LXXXIX.—*Substitution in Vicinal Trisubstituted Benzene Derivatives. Part IV.*

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THE investigation of substitution in dialkyloxybenzene derivatives of type (I) in which the group X is meta-directing has been conducted on a large number of compounds and discussed at length (Davies and Rubenstein, J., 1923, **123**, 2839; Rubenstein, J., 1925, **127**, 2268).* The continuation of that work is now described.

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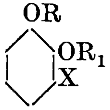
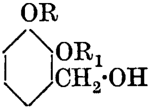
* The bromination of these dialkyloxyaldehydes has been stated (*loc. cit.*) to give only the 5-bromo-derivative, the argument being based upon (i) the position of substitution of the salicylaldehyde derivatives and (ii) the capacity of the brominated product to give a 6-nitro-compound. The position of the bromine atom in these compounds has now been proved by the direct preparation of 5-bromo-*o*-veratric acid from 5-nitro-*o*-veratric acid (see p. 652).

(I.)





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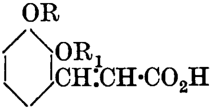

(III.)

Substitution processes have been investigated on vicinal substances of type (I) in which X is a weakly ortho-para-orienting group. The first series of compounds examined as fulfilling these requirements were the dialkyloxybenzyl alcohols, and the nitration and bromination of these substances were carried out. In the nitration of *o*-veratryl alcohol, 2 : 3-diethoxybenzyl alcohol, and 3-methoxy-2-ethoxybenzyl alcohol good yields of the 5-nitro-benzyl alcohol were obtained in each case, the position of the nitro-group being shown by oxidation of the benzyl alcohol derivative to the corresponding benzoic acid. Bromination did not proceed so smoothly, but moderate yields of the 5-bromo-benzyl alcohols were obtained, the place of substitution again being shown by oxidation. The second series of compounds examined were the dialkyloxycinnamic acids (III) in which the group X (I) is ortho-para-orienting and unsaturated. In this case again, 5-nitro-derivatives were produced exclusively in the case of 2 : 3-diethoxycinnamic and 3-methoxy-2-ethoxycinnamic acids. From these substances, the respective benzoic acids were reformed on oxidation. From 2 : 3-dimethoxycinnamic acid a mixture of isomerides was formed on nitration, and by fractionally separating first the acids and then the esters left in the residual mixture on esterification it was shown that 85% of the nitration mixture consisted of 5-nitro-2 : 3-dimethoxycinnamic acid, the rest being the 6-nitro-acid.

EXPERIMENTAL.

5-Nitro-2 : 3-dimethoxybenzyl Alcohol.—2 : 3-Dimethoxybenzyl alcohol (5·5 g.; prepared from *o*-veratraldehyde by means of the Cannizzaro reaction) dissolved in glacial acetic acid (20 c.c.) is treated gradually with a solution of nitric acid (5·5 c.c., *d* 1·42) in glacial acetic acid (5·5 c.c.); the temperature rises to 40—50°. After being maintained at 50° for 2 hours and at room temperature over-night, the brown solution is poured into water. The product, an oil which slowly solidifies, crystallises from methyl alcohol in colourless needles, m. p. 67° (yield 90%) (Found : N, 6·6. $C_9H_{11}O_5N$ requires N, 6·6%). On oxidation with alkaline permanganate solution and subsequent acidification with dilute hydrochloric acid 5-nitro-*o*-veratric acid is obtained, m. p. 176°, identical with the acid obtained by the nitration of *o*-veratric acid.

3-Methoxy-2-ethoxybenzyl Alcohol.—3-Methoxy-2-ethoxybenzaldehyde (12 g.) dissolved in methyl alcohol (16 c.c.) is treated with a solution of potassium hydroxide (17·6 g.) in methyl alcohol (45 c.c.). After 24 hours, the greater portion of the methyl alcohol is distilled off, the residue shaken with benzene, the extract washed a few times with concentrated sodium bisulphite solution and dried over potassium carbonate, and the benzene evaporated. The residual oil almost wholly distills at reduced pressure as a colourless liquid, b. p. 148°/13 mm. (yield, almost theoretical).

5-*Nitro*-3-*methoxy*-2-*ethoxybenzyl Alcohol*.—3-Methoxy-2-ethoxybenzyl alcohol (2 g.) dissolved in glacial acetic acid (2 c.c.) is treated with a solution of nitric acid (2 c.c.) in glacial acetic acid (2 c.c.), and the reddish-brown solution kept over-night. The 5-nitro-3-methoxy-2-ethoxybenzyl alcohol which separates in pale yellow, prismatic crystals is filtered off; more is obtained on pouring the filtrate into water and crystallising the oily product, which hardens, from alcohol; m. p. 132° (yield 65%) (Found : N, 6·4. $C_{10}H_{13}O_5N$ requires N, 6·2%). On oxidation with an alkaline solution of potassium permanganate 5-nitro-3-methoxy-2-ethoxybenzoic acid, m. p. 169°, is obtained.

