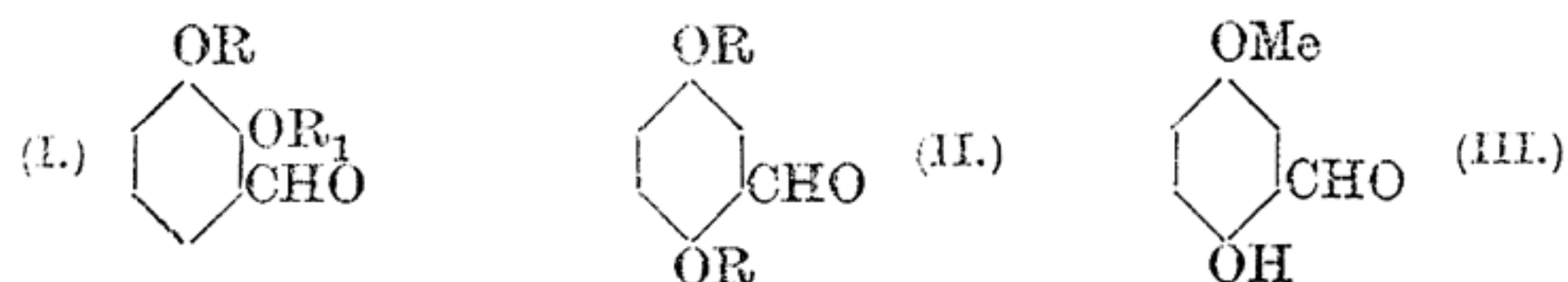


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# CCLXX.—Substitution in Derivatives of Quinol Ethers.

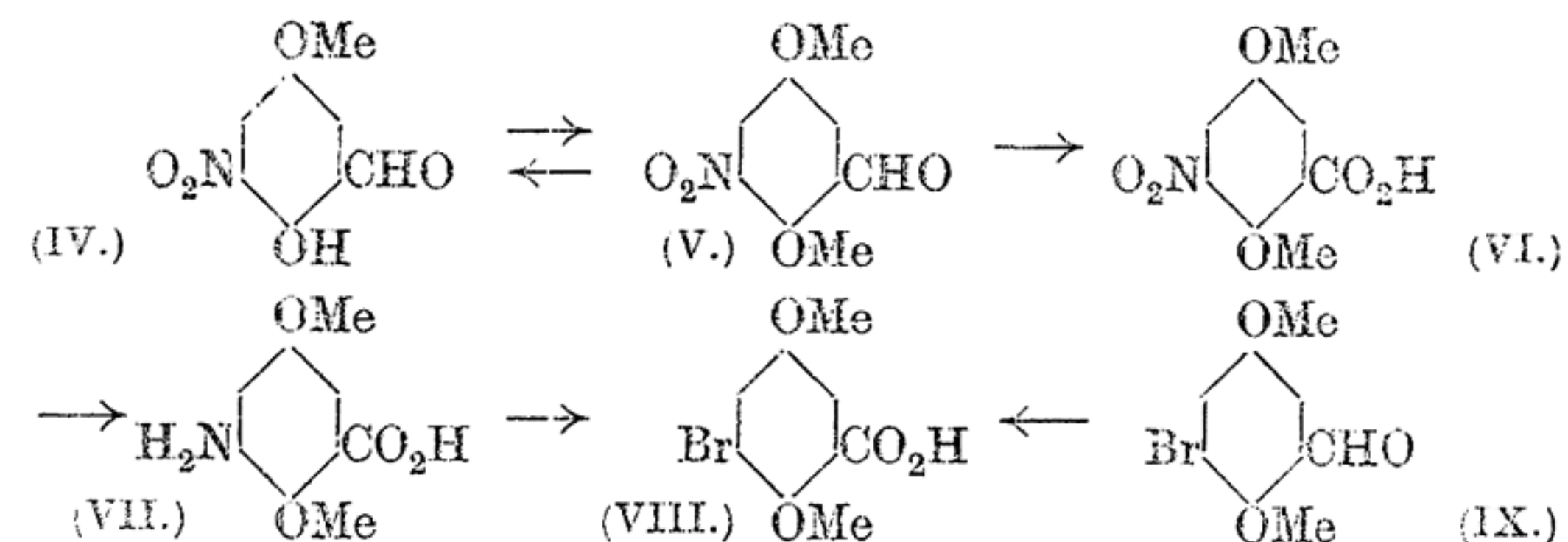
By LEON RUBENSTEIN.

