Orientation in the Nitration of Trisubstituted Benzenes.

TRISUBSTITUTED benzenes with a *meta*-directing substituent at position 1 and *ortho,para*-directing substituents at positions 2 and 5 undergo nitration extensively (in most cases predominantly) in the 6 position.[1] It has been suggested that such substitution, which is not predicted by the classical rules, results from stabilization of the intermediate cation (and the transition state involved in its formation) either by conjugation between the ring substituents[2] at positions 1 and 2, or by dipole–dipole interaction[3] between the entering electrophilic reagent and the substituent at position 1. The results of the present study are consistent with the first of these hypotheses but not with the second.

We have determined the isomer distributions resulting from the mononitration of a series of trisubstituted benzenes of general formula (I). Isomer distributions have been established for the nitration of 1,4-dimethoxy-2-nitrobenzene, α-chloro-2,5-dimethoxyaceto-phenone, α-bromo-2,5-dimethoxyacetophenone, 2,5-dimethoxybenzaldehyde, and 2,5-di-methoxyphenylacetic acid; those for 2,5-dimethoxyacetophenone and 2,5-dimethoxy-ethylbenzene have been reported previously.[4] While nitration of 2,5-dimethoxyphenyl-acetic acid and 1-ethyl-2,5-dimethoxybenzene occurs exclusively at ring position 4, nitration of the other compounds, in which G in each case represents an unsaturated, *meta*-directing group, occurs predominantly at ring position 6 (formula I). The results are summarized in the Table.

Isomer distributions for nitrations of (I).

G	NO$_2$	CO·CH$_2$Cl	CO·CH$_2$Br	COMe	CHO	CH$_2$·CO$_2$H	Et
6-Nitration (%) ...	93	92	89	78	76	—	—
4-Nitration (%) ...	7	*	11	22	24	100	100

* Not established.

Structure (II) illustrates the suggested stabilization of the intermediate cation involved in 6-nitration by conjugation between the ring substituents at positions 1 and 2; structure (III) illustrates the suggested stabilization by dipole–dipole interaction between the entering nitro-group and the substituent at position 1.
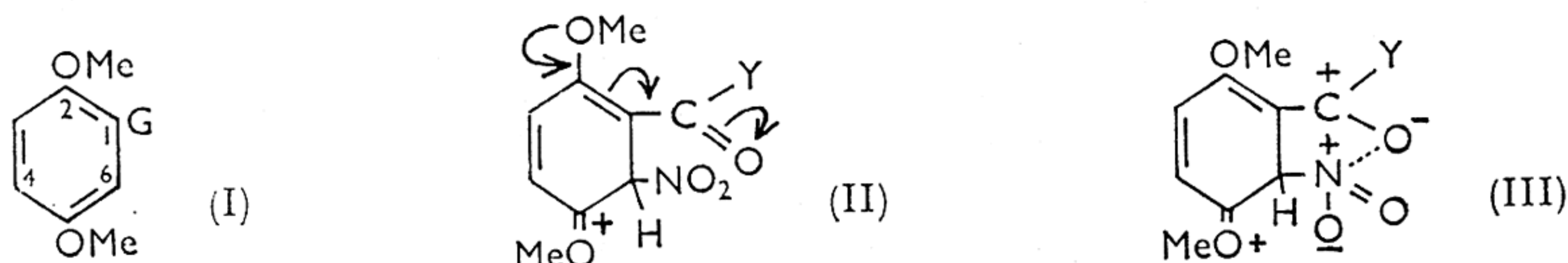
Our results are consistent with only the first of these modes of stabilization. The probable order of electron-attracting power for the G groups, based on the dipole moments of monosubstituted benzenes[5] and on σ values,[6] is NO$_2$ > CO·CH$_2$Cl > CO·CH$_2$Br > CHO ~ COMe > CH$_2$·CO$_2$H > Et. This order parallels that of the percentages of 6-nitration and is consistent with an increase in stabilization by conjugation with an increase in the electron-attracting power of G. No such stabilization is possible, of course, when G is CH$_2$·CO$_2$H or Et. On the other hand, the fact that nitration of the α-halogeno-2,5-dimethoxyacetophenones leads to a higher percentage of 6-substitution than does that of 2,5-dimethoxyacetophenone appears inconsistent with the second hypothesis. The

