151. *Substitution in the 2-Methoxy-nitrodiphenyl Ethers.*

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The directive influence of hydroxyl and methoxyl in binuclear systems has been examined in detail only in azobenzene and benzophenone (compare, *inter alia*, Hewitt, J., 1900, **77**, 99; Blakey, Jones, and Scarborough, J., 1927, 2865). In these two systems the linking bond is, by comparison, feebly *o*- or *p*- and *m*-directive respectively, so it is not surprising that the highly activating hydroxy- and methoxy-groups controlled successive stages in the substitution process.

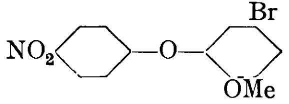
On the other hand, only a small number of observations have been made with the hydroxy- and methoxy-derivatives of diphenyl and diphenyl ether, where the linking bond is highly *o*- or *p*-directive. In the case of the diphenyl compounds it is known that the hydroxy-group controls two successive stages, and the methoxy-group one stage, of nitration. For the diphenyl ethers the only result on record is that 4-methoxydiphenyl ether yielded 3-nitro-4-methoxydiphenyl ether as sole product (Lea and Robinson, J., 1926, 411); from this result the conclusion was drawn that methoxyl was more highly activating than the phenoxy-group.

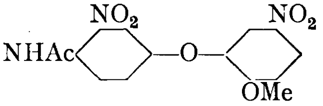
On more than one occasion attention has been directed to the fact that halogenation of the diphenyl ethers is a smooth and regular process, whereas nitration occurs violently and step-wise substitution is rarely attained. Further it has been suggested that " in all probability bromination is a more facile process than nitration and can take advantage of a smaller degree of polarisation occurring more frequently than the activation of greater amplitude required to facilitate nitration." Such a system as 4′-nitro-2-methoxydiphenyl ether might therefore be expected to show marked differences in the progress of halogenation and nitration.

The halogenation and nitration of 4′-nitro-2-methoxydiphenyl ether yielded single products, the substituent entering the 5-position to give 5-*chloro*- and 5-*bromo*-4′-*nitro*-2-*methoxydiphenyl ethers* (I) and 4′ : 5-*dinitro*-2-*methoxydiphenyl ether*. Further halogenation was readily effected, yielding 4 : 5-*dichloro*- and 4 : 5-*dibromo*-4′-*nitro*-2-*methoxydiphenyl ethers*. By passing chlorine into an acetic acid solution of the dichloro-ether, a *trichlorination product* was obtained, the structure of which has, however, not been determined. The corresponding tribromination product could not be obtained. The introduction of further nitro-groups into the molecule of 4′ : 5-dinitro-2-methoxydiphenyl ether did not yield products substituted in the 4-position. Similarly the bromination of 4′ : 5-dinitro-2-methoxydiphenyl ether and the nitration of 5-chloro-4′-nitro-2-methoxydiphenyl ether did not yield products which reacted with piperidine and are thus probably not substituted in the 4-position.

The substitution of 3′-nitro-2-methoxydiphenyl ethers was shown to follow on the same lines as in the 4′-nitro-compound; it would thus appear that the position of the nitro-group has little effect. The behaviour of 4′-nitro-2-hydroxydiphenyl ether was investigated and the first substituent was found to enter the 5-position; the introduction of a second halogen atom yielded products substituted in the 4 : 5-positions, a somewhat unexpected result when the very high activating effect of the hydroxy-group is taken into account. The conversion of the nitro-group in 4′-nitro-2-methoxydiphenyl ether into an acetamidogroup caused a difference in the sequence of nitration; under very mild conditions 3′-*nitro-4′-acetamido-2-methoxydiphenyl ether* was formed and then 3′ : 5-*dinitro-4′-acetamido-2-methoxydiphenyl ether* (II).

(I.)





(II.)