THE investigation of substitution in the case of dialkyloxy vicinal benzene derivatives of type I (Davies and Rubenstein, J., 1923, 123, 2830) showed that during nitration each alkyloxy-group OR, OR<sub>1</sub> exerts its para-directing influence independently of the other, whereas during bromination only the group -OR is potent in determining the orientation of the brominated product. The relative amounts of the isomerides produced in the nitration experiments, which could not then be estimated, have now been determined in the case of *o*-veratraldehyde (Perkin, Robinson, and Stoye, J., 1924, 125, 2355). The results obtained in those investigations made it desirable to examine the nitration and bromination of substances of type II in which only ortho-substitution with respect to the alkyloxy-groups can take place.



Experiments on the nitration of 2-hydroxy-5-methoxybenzaldehyde (III) indicate that the substance formed is the 3-nitro-benzaldehyde (IV), for when its methylation product (V) is hydrolysed 3-nitro-2-hydroxy-5-methoxybenzaldehyde is reformed. The bromin-

ation of 2-hydroxy-5-methoxybenzaldehyde yields the 3-bromo-benzaldehyde, as is shown in the following manner: 3-Nitro-2:5-dimethoxybenzaldehyde (V) is oxidised to 3-nitro-2:5-dimethoxybenzoic acid (VI), which is reduced to 3-amino-2:5-dimethoxybenzoic acid (VII); from this by the Sandmeyer process is produced 3-bromo-2:5-dimethoxybenzoic acid (VIII), identical with the acid obtained by oxidising bromo-2-hydroxy-5-methoxybenzaldehyde after methylation (IX).



The nitration of 2:5-dimethoxybenzaldehyde gives a mixture of 6-nitro-2:5-dimethoxybenzaldehyde (80%) and 3-nitro-2:5-dimethoxybenzaldehyde (20%). The former substance has its nitro-group in the ortho-position with respect to the aldehyde group, for it gives an indigotin derivative when treated with acetone and alkali. It yields 6-nitro-2:5-dimethoxybenzoic acid on oxidation. The bromination of 2:5-dimethoxybenzaldehyde gives 6-bromo-2:5-dimethoxybenzaldehyde as the only product, and from this 6-bromo-2:5-dimethoxybenzoic acid is obtained by oxidation.

The remaining portion of the work consists in the investigation of the nitration and the bromination of 2:5-dimethoxyacetanilide. The nitration of this substance yields 4-nitro-2:5-dimethoxyacetanilide, as is shown by the fact that hydrolysis converts it into the nitro-2:5-dimethoxyaniline which on diazotisation and subsequent treatment in the Sandmeyer manner yields 3-bromo-6-nitroquinol dimethyl ether. On bromination, 2:5-dimethoxyacetanilide yields 4-bromo-2:5-dimethoxyacetanilide, the usual proof being applied, namely, conversion into the 4-bromo-2:5-dimethoxyaniline, diazotisation, and treatment with cuprous bromide to give dibromoquinol dimethyl ether.

## EXPERIMENTAL.

2-Hydroxy-5-methoxybenzaldehyde was obtained by Tiemann and Müller (*Ber.*, 1881, 14, 1990) in small yield, but the following modification gives much better results. Quinol monomethyl ether (40 g.) dissolved in a concentrated aqueous solution of sodium hydroxide (19 g. in 55 c.c. of water) is heated on a water-bath



while chloroform (42 g.) and sodium hydroxide solution (56 g. in 60 c.c. of water) are added alternately during 2 hours. The mixture is then heated for 1 hour, the sodium salt of the aldehyde separating in yellow, metallic crystals. The whole is strongly acidified, steam-distilled, the distillate extracted with ether, and the ethereal extract kept for some time over a concentrated solution of sodium bisulphite. The major portion of the ether is distilled off and the bisulphite compound of the aldehyde, which separates, is removed, decomposed by hot dilute sulphuric acid, and the aldehyde extracted with ether. The ether is removed and the residue distilled under reduced pressure, when 2-hydroxy-5-methoxybenzaldehyde is obtained as a light yellow, refracting liquid, b. p. 124°/12 mm. (yield 8.5 g., i.e., 25%).

