CCCIX.—*Substitution Products of 4-Nitro- and 4-Acetamido-diphenyl Ether.*

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THE relative directive influence of the phenoxyl group has been the subject of several investigations; for instance, Lea and Robinson (J., 1926, 411) examined the nitration of 4-methoxydiphenyl ether and showed that the sole product was 3-nitro-4-methoxydiphenyl ether and from this result they deduced that the phenoxyl and *p*-methoxyphenoxyl groups in comparison with the methoxyl group were of small directive power and suggested that this lessened directive power was due to the conjugation of the oxygen atom on both sides.

Again, Groves, Turner, and Sharp (this vol., p. 512) examined the nitration of 2 : 4 : 4′-trichloro-, 2 : 4 : 4′-trichloro-2′-nitro-, and 2 : 4-dichloro-2′ : 4′-dinitro-diphenyl ethers and found that in the first case the entering nitro-group occupied the 2′-position and in the other cases the 5-position. These authors conclude that their results are in agreement with the views put forward by Lea and Robinson (*loc. cit.*) if the phenoxyl group is assumed to be weakly directive and due consideration is paid to the complexity of the cases studied.

It has appeared from previous work on substitution in compounds containing two benzene nuclei that the amino-, acetamido-, hydroxy-, and methoxy-groups have so pronounced directive effects that the halogens and alkyl groups appear to be extremely weak directing groups. Further, in such systems it would seem that comparatively small differences in directive power may lead to the formation of a single compound and not a mixture of isomerides as might be expected. These considerations seem to require a more extensive investigation of the substitution products of diphenyl ether before the relative directive effects of the phenoxyl or substituted phenoxyl groups can be correctly assessed.

The nitration of diphenyl ether under carefully regulated conditions was first undertaken, but the products were invariably mixtures of mono-, di-, and higher nitrodiphenyl ethers.

The halogenation of 4-nitrodiphenyl ether proceeded smoothly, the first substituent entering the 4′-position. Under very drastic conditions a second bromine atom could be introduced into the molecule in the 2′-position. The structures of the chloro- and bromo-compounds were established by synthesis from the potassium salt of the appropriately substituted phenol and *p*-chloronitrobenzene. The structure of the *iodo*-compound was dêtermined by conversion into 4-*bromo*-4′-*iododiphenyl ether* and comparison with a sample of this substance prepared from 4-bromo-4′nitrodiphenyl ether.

The direct substitution of 4-aminodiphenyl ether was attempted, but the product was invariably a highly coloured gum.

Chlorination of 4-acetamidodiphenyl ether in acetic acid solution yielded a dichloro-4-acetamidodiphenyl ether (m. p. 134°), and the same product was obtained by the chlorination of 4-*chloro*-4′-*acetamidodiphenyl ether*, thus establishing the position of one chlorine atom.

In acetic acid solution the bromination of 4-acetamidodiphenyl ether yielded 4-*bromo*-4′-*acetamidodiphenyl ether ;* since 4-bromo-

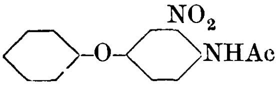
4′-nitrodiphenyl ether yielded the same compound on reduction and acetylation, the structure of this compound was established.

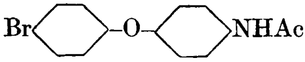
The introduction of a second bromine atom into the molecule of 4-acetamido- or 4-bromo-4′-acetamidodiphenyl ether was accompanied by considerable tarring, as was the case for the dichloro-compound, but a small quantity of a dibromo-4-acetamidodiphenyl ether (m. p. 145°) was isolated. The position of one bromine atom is fixed; that the second bromine atom is not in the 2-position in the same ring was proved by the reduction and acetylation of 2 : 4-*dibromo-4′-nitrodiphenyl ether*; the suggested structure is 3 : 4′-dibromo-4-acetamidodiphenyl ether.

Iodination of 4-acetamidodiphenyl ether was carried out in acetic acid solution with iodine monochloride. The structure of the product was determined by the reduction and acetylation of 4-*iodo-4′-nitrodiphenyl ether.*

The nitration of 4-acetamidodiphenyl ether and of those halogen derivatives obtained by direct substitution was carried out in glacial acetic acid solution at 80°. In each case a single product was obtained, the nitro-group entering the 3-position. Attempts were made to reduce the nitroacetamido-compound to the diamine and condense the product with benzaldehyde or benzil, but the products were highly coloured and not definitely crystalline. The structure assigned was based on the following facts: The nitro-base obtained on deacetylation did not yield a salt with a mineral acid; 3-acetamidodiphenyl ether was obtained on deamidation, reduction, and acetylation; the same product was obtained by bromination of 3-*nitro*-4-*acetamidodiphenyl ether* (I) as by nitration of 4-bromo-4′-acetamidodiphenyl ether (II); and 3-*nitro*-4-*aminodiphenyl ether* on deamination and bromination yielded the same product as deacetylation and deamination of 4′-*bromo*-3-*nitro*-4-*acetamidodiphenyl ether* (III). The last observation proves conclusively that the nitro-group and the bromine atom are not in the same nucleus. Nitration of 4-acetamidodiphenyl ether under other conditions was attempted, but no pure products could be isolated.