[1] Howe and Howe, *J.*, 1963, 6064.
[2] Dewar, *J.*, 1949, 463.
[3] Hammond, Modic, and Hedges, *J. Amer. Chem. Soc.*, 1953, **75**, 1388.
[4] Howe, Hamel, Stedman, and Hyman, *J. Org. Chem.*, 1960, **25**, 1245.
[5] McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Company, San Francisco, 1963.
[6] Jaffe, *Chem. Rev.*, 1953, **53**, 191.

negative charge on the carbonyl oxygen should be reduced by an α-halogen atom, thus decreasing the dipole–dipole interaction between the carbonyl oxygen and the entering nitro-group. Moreover, 2,5-dimethoxyphenylacetic acid, which might be expected to undergo 6-nitration through stabilization of the intermediate cation by dipole–dipole interaction (resulting in a six-membered cyclic structure), reacts exclusively at the 4-position.

Nitrations were carried out in concentrated nitric acid at low temperature in order to prevent side-reactions, minimize steric effects, and ensure high selectivity. The nitration products were analysed quantitatively either by gas chromatography or by infrared spectrophotometry.

Experimental.—*Nitration of* 1,4-*dimethoxy-2-nitrobenzene.* 1,4-Dimethoxy-2-nitrobenzene (3·0 g.), m. p. 72—74°, was added slowly with stirring to concentrated nitric acid (*d* 1·42; 20 ml.) at −10°. The mixture was stirred for 2 hr. at −10°, then poured into ice–water. The crude product was isolated by filtration, washed, and dried. The yellow powder (3·3 g.), m. p. 160—175°, thus obtained was analysed by gas chromatography in a 2-ft. column (internal diam. 4 mm.) packed with 15% QF-1-0065 fluorosilicone on Chromosorb P, at 210°; 7-methoxy-6-nitrohomochroman-5-one [7] was used as the internal standard; response factors were determined with artificial mixtures of the internal standard, starting material, and authentic samples of 1,4-dimethoxy-2,3-dinitrobenzene, m. p. 186—187°,[8] and 1,4-dimethoxy-2,5-dinitrobenzene, m. p. 203—204°.[9] The mixture was shown to consist of 1,4-dimethoxy-2,3-dinitrobenzene (93%) and 1,4-dimethoxy-2,5-dinitrobenzene (7%), exclusive of a small amount of starting material. No evidence for the presence of 1,4-dimethoxy-2,6-dinitrobenzene was obtained. A second nitration, carried out in identical conditions, gave the same results.

Nitration of α-*Chloro-2,5-dimethoxyacetophenone.* α-Chloro-2,5-dimethoxyacetophenone (8·0 g.), m. p. 86—87°,[10] was nitrated at −15° by the procedure described above. The crude product was obtained as a yellow powder (9·2 g.), m. p. 94—106°. Crystallization from methanol yielded α-*chloro-3,6-dimethoxy-2-nitroacetophenone,* yellow needles, m. p. 109—110° (Found: C, 45·8; H, 3·9; N, 5·5. $C_{10}H_{10}ClNO_5$ requires C, 46·2; H, 3·8; N, 5·4%), which gave an indigotin on treatment with yellow ammonium sulphide solution.[11] No other component was isolated from the nitration mixture in a pure condition. The mixture was analysed by gas chromatography as above at a temperature of 175—275°, programmed for a temperature rise of 4° per min.; *p*-nitroacetophenone was used as the internal standard; response factors were determined with artificial mixtures. α-Chloro-3,6-dimethoxy-2-nitroacetophenone was shown to represent approximately. 92% of the nitration mixture, exclusive of a small amount of starting material. A second nitration, carried out in identical conditions, gave the same results.