*3-Nitro-2-hydroxy-5-methoxybenzaldehyde*.—To a cold solution of 2-hydroxy-5-methoxybenzaldehyde (10 g.) in glacial acetic acid (50 c.c.) is added with cooling and stirring a solution of nitric acid (50 c.c.;  $d$  1.42) in glacial acetic acid (50 c.c.), the temperature being maintained between 10° and 20°. 3-Nitro-2-hydroxy-5-methoxybenzaldehyde, which soon begins to separate, is collected after a few hours (yield 6.5 g.; m. p. 127°). The glacial acetic acid solution is diluted with water, neutralised with sodium bicarbonate, and extracted with ether; from the extract a further 4.5 g. of the substance is obtained (total yield 88%). 3-Nitro-2-hydroxy-5-methoxybenzaldehyde crystallises in bright yellow needles, m. p. 132°. It does not yield an indigotin derivative when treated with acetone and sodium hydroxide solution. With ferric chloride solution, it gives a red coloration.

The *p*-nitrophenylhydrazone crystallises in scarlet prisms, decomp. 250°.

*3-Nitro-2 : 5-dimethoxybenzaldehyde*.—A solution of 3-nitro-2-hydroxy-5-methoxybenzaldehyde (6 g.) in dry chloroform (20 c.c.) and methyl iodide (10 c.c.) is heated on a water-bath while finely powdered silver oxide (6 g.) is added during 2 hours. After being heated for a further 1 hour, the mixture is filtered hot, some of the chloroform evaporated, and the solution cooled; 3-nitro-2 : 5-dimethoxybenzaldehyde then crystallises in pale yellow needles, m. p. 113°. More of the substance is obtained from the mother-liquors (yield almost theoretical).

When it is boiled for a short time with 10% sodium hydroxide, and the solution is acidified, 3-nitro-2-hydroxy-5-methoxybenzaldehyde can be extracted from the precipitate obtained.

*3-Bromo-2-hydroxy-5-methoxybenzaldehyde*.—2-Hydroxy-5-meth-

oxybenzaldehyde (6 g.) is dissolved in glacial acetic acid (30 c.c.), and powdered, freshly-fused sodium acetate (3.6 g.) added. The suspension is well stirred, cooled to 5°, and treated with a solution of bromine (6 g.) in glacial acetic acid (12 c.c.), when 3-bromo-2-hydroxy-5-methoxybenzaldehyde rapidly separates. After remaining for a few hours, the mixture is diluted with water and the solid collected (yield 7.3 g. or 80%). It crystallises from aqueous alcohol in light brown needles, m. p. 107°.

The *p*-nitrophenylhydrazone forms scarlet prisms, decomp. above 250°.

*3-Bromo-2 : 5-dimethoxybenzaldehyde*.—A solution of 3-bromo-2-hydroxy-5-methoxybenzaldehyde (6.5 g.) in alcohol (59 c.c.) is boiled under reflux during the gradual addition of methyl *p*-toluenesulphonate (10.5 g.) and 30% sodium hydroxide solution (4 c.c.). After boiling for 3 hours, the red alcoholic solution is diluted with water and the solid collected; after twice crystallising from aqueous alcohol, it forms needles, m. p. 63°.

*Nitration of 2 : 5-Dimethoxybenzaldehyde*.—Finely-powdered 2 : 5-dimethoxybenzaldehyde (3 g.) was added with cooling and stirring to cold nitric acid (12 c.c.;  $d$  1.42). After remaining at room temperature for several hours, the mixture was diluted with water, and the solid (3.4 g.) collected. The mixture, m. p. 130—153°, was fractionally crystallised from alcohol, the main product being 6-nitro-2 : 5-dimethoxybenzaldehyde (*vide ante*), m. p. 159°. The mother-liquors deposited a small amount of 3-nitro-2 : 5-dimethoxybenzaldehyde (m. p. 113°), which gave no depression of melting point when mixed with a sample of 3-nitro-2 : 5-dimethoxybenzaldehyde prepared by the methylation of 3-nitro-2-hydroxy-5-methoxybenzaldehyde (p. 2000).