The constitutions of the various substitution products have been established by condensing *p*-chloronitrobenzene with the potassium salt of an appropriately substituted guaiacol; a second control has been obtained by reduction of the substituted nitro-compounds to the amine, acetylation, nitration, deamination, and a synthesis of the derivative of 3′-nitro-2-methoxydiphenyl ether thus formed.

EXPERIMENTAL.

4′-Nitro-2-methoxydiphenyl ether was obtained when *p*-chloronitrobenzene and the potassium salt of guaiacol were heated for 5 hours at 210°. The crude product, distilled in steam, taken into chloroform, washed, and dried, distilled at 235°/20 mm. It crystallised from alcohol in long, heavy, yellowish needles, m. p. 106°.

4′-*Nitro-2-hydroxydiphenyl ether*, prepared by refluxing the methoxy-derivative with a mixture of hydrobromic acid (*d* 1·4) and acetic acid for 6 hours, separated from benzene in needles, m. p. 109° (Found : N, 6·05. $C_{12}H_9O_4N$ requires N, 6·05%).

4′-*Amino-2-methoxydiphenyl ether*, obtained by reduction of the nitro-compound with stannous chloride in ethereal hydrogen chloride, crystallised from dilute methyl alcohol in needles, m. p. 97° (Found : N, 6·5. $C_{13}H_{13}O_2N$ requires N, 6·5%). The *acetyl* derivative, formed on refluxing the base with a mixture of acetic anhydride and acid (1 : 8) for 8 hours, separated from dilute acetic acid in needles, m. p. 118° (Found : N, 5·5. $C_{15}H_{15}O_3N$ requires N, 5·45%).

3′-*Nitro-4′-acetamido-2-methoxydiphenyl ether*, prepared by the nitration of the acetyl derivative in acetic acid at 15° with the calculated quantity of nitric acid (*d* 1·5), crystallised from methyl alcohol in yellow needles, m. p. 124° (Found : N, 9·25. $C_{15}H_{14}O_5N_2$ requires N, 9·25%). The *base* was formed on treatment with dilute sulphuric acid (1 : 1) at water-bath temperature, and crystallised from light petroleum (b. p. 60—80°) or methyl alcohol in red plates, m. p. 98° (Found : N, 10·7. $C_{13}H_{12}O_4N_2$ requires N, 10·8%).

3′-*Nitro-2-methoxydiphenyl ether*, obtained by deamination of the base, or by condensation of *m*-iodonitrobenzene with the potassium salt of guaiacol for 12 hours at 250° in presence of copper powder, separated from methyl alcohol in faintly yellow prisms, m. p. 86° (Found : N, 5·8. $C_{13}H_{11}O_4N$ requires N, 5·7%).

3′ : 5-*Dinitro-4′-acetamido-2-methoxydiphenyl ether* was obtained when an acetic acid solution of 2-methoxy- or 2-methoxy-3′-nitro-4′-acetamidodiphenyl ether was treated with excess of nitric acid (*d* 1·5) at 80°; after 30 minutes the mixture was poured on ice and the product collected at once. It crystallised from alcohol in yellow needles, m. p. 181° (Found : N, 12·0. $C_{15}H_{13}O_7N_3$ requires N, 12·1%). The *base*, formed on deacetylation with dilute sulphuric acid, separated from alcohol in deep red needles, m. p. 163° (Found : N, 13·85. $C_{13}H_{11}O_7N_3$ requires N, 13·75%).

3′ : 5-*Dinitro-2-methoxydiphenyl ether*, formed by condensation of *m*-iodonitrobenzene with the potassium salt of 5-nitroguaiacol at 220°, by the deamination of the base, and by keeping a solution of 3′-nitro-2-methoxydiphenyl ether in nitric acid (*d* 1·4) for 2 hours, separated from light petroleum (b. p. 60—80°) in needles, m. p. 123° (Found : N, 9·75. $C_{13}H_{10}O_6N_2$ requires N, 9·65%).