2 : 3-*Diethoxybenzyl Alcohol*.—This is obtained from 2 : 3-diethoxybenzaldehyde and purified substantially by the process described under 3-methoxy-2-ethoxybenzyl alcohol. It is a colourless oil, b. p. 163°/11 mm., 167°/19 mm., which solidifies on cooling and can be crystallised from light petroleum (b. p. 60—80°), separating in colourless needles, m. p. 35° (Found : C, 67·6; H, 8·0. $C_{11}H_{16}O_3$ requires C, 67·4; H, 8·2%).

5-*Nitro*-2 : 3-*diethoxybenzyl Alcohol*.—This is obtained from 2 : 3-diethoxybenzyl alcohol (1·5 g. in glacial acetic acid, 2 c.c.) and nitric acid (1·5 c.c. in glacial acetic acid, 1·5 c.c.) by the method described under 5-nitro-2 : 3-dimethoxybenzyl alcohol. It crystallises from alcohol in colourless needles, m. p. 75° (yield 1·7 g. or 90%) (Found : N, 7·2. $C_{11}H_{15}O_5N$ requires N, 7·1%), and on oxidation with 1% alkaline permanganate yields 5-nitro-2 : 3-diethoxybenzoic acid, m. p. 118°, identical with the nitration product of 2 : 3-diethoxybenzoic acid.

5-*Bromo*-2 : 3-*dimethoxybenzyl Alcohol*.—*o*-Veratryl alcohol (5 g.), dissolved in glacial acetic acid (25 c.c.) containing sodium acetate (7·5 g.), is treated with bromine (5 g.) in glacial acetic acid (20 c.c.). After 2 days, the mixture is poured into water. The oil that separates, and hardens slowly, is removed (3·5 g.), and the filtrate treated with solid sodium bicarbonate; a further 3·7 g. of solid are then obtained. The combined products, crystallised from light petroleum a few times, yield 5-*bromo*-2 : 3-*dimethoxybenzyl alcohol* in colourless needles, m. p. 82° (Found : Br, 31·8. $C_9H_{11}O_3Br$ requires Br, 32·1%). The acid produced by its oxidation with

1% alkaline potassium permanganate at 60—70°, after crystallisation from light petroleum, melts at 120° and does not depress the m. p. of 5-bromo-*o*-veratric acid obtained by oxidation of 5-bromo-*o*-veratraldehyde.

5-*Bromo*-3-*methoxy*-2-*ethoxybenzyl Alcohol*.—3-Methoxy-2-ethoxybenzyl alcohol (2 g.) is brominated by the foregoing method. The oil produced on dilution, after hardening, is isolated by means of benzene and crystallised twice from light petroleum (b. p. 60—80°); 5-*bromo*-3-*methoxy*-2-*ethoxybenzyl alcohol* is thus obtained in white prisms, m. p. 55—56° (Found: Br, 30·3. $C_{10}H_{13}O_3Br$ requires Br, 30·6%).

5-*Bromo*-2 : 3-*diethoxybenzyl Alcohol*.—2 : 3-Diethoxybenzyl alcohol (2·5 g.) dissolved in glacial acetic acid (13 c.c.) containing sodium acetate (4 g.) is treated at 20—25° with bromine (2 g.) in glacial acetic acid (7 c.c.). After remaining in sunlight for a few days, the mixture is poured into water; the oil obtained partly solidifies after several days. The oily portion is removed as completely as possible, and the residue crystallised three times from light petroleum; 5-*bromo*-2 : 3-*diethoxybenzyl alcohol* is thus obtained in colourless, prismatic crystals, m. p. 60° (Found: Br, 28·6. $C_{11}H_{15}O_3Br$ requires Br, 29·1%).

Nitration of 2 : 3-*Dimethoxycinnamic Acid*.—The finely powdered acid (5 g.) is added in small portions and with stirring to nitric acid (25 c.c.; *d* 1·42). After 3 hours, the mixture is poured over ice. The cream-coloured precipitate (6 g.) is dried and dissolved in boiling alcohol. By careful fractional separation 3·3 g. of a substance, m. p. 205—227°, are obtained. The alcoholic filtrate is evaporated to small bulk, saturated with hydrogen chloride, and heated on a water-bath for 1 hour. Fractional separation of the mixture of esters thus produced yields first *ethyl* 5-*nitro*-2 : 3-*dimethoxycinnamate*, which crystallises from alcohol in cream, prismatic needles, m. p. 111° (Found: N, 5·2. $C_{13}H_{15}O_6N$ requires N, 5·0%). [5-*Nitro*-2 : 3-*dimethoxycinnamic acid* is obtained, by twice crystallising the product, m. p. 205—227°, in pale yellow prisms, m. p. 229° (Found: equiv., 256. $C_{11}H_{11}O_6N$ requires equiv., 253). Oxidation with potassium permanganate gives 5-nitro-*o*-veratric acid.] *Ethyl* 6-*nitro*-2 : 3-*dimethoxycinnamate* is obtained from later fractions and crystallises from aqueous alcohol in long, white needles, m. p. 86°. It is hydrolysed by boiling for a few minutes with equal volumes of water, glacial acetic acid, and sulphuric acid, giving 6-*nitro*-2 : 3-*dimethoxycinnamic acid*, which crystallises from aqueous alcohol in brown needles, m. p. 210—215° (decomp.). On oxidation with alkaline potassium permanganate solution at 90° and acidification, it gives a substance of high m. p.

