m. p. (to 42·23°) indicated a depression (0·07°) of the original m. p. by impurities.

(5) Experiment (3) was repeated, but sodium acetate was not added and the reaction mixture was kept for 20 minutes at 27°. As the colour of the mixture was light brown owing to suspended matter, the solid was dissolved in pure ether, the solution filtered, and the solvent removed: the m. p. was unchanged. 2-Nitro-4-cetyloxyanisole (0·0584 g.) was added to the nitration product (0·6451 g.): the mean f. p.–m. p. was then 42·84°, corresponding to 62·5% of the 3-nitro-isomeride and indicating the presence of 68·2% of this isomeride in the nitration product.

In the quinol series, therefore, the directive power of cetoxyl relative to methoxyl (100) is 212 at 0°.

Benzyl Chloride.—A " Kahlbaum " specimen, after being washed with water, dried over anhydrous sodium sulphate, and distilled three times (b. p. 63°/11 mm.), only the middle fractions being retained, had $d_{18^\circ}^{18^\circ}$ 1·1027 (Landolt–Börnstein, " Tabellen," 5th edn., $d_{18^\circ}^{18^\circ}$ 1·10271). Found: Cl, by Stepanov's method, 28·0, 28·0 (calc., 28·0%), showing the absence of nuclear chlorine.

4-*Benzyloxyanisole.*—Quinol monomethyl ether (6·2 g.) in acetone (25 c.c.) was added to sodium methoxide solution (1·15 g. of sodium in 25 c.c. of methyl alcohol). After addition of benzyl chloride (6 c.c.; 1·03 mols.) the mixture was heated at 90° (pressure bottle) for 1 hour. The product (9·4 g.; 95% yield) crystallised from alcohol in plates, m. p. 71° (capillary tube) (Found: C, 78·5; H, 6·9. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%). The plates, f. p. 69·65°, m. p. 69·70°, were unstable, changing to needles, f. p. 71·3°, m. p. 71·5° (capillary tube, 73°).

2-*Nitro*-4-*benzyloxyanisole.*—3-Nitro-4-methoxyphenol (4·25 g.; 1 mol.) in acetone (30 c.c.) was added to a solution of potassium (0·95 g.; 0·97 mol.) in methyl alcohol (20 c.c.). After addition of benzyl chloride (5 c.c.; 1·7 mols.) the mixture was heated at 90° (pressure bottle) for 1 hour, and yielded 5·3 g. (80%) of light yellow solid. Recrystallised from methyl alcohol (50 c.c.) and heated in a vacuum to 125°, this had f. p. 59·55° and m. p. 59·75°. Again recrystallised, it had f. p. 59·65° and m. p. 59·80°, unchanged by further crystallisation. It was very soluble in benzene, ethyl acetate and acetic acid, and moderately easily soluble in ligroin. A second preparation, from sodium methoxide and a different specimen of 3-nitro-4-methoxyphenol and recrystallised from ethyl alcohol until the values were constant, had f. p. 59·67° and m. p. 59·8° (capillary tube, 60—61°) (Found : C, 64·7; H, 5·0. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0%).

3-*Nitro*-4-*benzyloxyanisole.*—A solution of 2-nitro-4-methoxyphenol (6·33 g.; 1 mol.) in methyl alcohol (25 c.c.) was added to potassium methoxide solution (from 1·47 g. of potassium, 1 mol., in 30 c.c. of methyl alcohol). Benzyl chloride (10 c.c.; 2·3 mols.) was added, and the mixture heated at 90° for 8 hours, a further 5 c.c. of benzyl chloride being added meanwhile. The brownish-red reaction mixture yielded 5·6 g. of a brown solid, which, crystallised from methyl alcohol, gave 5·1 g. (50%) of yellow crystals, f. p. 61·0°, m. p. 61·2° and finally 61·2° and 61·3° respectively (capillary tube, 63°) (Found: C, 65·0; H, 5·0. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·0%). A second preparation (heating for 10 hours; 50% yield) was recrystallised from methyl alcohol until the f. p. and m. p. were constant at 61·15° and 61·3° respectively.