4′ : 5-*Dinitro-2-methoxydiphenyl ether* was obtained when (1) 4′-nitro-2-methoxydiphenyl ether was nitrated in acetic acid at 80° with a small excess of nitric acid (*d* 1·5), (2) the same compound was dissolved in nitric acid (*d* 1·4), and the solution kept for 3 hours at 15°, and (3) *p*-chloronitrobenzene was condensed with the potassium salt of 5-nitroguaiacol for 6 hours at 210°. It separated from alcohol in needles, m. p. 121° (Found : N, 9·65. $C_{13}H_{10}O_6N_2$ requires N, 9·65%).

4′ : 5-*Dinitro-2-hydroxydiphenyl ether*, prepared by demethylation of the methoxy- compound, separated from dilute alcohol in faintly yellow needles, m. p. 157° (Found : N, 10·15. $C_{12}H_8O_6N_2$ requires N, 10·15%).

4-*Chloro-4′-nitro-2-methoxydiphenyl ether*, formed by condensation of *p*-chloronitrobenzene with the potassium salt of 4-chloroguaiacol at 220° for 5 hours, crystallised from alcohol in needles, m. p. 104° (Found : Cl, 12·75. $C_{13}H_{10}O_4NCl$ requires Cl, 12·8%).

4-*Chloro-4′-nitro-2-hydroxydiphenyl ether*, obtained by demethylation of the preceding compound, crystallised from light petroleum (b. p. 60—80°) in faintly yellow needles, m. p. 121° (Found : Cl, 13·6. $C_{12}H_8O_4NCl$ requires Cl, 13·4%).

5-*Chloro-4′-nitro-2-methoxydiphenyl ether*, prepared by the action of a small excess of chlorine on an acetic acid solution of 4′-nitro-2-methoxydiphenyl ether, or by the action of sulphuryl chloride on the same compound at room temperature, crystallised from alcohol in large prisms, m. p. 94° (Found : Cl, 12·7. $C_{13}H_{10}O_4NCl$ requires Cl, 12·8%).

5-*Chloro-4′-nitro-2-hydroxydiphenyl ether*, prepared by the action at 0° of sulphuryl chloride on 4′-nitro-2-hydroxydiphenyl ether, or by demethylation of the preceding compound, separated from light petroleum (b. p. 60—80°) in radial needles, m. p. 94° (Found : Cl, 13·35. $C_{12}H_8O_4NCl$ requires Cl, 13·4%).

5-*Chloro-4′-amino-2-methoxydiphenyl ether*, obtained by reduction of the nitro-compound, crystallised from dilute alcohol in needles, m. p. 90° (Found : Cl, 14·3. $C_{13}H_{12}O_2NCl$ requires Cl, 14·2%). The *acetyl* derivative separated from dilute acetic acid in leaves, m. p. 192° (Found : Cl, 12·15. $C_{15}H_{14}O_3NCl$ requires Cl, 12·2%).

5-*Chloro-3′-nitro-4′-acetamido-2-methoxydiphenyl ether* was prepared by adding an excess of nitric acid (*d* 1·5) to an acetic acid solution of the preceding acetyl derivative at 90° and keeping the mixture for 30 minutes and then pouring it on ice. The product was collected at once; it separated from alcohol in yellow needles, m. p. 163° (Found : Cl, 10·45. $C_{15}H_{13}O_5N_2Cl$ requires Cl, 10·55%). The *base* crystallised from alcohol in red prisms, m. p. 105° (Found : Cl, 12·05. $C_{13}H_{11}O_4N_2Cl$ requires Cl, 12·05%).

5-*Chloro-3′-nitro-2-methoxydiphenyl ether*, obtained by deamination of the base, or by the action of sulphuryl chloride on 3′-nitro-2-methoxydiphenyl ether at 0°, crystallised from alcohol or light petroleum in needles, m. p. 85° (Found : Cl, 12·8. $C_{13}H_{10}O_4NCl$ requires Cl, 12·7%).