(I.)





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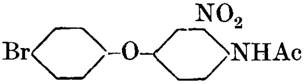

(III.)

The results obtained show that the presence of a nitro-group in one nucleus determines the entry of the second and the third substituent into the other nucleus. This effect would seem to be independent of the relative directive strengths of any other groups in the molecule. The substitution of 4-acetamidodiphenyl ether leads to conflicting results, since the halogens enter the 4′-position first, or, in the case of chlorine, the 3- and 4′-positions simultaneously, whereas the nitro-group enters the 3-position first. Thus, considering the introduction of the halogens, the acetamido- and the acetamidophenoxy-group would appear to be comparable in directive effect, the latter being rather the stronger. The position taken up by the nitro-group when substitution is effected in glacial acetic acid solution leads to the conclusion that the acetamido- is more strongly directive than the phenoxy-group. But, as work in the diphenyl series (J., 1927, 91, 3002) and in the azobenzene series has shown, the position taken up by a nitro-group is very susceptible to experimental conditions and the use of a strong mineral acid as solvent leads to substitution in the nucleus opposite to that containing the acetamido- or methoxy-group.

EXPERIMENTAL.

4-Nitrodiphenyl ether was prepared by heating, at 170—180° for 12 hours, a mixture of 2 parts of *p*-chloronitrobenzene and 1 part of sodium phenoxide in the presence of copper powder. The product was extracted in the manner described by Haussermann and Teichmann (*Ber.*, 1896, **29**, 1446).

4-Chloro-4′-nitrodiphenyl ether was obtained by (*a*) saturating a 5% solution of 4-nitrodiphenyl ether in acetic acid with chlorine and keeping it for 48 hours; (*b*) condensing potassium *p*-chlorophenoxide with *p*-chloronitrobenzene. It separated from methyl alcohol in needles, m. p. 76° (Found: Cl, 14·3. Calc. for $C_{12}H_8O_3NCl$: Cl, 14·2%).

4-Bromo-4′-nitrodiphenyl ether was prepared by (*a*) adding a slight excess of bromine to 4-nitrodiphenyl ether in acetic acid solution; (*b*) condensing *p*-chloronitrobenzene with potassium *p*-bromophenoxide. It separated from methyl alcohol in faintly yellow prisms, m. p. 61° (Found: C, 49·2; H, 2·8; Br, 27·1. Calc. for $C_{12}H_8O_3NBr$: C, 49·0; H, 2·7; Br, 27·2%).

4-*Iodo*-4′-*nitrodiphenyl Ether*.—10 G. of 4-nitrodiphenyl ether dissolved in 100 c.c. of acetic acid were gently warmed with 15 g. of iodine monochloride. The *product* crystallised from methyl alcohol in faintly yellow plates, m. p. 71° (Found: I, 37·3. $C_{12}H_8O_3NI$ requires I, 37·3%).

A stable *iododichloride* was precipitated, as yellow needles, when chlorine was led into an ice-cold solution of 4-iodo-4′-nitrodiphenyl ether in carbon tetrachloride (Found: Cl, 16·95. $C_{12}H_8O_3NCl_2I$ requires Cl, 17·2%).

2 : 4-*Dibromo*-4′-*nitrodiphenyl ether* was obtained when (*a*) a solution of 4-nitro- or 4-bromo-4′-nitro-diphenyl ether in dry bromine was kept for 24 hours; (*b*) potassium 2 : 4-dibromophenoxide was condensed with *p*-chloronitrobenzene at 210°. It separated from methyl alcohol in prisms, m. p. 81° (Found : C, 38·6; H, 2·05; Br, 42·85. $C_{12}H_7O_3NBr_2$ requires C, 38·6; H, 1·9; Br, 42·9%).

4-*Acetamidodiphenyl Ether*.—4-Nitrodiphenyl ether was reduced in alcoholic or ethereal hydrogen chloride solution with stannous chloride. The base was liberated from the tin double salt with 30% sodium hydroxide solution and extracted in the usual manner. The *hydrochloride* of the base separated from its solution in dilute hydrochloric acid in long needles, m. p. 238° (Found : HCl, 16·35. $C_{12}H_{11}ON,HCl$ requires HCl, 16·45%). The base was acetylated by refluxing it in acetic acid solution for 6 hours and the product separated from dilute methyl alcohol in heavy prisms, m. p. 127°.