Mixtures of 2-*Nitro*-4-*benzyloxyanisole and* 3-*Nitro*-4-*benzyloxyanisole.*—The mixtures were viscous and reproducible f. p.'s were not obtainable; the m. p.'s were normal. From the following values smooth curves were drawn (the first number of each pair gives the % of 3-nitro-isomeride): 100%, 61·0° [*]; 81·2%, 53·65°; 69·0%, 48·35°; 59·2%, 42·95°; 54·8%, 40·25°; 50·0%, 37·25°; 2nd. series, 51·7%, 38·4°; 47·9%, 36·0°; 41·15%, 39·9°; 34·45%, 43·8°; 3rd. series, 0%, 59·5°; 11·1%, 54·8°; 25·2%, 48·45°; 37·6%, 41·7°. Lower m. p.'s (eutectics, taken as temp. of viscous mass melting): 59·2%, 35·6°; 50·0%, 35·5°; 37·6%, 35·5°; 45·1%, 35·55°. The curves intersect at 47·5%, 35·55°. Near the composition of the nitration product, ΔT 0·2° corresponds to Δ% 0·3.

Nitration of 4-*Benzyloxyanisole.*—The results are summarised in the following table :

Nitration.	Temp.	Yield.	Eutectic.	M. p.	% 3-Nitro-isomeride.	Average.	(MeO = 100) CH$_2$Ph·O.
a	28°	97%	35·4°	37·85°	50·9 51·1	51·0	104
b	28	98	35·5	37·92	50·9 51·0		
c	14	97	35·5	38·2	51·4	51·4	105·5
d	14	—	35·4	38·2	51·4 51·3		

(*a*) A solution of 4-benzyloxyanisole (2·0 g.) in acetic acid (f. p. 16·0°) (20 c.c.) was stirred at 28° and a mixture of nitric acid (colourless, 69%) (1 c.c.; 1·66 mols.) and acetic acid (4 c.c.) at 28° was added in one portion. After 3 minutes, the yellow solution was

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[*] Uncorrected. The corrections are : at 35°, + 0·05°; 40°, + 0·08°; 46°, + 0·11°; 50°, + 0·15°; 55°, + 0·23°; 60°, + 0·27°; 63°, + 0·31°.

cooled. The oil precipitated on addition of ice-water soon solidified. The solid was collected after 4 hours and dissolved in pure ether, the solution washed twice with sodium bicarbonate solution (the first extract was orange), and with water, and dried, and the solvent removed in a tared f. p.-tube, finally at 120° in a vacuum (yield, 2·34 g. of light yellow material). Purity test: the nitration product (0·8 g., m. p. 37·85°) was mixed with a synthetic mixture (0·6 g., m. p. 37·88°); the new mixture melted at 37·90°, a rise of 0·04°. This corresponds to a depression of 0·09° in the m. p. of the nitration product, and a corrected composition of 51·1%.

(*b*) The nitration was done at 28° with the quantities given in (*a*), but the nitrating mixture (1·1 mols. of HNO_3) was added gradually with efficient stirring. When 0·2140 g. of the 3-nitro-isomeride was added to 1·6315 g. of the nitration product the m. p. became 41·40° (56·7%), indicating the presence of 51·0% of the 3-nitro-isomeride in the nitration product.

(*c*) The ether (1·5 g.), suspended in acetic acid (10 c.c.), was nitrated at 14° gradually with 1 c.c. of a mixture of equal volumes of nitric and acetic acids (1·1 mols. HNO_3), the crystals dissolving on shaking (3 minutes) to a clear yellow solution. A further 0·6 c.c. of nitration mixture was added, the solution cooled, and the product isolated.

(*d*) At 14°, exactly as (*c*). 1·3237 G. of the product, mixed with 0·2044 g. of the 3-nitro-isomeride, melted at 42·07° (57·8%), indicating in (*d*) 51·3% of 3-nitro-4-benzyloxyanisole.

From the values at 28° and 14° the directive power at 0° of the benzyloxy-group (methoxyl = 100) is estimated to be 107·5.

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