4 : 5-*Dichloro-4′-nitro-2-methoxydiphenyl Ether.*—2-Methoxy-, 4-chloro-2-methoxy-, or 5-chloro-2-methoxy-4′-nitrodiphenyl ether was treated in acetic acid with a small excess of chlorine at room temperature. The same product was formed by the action of excess of sulphuryl chloride on the three ethers; or by condensation of *p*-chloronitrobenzene and the potassium salt of 4 : 5-dichloroguaiacol. It separated from alcohol or acetic acid in needles, m. p. 147° (Found : Cl, 22·55. $C_{13}H_9O_4NCl_2$ requires Cl, 22·6%).

4 : 5-*Dichloro-4′-nitro-2-hydroxydiphenyl ether*, prepared by the demethylation of the methoxy-compound, or by addition of the calculated quantity of chlorine to an acetic acid solution of 2-hydroxy- or 5-chloro-2-hydroxy-4′-nitrodiphenyl ether, crystallised from alcohol or light petroleum (b. p. 60—80°) in needles, m. p. 132° (Found : Cl, 23·55. $C_{12}H_7O_4NCl_2$ requires Cl, 23·65%).

4 : 5-*Dichloro-4′-amino-2-methoxydiphenyl ether*, obtained by reduction of the nitro-compound, separated from light petroleum in needles, m. p. 122° (Found : Cl, 24·8. $C_{13}H_{11}O_2NCl_2$ requires Cl, 25·0%). The *acetyl* derivative crystallised from dilute acetic acid in needles, m. p. 189° (Found : Cl, 21·9. $C_{15}H_{13}O_3NCl_2$ requires Cl, 21·8%).

4 : 5-*Dichloro-3′-nitro-4′-acetamido-2-methoxydiphenyl ether*, obtained by addition of excess of nitric acid (*d* 1·5) to the acetyl compound in acetic acid at 80°, crystallised from alcohol in yellow needles, m. p. 164° (Found : Cl, 19·1. $C_{15}H_{12}O_5N_2Cl_2$ requires Cl, 19·2%). The *base* separated from alcohol in red prisms, m. p. 174° (Found : Cl, 21·5. $C_{13}H_{10}O_4N_2Cl_2$ requires Cl, 21·6%).

4 : 5-*Dichloro-3′-nitro-2-methoxydiphenyl ether*, obtained by deamination of the base, or by chlorination of 3′-nitro- and 5-chloro-3′-nitro-2-methoxydiphenyl ethers in acetic acid, crystallised from light petroleum in needles, m. p. 123° (Found : Cl, 22·5. $C_{13}H_9O_4NCl_2$ requires Cl, 22·6%).

4-*Bromo-4′-nitro-2-methoxydiphenyl ether*, formed by condensation of *p*-chloronitrobenzene with the potassium salt of 4-bromoguaiacol for 6 hours at 220°, separated from alcohol or light petroleum in needles, m. p. 107° (Found : Br, 24·6. $C_{13}H_{10}O_4NBr$ requires Br, 24·7%).

5-*Bromo-4′-nitro-2-methoxydiphenyl Ether.*—*p*-Chloronitrobenzene was condensed with the potassium salt of 5-bromoguaiacol at 210°; or the calculated quantity of bromine was added to 4′-nitro-2-methoxydiphenyl ether in acetic acid, the mixture being kept for 24 hours. The *ether* separated from dilute acetic acid in prisms, m. p. 96° (Found : Br, 24·8. $C_{13}H_{10}O_4NBr$ requires Br, 24·7%).

5-*Bromo-4′-nitro-2-hydroxydiphenyl ether*, prepared by demethylation of the methoxy-derivative or by addition of bromine (1 mol.) to 4′-nitro-2-hydroxydiphenyl ether in acetic acid, crystallised from light petroleum in faintly yellow needles, m. p. 89° (Found : Br, 25·55. $C_{12}H_8O_4NBr$ requires Br, 25·7%).