6-Nitro-2 : 5-dimethoxybenzaldehyde crystallises from alcohol in pale yellow needles, m. p. 159°.

The *p*-nitrophenylhydrazone forms scarlet prisms, m. p. 245—250° (decomp.).

*6-Bromo-2 : 5-dimethoxybenzaldehyde*.—A cooled solution of 2 : 5-dimethoxybenzaldehyde (2.8 g.) in glacial acetic acid (16 c.c.) is treated with bromine (2.8 g.) in glacial acetic acid (8 c.c.), kept for 2 days, and diluted with water; an oil then separates which rapidly solidifies. It crystallises from alcohol in pale grey needles, m. p. 125—126°, which become pink on exposure to the air.

The *p*-nitrophenylhydrazone consists of hexagonal, scarlet prisms, m. p. 204—206°.

*3-Nitro-2 : 5-dimethoxybenzoic Acid*.—3-Nitro-2 : 5-dimethoxybenzaldehyde (6 g.) is added to water (60 c.c.) containing potassium



bicarbonate (4.2 g.), and boiled during the addition of potassium permanganate solution (6 g. in 60 c.c. of water). The hot solution is filtered, allowed to cool, and unchanged aldehyde collected. The reddish-yellow aqueous solution is acidified with dilute hydrochloric acid, when 3-nitro-2 : 5-dimethoxybenzoic acid (3.5 g.) is precipitated. It crystallises from hot water in long needles, m. p. 182—183°.

*6-Nitro-2 : 5-dimethoxybenzoic Acid.*—6-Nitro-2 : 5-dimethoxybenzaldehyde is oxidised as described above. The acid crystallises from hot water in pale yellow prisms, m. p. 192°.

*3-Amino-2 : 5-dimethoxybenzoic Acid.*—A mixture of 3-nitro-2 : 5-dimethoxybenzoic acid (7 g.) and concentrated hydrochloric acid (24 c.c.) is gradually treated with tin (7 g.) and heated on a water-bath for 3 hours, water (50 c.c.) is added, and the tin removed from the hot solution as sulphide. The colourless filtrate is evaporated under reduced pressure, when the *hydrochloride* of 3-amino-2 : 5-dimethoxybenzoic acid separates in long, white needles (yield 5 g. or 80%).

The hydrochloride is easily soluble in water or alcohol, more difficultly soluble in concentrated hydrochloric acid, from which it can be crystallised. The solutions turn pink and then red on exposure to the air. When heated, the solid becomes very dark at 170° and decomposes at 215°. 3-Amino-2 : 5-dimethoxybenzoic acid is obtained by treating a solution of the hydrochloride in a small quantity of water with solid sodium carbonate until it is just acid to Congo-red, and evaporating under reduced pressure; after a long time, the acid separates in white, slender needles which turn black at 170° and decompose at 210—215°. It is soluble in acids, alkalis, and hot water; the latter two solutions turn green on exposure to the air.

*3-Bromo-2 : 5-dimethoxybenzoic Acid.*—A mixture of 3-bromo-2 : 5-dimethoxybenzaldehyde (5.5 g.), water (55 c.c.), and potassium bicarbonate (3.8 g.) is boiled during the addition of 10% potassium permanganate (55 c.c.), filtered hot, cooled, and again filtered. The colourless filtrate is acidified with dilute hydrochloric acid, and the precipitated 3-bromo-2 : 5-dimethoxybenzoic acid (yield 4.5 g. or 85%) is crystallised from aqueous alcohol, when it is obtained in white, microscopic prisms, m. p. 132°.

*6-Bromo-2 : 5-dimethoxybenzoic Acid.*—6-Bromo-2 : 5-dimethoxybenzaldehyde is oxidised as described above. The acid crystallises from aqueous alcohol in white, microscopic prisms, m. p. 164—165°.