Nitration of α-*bromo-2,5-dimethoxyacetophenone.* α-Bromo-2,5-dimethoxyacetophenone (8·0 g.), m. p. 86°,[11] was nitrated at −20° by the procedure described above. The crude product was obtained as a yellow powder (9·4 g.) which was shown to consist of α-bromo-3,6-dimethoxy-2-nitroacetophenone (90%) and α-bromo-2,5-dimethoxy-4-nitroacetophenone (10%) by infrared spectral analysis [8] (solvent: carbon disulphide; analytical bands: 7·90 and 8·17 μ, respectively). Reference samples of the two nitro-compounds, m. p.s 102—103° and 117—118°, respectively,[11] were obtained by fractional crystallization of the crude nitration product. No evidence for the presence of α-bromo-2,5-dimethoxy-3-nitroacetophenone was obtained. Comparison of the infrared spectrum of the mixture with those of the reference samples showed no extraneous absorption bands. A second nitration, carried out at 0°, yielded 88% and 12% of the two isomers.

Nitration of 2,5-dimethoxybenzaldehyde. 2,5-Dimethoxybenzaldehyde (3·0 g.), m. p. 49—50°, was nitrated at −20° by the procedure described above. The crude product was obtained as a yellow powder (3·6 g.). Fractional crystallization from ethanol yielded 3,6-dimethoxy-2-nitrobenzaldehyde as pale yellow needles, m. p. 164—165° [12] (Found: C, 51·0; H, 4·6; N, 6·6.

[7] Musselman, Thesis, Clarkson College of Technology, New York, U.S.A., 1963.
[8] Howe, Pecore, and Clinton, *J. Org. Chem.*, 1962, **27**, 1923.
[9] Nietzki and Rechberg, *Ber.*, 1890, **23**, 1211.
[10] Auwers and Pohl, *Ann.*, 1914, **405**, 281.
[11] Bost and Howe, *J. Amer. Chem. Soc.*, 1951, **73**, 5864.
[12] Rubenstein, *J.*, 1925, **127**, 1998.

Calc. for $C_9H_9NO_5$: C, 51·2; H, 4·3; N, 6·6%), and 2,5-*dimethoxy-4-nitrobenzaldehyde* as orange-yellow needles, m. p. 163—165° (Found: C, 51·2; H, 4·3; N, 6·4%); mixed m. p. 135—147°. Oxidation of these compounds with alkaline permanganate yielded 3,6-dimethoxy-2-nitrobenzoic acid, m. p. 193—194°, and 2,5-dimethoxy-4-nitrobenzoic acid, m. p. 192—194°, respectively, identical (mixed m. p.s and spectra) with authentic samples.[4] The crude nitration product was analysed by gas chromatography in a 10-ft. column (internal diam. 4 mm.) packed with 20% silicone gum rubber on Chromosorb P, at 235°; *p*-nitroacetophenone was used as the internal standard; response factors were determined with artificial mixtures. The nitration product was shown to consist of 3,6-dimethoxy-2-nitrobenzaldehyde (76%) and 2,5-dimethoxy-4-nitrobenzaldehyde (24%), exclusive of a small amount of starting material. A second nitration, carried out in identical conditions, gave the same results. Nitrations carried out at higher temperatures as reported by Rubenstein [12] resulted in low yields of a crude product of high nitrogen content.

Nitration of 2,5-dimethoxyphenylacetic acid. 2,5-Dimethoxyphenylacetic acid (3·0 g.), m. p. 120—122°, was nitrated at −10° by the procedure described above except that the ageing period was shortened to 30 min. The crude product was obtained as a yellow powder (3·2 g.), m. p. 199—202°, which gave one discrete band on gas chromatography on a silicone gum rubber column and which had an infrared spectrum identical with that of 2,5-*dimethoxy-4-nitrophenyl-acetic acid*, yellow needles, m. p. 203—204° (Found: C, 50·1; H, 4·7; N, 5·6. $C_{10}H_{11}NO_6$ requires C, 49·8; H, 4·6; N, 5·8%). This compound, obtained by crystallization of the crude product from ethanol, on treatment with alkaline permanganate yielded 2,5-dimethoxy-4-nitrobenzoic acid, m. p. 193—194°, identical (mixed m. p. and infrared spectra) with an authentic sample.[4]