5-*Bromo*-4′-*amino*-2-*methoxydiphenyl ether*, prepared by reduction of the nitro-compound, separated from light petroleum in needles, m. p. 105° (Found : Br, 27·3. $C_{13}H_{12}O_2NBr$ requires Br, 27·2%). The *acetyl* derivative crystallised from alcohol in plates, m. p. 195° (Found : Br, 23·7. $C_{15}H_{14}O_3NBr$ requires Br, 23·7%).

5-*Bromo*-3′-*nitro*-4′-*acetamido*-2-*methoxydiphenyl ether* was prepared by nitration of the acetyl derivative in acetic acid at 90°. It crystallised from alcohol in yellow needles, m. p. 142° (Found : Br, 21·0. $C_{15}H_{13}O_5N_2Br$ requires Br, 21·0%). The *base* separated from light petroleum in red prisms, m. p. 112° (Found : Br, 23·6. $C_{13}H_{11}O_4N_2Br$ requires Br, 23·6%).

5-*Bromo*-3′-*nitro*-2-*methoxydiphenyl ether*, obtained by deamination of the base, or by bromination of 3′-nitro-2-methoxydiphenyl ether in acetic acid, crystallised from light petroleum or alcohol in radial needles, m. p. 93° (Found : Br, 24·5. $C_{13}H_{10}O_4NBr$ requires Br, 24·65%).

4 : 5-*Dibromo*-4′-*nitro*-2-*methoxydiphenyl Ether*.—*p*-Chloronitrobenzene was condensed with the potassium salt of 4 : 5-dibromoguaiacol for 6 hours at 210°; or an excess of bromine was added to 2-methoxy-, 4-bromo-2-methoxy-, and 5-bromo-2-methoxy-4′-nitrodiphenyl ethers in acetic acid, and the solutions kept at 80° for 5 hours. The *ether* separated from dilute acetic acid in needles, m. p. 156° (Found : Br, 39·6. $C_{13}H_9O_4NBr_2$ requires Br, 39·7%).

4 : 5-*Dibromo*-4′-*nitro*-2-*hydroxydiphenyl ether*, prepared by demethylation of the methoxy-derivative or bromination of 2-hydroxy- and 5-bromo-2-hydroxy-4′-nitrodiphenyl ethers in acetic acid, crystallised from light petroleum in needles, m. p. 153° (Found: Br, 41·1. $C_{12}H_7O_4NBr_2$ requires Br, 41·1%).

4 : 5-*Dibromo*-4′-*amino*-2-*methoxydiphenyl ether*, obtained by reduction of the nitro-compound, separated from methyl alcohol or light petroleum in radial needles, m. p. 106° (Found : Br, 42·8. $C_{13}H_{11}O_2NBr_2$ requires Br, 42·9%). The *acetyl* derivative crystallised from dilute acetic acid in radial needles, m. p. 190° (Found : Br, 38·6. $C_{15}H_{13}O_3NBr_2$ requires Br, 38·6%).

4 : 5-*Dibromo*-3′-*nitro*-4′-*acetamido*-2-*methoxydiphenyl ether*, obtained by nitration of the acetyl derivative in acetic acid at 90°, separated from alcohol in yellow needles, m. p. 165° (Found : Br, 34·7. $C_{15}H_{12}O_5N_2Br_2$ requires Br, 34·8%). The *base* crystallised from alcohol in bronze needles, m. p. 179° (Found : Br, 38·15. $C_{13}H_{10}O_4N_2Br_2$ requires Br, 38·3%).

4 : 5-*Dibromo*-3′-*nitro*-2-*methoxydiphenyl ether*, prepared by (1) deamination of the base, (2) bromination of 2-methoxy- or 5-bromo-2-methoxy-3′-nitrodiphenyl ether in acetic acid at 90° for 5 hours, crystallised from alcohol or light petroleum in needles, m. p. 131° (Found : Br, 39·5. $C_{13}H_9O_4NBr_2$ requires Br, 39·7%).

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