4-*Chloro*-4′-*acetamidodiphenyl Ether*.—4-Chloro-4′-nitrodiphenyl ether was reduced in the usual manner. The base separated from methyl alcohol in prisms, m. p. 101°. The *acetyl* derivative crystallised from methyl alcohol in plates, m. p. 146° (Found : Cl, 13·6. $C_{14}H_{12}O_2NCl$ requires Cl, 13·6%).

4′-*Chloro*-3-*nitro*-4-*acetamidodiphenyl Ether*.—The nitration of 4-chloro-4′-acetamidodiphenyl ether was carried out in acetic acid solution at 80° with excess of nitric acid (*d* 1·5). A small yield of the same *product* was obtained when 3-nitro-4-acetamidodiphenyl ether was chlorinated in cold acetic acid solution. It separated from methyl alcohol in long yellow needles, m. p. 98° (Found : N, 9·25. $C_{14}H_{11}O_4N_2Cl$ requires N, 9·15%). On hydrolysis with ethylalcoholic hydrochloric acid 4′-*chloro*-3-*nitro*-4-*aminodiphenyl ether* resulted. The base separated from methyl alcohol in bright red needles, m. p. 114° (Found : N, 10·7; Cl, 13·4. $C_{12}H_9O_3N_2Cl$ requires N, 10·6; Cl, 13·4%). The base on deamination yielded 4′-*chloro*-3-*nitrodiphenyl ether*, which crystallised from light petroleum (b. p. 60—80°) in yellow prisms, m. p. 60° (Found : Cl, 14·3. $C_{12}H_8O_3NCl$ requires Cl, 14·2%).

4-*Bromo*-4′-*acetamidodiphenyl Ether*.—4-Acetamidodiphenyl ether was brominated in acetic acid solution in the presence of fused sodium acetate, or 4-bromo-4′-nitrodiphenyl ether was reduced and the base acetylated. The *acetyl* derivative separated from methyl alcohol in needles, m. p. 161° (Found : Br, 25·95. $C_{14}H_{12}O_2NBr$ requires Br, 26·1%).

4′-*Bromo*-3-*nitro*-4-*acetamidodiphenyl ether* was obtained when (*a*) 4-bromo-4′-acetamidodiphenyl ether was nitrated in acetic acid solution at 80° with excess of nitric acid (*d* 1·5); (*b*) 3-nitro-4-acetamidodiphenyl ether was brominated in acetic acid solution in presence of fused sodium acetate. It crystallised from methyl alcohol in matted yellow needles, m. p. 107° (Found : N, 7·95. $C_{14}H_{11}O_4N_2Br$ requires N, 7·95%). On hydrolysis with ethyl-alcoholic hydrochloric acid *4′-bromo-3-nitro-4-aminodiphenyl ether* was precipitated. The base separated from methyl alcohol in scarlet prisms, m. p. 144° (Found : Br, 25·95. $C_{12}H_9O_3N_2Br$ requires Br, 25·9%).

4′-Bromo-3-nitrodiphenyl ether was obtained by the deamination of the base. It crystallised from methyl alcohol in yellow prisms, m. p. 64° (Found : Br, 27·25. $C_{12}H_8O_3NBr$ requires Br, 27·25%).

4-Iodo-4′-acetamidodiphenyl ether was prepared by (*a*) iodination of 4-acetamidodiphenyl ether with iodine monochloride in acetic acid solution in the presence of fused sodium acetate; (*b*) the reduction of 4-iodo-4′-nitrodiphenyl ether in the usual manner and the acetylation of the base. It separated from methyl alcohol in plates, m. p. 174° (Found : I, 35·95. $C_{14}H_{12}O_2NI$ requires I, 35·95%). On hydrolysis of the acetyl derivative with ethyl-alcoholic hydrochloric acid *4-iodo-4′-aminodiphenyl ether* was liberated. It crystallised from methyl alcohol in prisms, m. p. 91° (Found : I, 40·8. $C_{12}H_{10}ONI$ requires I, 40·8%).