(above 280°) which appears to be identical with the *6-nitro-3-hydroxy-2-methoxybenzoic acid* obtained by boiling 6-nitro-2 : 3-dimethoxybenzoic acid for 15 hours with 2·5 *N*-sodium hydroxide.

3-Methoxy-2-ethoxycinnamic Acid.—3-Methoxy-2-ethoxybenzaldehyde (6 g.) is added to pyridine (20 c.c.) containing malonic acid (7·2 g.), 6 drops of piperidine are added, and the solution is heated under reflux on a steam-bath for 1 hour; the evolution of carbon dioxide is then completed by boiling the solution for 5 minutes. The cooled solution is poured into water acidified with concentrated hydrochloric acid, and the precipitate of 3-methoxy-2-ethoxycinnamic acid (yield almost quantitative) collected. It crystallises from alcohol in colourless needles, m. p. 151° (Found : equiv., 220. $C_{12}H_{14}O_4$ requires equiv., 222).

5-Nitro-3-methoxy-2-ethoxycinnamic Acid.—Finely divided 3-methoxy-2-ethoxycinnamic acid (1 g.) is added gradually to nitric acid (10 c.c.; *d* 1·42), and the mixture kept over-night. On dilution with water *5-nitro-3-methoxy-2-ethoxycinnamic acid* is obtained in quantitative yield. Crystallised from alcohol, it gives cream needles, m. p. 200—201° (Found : equiv., 269. $C_{12}H_{13}O_6N$ requires equiv., 267).

2 : 3-Diethoxycinnamic Acid.—This acid, prepared from 2 : 3-diethoxybenzaldehyde (5 g.) by the pyridine method described above (yield 5·3 g. or 90%), crystallises from alcohol in long, slender, colourless needles, m. p. 161° (Found : equiv., 235. $C_{13}H_{16}O_4$ requires equiv., 236).

5-Nitro-2 : 3-diethoxycinnamic Acid.—Prepared (at 20—25°) from 2 : 3-diethoxycinnamic acid (1 g.) and isolated by the method described under 5-nitro-3-methoxy-2-ethoxycinnamic acid, this acid is obtained in quantitative yield. It crystallises in long, cream prisms, m. p. 199° (Found : equiv., 280·5. $C_{13}H_{15}O_6N$ requires equiv., 281).

The following is an account of the preparation of 5-bromo-*o*-veratric acid from 5-nitro-*o*-veratric acid.

5-Nitro-2 : 3-dimethoxybenzoic acid (4·5 g.) is heated with concentrated hydrochloric acid (15 c.c.) and tin (4·5 g.) on a steam-bath for a few hours, the solution diluted with water, the tin removed as sulphide, and the colourless filtrate evaporated under reduced pressure; white, prismatic crystals of the hydrochloride of 5-amino-2 : 3-dimethoxybenzoic acid are deposited (yield 80%).

The hydrochloride is soluble in water or alcohol and in warm concentrated hydrochloric acid, from which it can be crystallised. The solutions turn pink and then red in the air, especially if in presence of an excess of acid. 5-Amino-2 : 3-dimethoxybenzoic acid is obtained by treating a concentrated solution of the hydrochloride with solid sodium carbonate until it is just acid to Congo-red. The colourless needles, m. p. 250° (decomp.), soon become deep-red owing to oxidation, and are soluble in acids and in alkalis (Found : N, 6·9. $C_9H_{12}O_4N$ requires N, 7·0%).

The hydrochloride (4 g.) is dissolved in water (17 c.c.), neutralised with solid sodium carbonate, treated with hydrobromic acid (7·5 c.c.; *d* 1·50), and diazotised at 0° with sodium nitrite (1·2 g. in water, 3 c.c.). The black, semi-crystalline solid obtained by heating the diazonium solution with cuprous bromide and concentrated hydrobromic acid is boiled with alcohol and animal charcoal, and the hot filtered solution cooled after addition of a little water. Long, cream needles are deposited, m. p. 112—113°, which, after further treatment with animal charcoal and recrystallisation from aqueous alcohol, melt at 120° and do not depress the m. p. of 5-bromo-*o*-veratric acid obtained by oxidation of 5-bromo-*o*-veratraldehyde.

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