*4 : 4' : 7 : 7'-Tetramethoxyindigotin.*—Aqueous potash (1 c.c. of 10%) is added to a solution of 6-nitro-2 : 5-dimethoxybenzaldehyde (0.4 g.) in acetone (2 c.c.). The deep blue liquid is mixed with water (20 c.c.) and boiled for a few minutes; the indigotin then separates. It has a rich deep blue appearance and crystallises from nitrobenzene in deep purple rhombs which sublime at 350°.

*4-Bromo-2 : 5-dimethoxyacetanilide.*—When 2 : 5-dimethoxyacetanilide (5 g.) dissolved in glacial acetic acid (25 c.c.) is treated with bromine (3.3 g.) in 4 c.c. of glacial acetic acid, 4-bromo-2 : 5-dimethoxyacetanilide soon separates from the well-cooled solution. After the mixture has been diluted with water, and the acetic acid neutralised with sodium carbonate, ether extracts the product, which crystallises from dilute alcohol in pale pink rhombs, m. p. 122° (yield 5.6 g. or 80%).

*4-Bromo-2 : 5-dimethoxyaniline Hydrochloride.*—4-Bromo-2 : 5-dimethoxyacetanilide (12 g.) is boiled with 20% alcoholic hydrochloric acid (20 c.c.) for 15 minutes; the 4-bromo-2 : 5-dimethoxyaniline hydrochloride which separates crystallises from alcohol in white, microscopic plates which become blue at 160° and decompose above 300°.

4-Bromo-2 : 5-dimethoxyaniline forms pale pink prisms, m. p. 106°. The hydrobromide is obtained by keeping an ethereal solution of the base in contact with hydrobromic acid (*d* 1.5), when it slowly separates in fine, yellow needles which turn blue at 160° and decompose slowly above this temperature.

*Diazotisation.* Methyl nitrite is passed through a solution of 4-bromo-2 : 5-dimethoxyaniline hydrobromide (20 g.) in glacial acetic acid (60 c.c.) at 10°. The deep brown solution of 4-bromo-2 : 5-dimethoxybenzenediazonium bromide is poured into dry ether, the ether decanted off, and the solid diazonium salt dissolved in ice-cold water (40 c.c.). The aqueous solution is added cautiously to a solution of cuprous bromide in concentrated hydrobromic acid and heated on a water-bath; nitrogen is then evolved and 2 : 5-dibromoquinol dimethyl ether separates. This crystallises from alcohol in colourless needles, m. p. 143°, not depressed on admixture with the dibromoquinol dimethyl ether prepared by the bromination of quinol dimethyl ether.

*4-Nitro-2 : 5-dimethoxyacetanilide.*—A solution of 2 : 5-dimethoxyacetanilide (10 g.) in glacial acetic acid (50 c.c.) is treated at 5° with nitric acid (*d* 1.42; 10 c.c. in 50 c.c. of glacial acetic acid). After 1 hour, water is added. The 4-nitro-2 : 5-dimethoxyacetanilide which separates (yield 11 g. or 90%) crystallises from alcohol in yellow prisms, m. p. 165°.



*4-Nitro-2 : 5-dimethoxyaniline Hydrochloride.*—4-Nitro-2 : 5-dimethoxyacetanilide (10 g.) is boiled with 20% alcoholic hydrochloric acid (25 c.c.) for 1 hour. The grey crystals of the *hydrochloride* that separate on cooling (yield theoretical) crystallise from alcohol in yellow, metallic prisms, m. p. 160° (decomp.)

*4-Nitro-2 : 5-dimethoxyaniline* forms yellow prisms, m. p. 153°.

*Diazotisation of 4-Nitro-2 : 5-dimethoxyaniline Hydrobromide.*—The solution obtained by diazotising 4-nitro-2 : 5-dimethoxyaniline hydrobromide (4 g.) in concentrated hydrobromic acid (20 c.c.) and water (25 c.c.) at 0° with 2.5 c.c. of 40% sodium nitrite is filtered, added cautiously to a solution of cuprous bromide in concentrated hydrobromic acid, and the mixture heated on a water-bath for a short time. The 2-bromo-5-nitroquinol dimethyl ether that separates is washed with concentrated hydrobromic acid and with water and crystallised from alcohol. The product, pale yellow prisms, m. p. 154°, does not depress the m. p. of 2-bromo-5-nitroquinol dimethyl ether obtained by bromination of nitroquinol dimethyl ether.