4′-Iodo-3-nitro-4-acetamidodiphenyl ether was obtained when (*a*) 4-iodo-4′-acetamidodiphenyl ether was nitrated in glacial acetic acid solution at 80°; (*b*) in small yield when 3-nitro-4-acetamidodiphenyl ether was iodinated with iodine monochloride in acetic acid solution. The product separated from methyl alcohol in yellow needles, m. p. 123° (Found : I, 31·95. $C_{14}H_{11}O_4N_2I$ requires I, 31·9%). On hydrolysis with ethyl-alcoholic hydrochloric acid *4′-iodo-3-nitro-4-aminodiphenyl ether* was precipitated. The base crystallised from methyl alcohol in scarlet needles, m. p. 155° (Found : I, 35·6. $C_{12}H_9O_3N_2I$ requires I, 35·7%).

3-Nitro-4-acetamidodiphenyl ether was obtained by the nitration of 4-acetamidodiphenyl ether in acetic acid solution at 80°. It separated from methyl alcohol in deep yellow needles, m. p. 100° (Found : N, 10·45. $C_{14}H_{12}O_4N_2$ requires N, 10·35%). On hydrolysis with ethyl-alcoholic hydrochloric acid *3-nitro-4-aminodiphenyl ether* was precipitated as a black oil. The base crystallised from dilute methyl alcohol in bright red prisms, m. p. 82° (Found : N, 12·1. $C_{12}H_{10}O_3N_2$ requires N, 12·2%). On deamination the base yielded an oil, b. p. 205°/15 mm., which was reduced and acetylated in the usual manner. The product crystallised from dilute methyl alcohol in needles, m. p. 83° (Found : N, 6·25. Calc. for $C_{14}H_{13}O_2N$: N, 6·15%). This acetyl derivative thus corresponds to 3-acetamidodiphenyl ether which was prepared by Ullmann (*Annalen*, 1906, **350**, 103) from *m*-chloronitrobenzene and potassium phenoxide in the presence of copper powder and subsequent reduction and acetylation of the condensation product.

2 : 4-*Dibromo-4′-acetamidodiphenyl ether* was obtained by the reduction of 2 : 4-dibromo-4′-nitrodiphenyl ether in the usual manner and subsequent acetylation of the base. It separated from dilute acetone or dilute acetic acid in needles, m. p. 158° (Found : Br, 41·7. $C_{14}H_{11}O_2NBr_2$ requires Br, 41·5%).

2 : 4-*Dibromo-3′-nitro-4′-acetamidodiphenyl ether* was obtained when 2 : 4-dibromo-4′-acetamidodiphenyl ether was nitrated in glacial acetic acid solution at 80°. It crystallised from methyl alcohol in long yellow needles, m. p. 141° (Found : C, 39·05; H, 2·3. $C_{14}H_{10}O_4N_2Br_2$ requires C, 39·05; H, 2·3%).

On hydrolysis with ethyl-alcoholic hydrochloric acid 2 : 4-*dibromo-3′-nitro-4′-aminodiphenyl ether* was precipitated. The base separated from methyl alcohol in yellow prisms, m. p. 107° (Found : Br, 41·3. $C_{12}H_8O_3N_2Br_2$ requires Br, 41·25%).

2 : 4-*Dibromo-3′-nitrodiphenyl ether* was obtained by the deamination of 2 : 4-dibromo-3′-nitro-4′-aminodiphenyl ether. It separated from dilute methyl alcohol in thick orange needles, m. p. 72° (Found : Br, 42·8. $C_{12}H_7O_3NBr_2$ requires Br, 42·9%).

4-*Iododiphenyl ether* was obtained by the diazotisation of 4-aminodiphenyl ether in dilute hydrochloric acid solution and treatment with potassium iodide. The product, obtained in a crude state by distillation in steam, separated from dilute methyl alcohol in plates, m. p. 48° (Found : I, 42·9. $C_{12}H_9OI$ requires I, 42·9%). A stable *dichloride* separated in yellow needles when chlorine was passed into a 5% solution of 4-iododiphenyl ether in carbon tetrachloride (Found: Cl, 19·0. $C_{12}H_9OCl_2I$ requires Cl, 19·3%).

4-*Bromo-4′-iododiphenyl ether* was prepared (*a*) by bromination of 4-iododiphenyl ether in acetic acid solution, and (*b*) by diazotisation of 4-bromo-4′-aminodiphenyl ether and treatment with potassium iodide. It separated from dilute methyl alcohol in plates, m. p. 72° (0·1426 g. gave 0·1611 g. of silver halides. Theory requires 0·1608 g.). 4 : 4′-*Di-iododiphenyl ether* was obtained when (*a*) diphenyl ether was treated with an excess of iodine monochloride in acetic acid solution, and (*b*) 4-iodo-4′-aminodiphenyl ether was diazotised and treated with potassium iodide. It separated from methyl alcohol in plates, m. p. 139° (Found : I, 60·1. $C_{12}H_8OI_2$ requires I, 60·2%).

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