CLVI.—*Higher Substitution Products of 4-Aminodiphenyl.*

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THE study of the substitution reactions of the monoacid bases of the diphenyl series (J., 1926, 557; this vol., p. 89) has been extended to include an examination of the products obtained by the further substitution of 3-chloro-4-aminodiphenyl, 3-nitro-4-aminodiphenyl, and their acetyl derivatives.

In every case, the introduction of one more substituent group into the free base proceeds with great ease at room temperature, and leads invariably to a product substituted in the 5-position. Thus 3-chloro- and 3-nitro-4-aminodiphenyl, on treatment with bromine in dilute acetic acid solution, yield 3-chloro-5-bromo-4-aminodiphenyl and 5-bromo-3-nitro-4-aminodiphenyl respectively. The introduction of any further substituent requires more drastic methods, particularly in the case of the 5-bromo-3-nitro-4-aminodiphenyl, and the substituent enters the 4′-position.

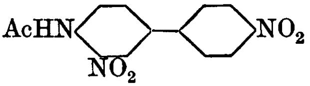
In contrast to the observed reactivity of the free bases, it is found that the further substitution of their acetyl derivatives proceeds only at high temperatures, in the presence of catalysts, or under other drastic conditions, and in every case the substituent enters the 4′-position. Thus 3-chloro-4-acetamidodiphenyl can be monobrominated by the use of pyridine as a catalyst, and mononitrated by dissolving it in nitric acid (*d* 1·4) at room temperature.

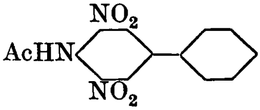
By still more drastic treatment, it has been found possible to obtain a dinitro-substitution product, which is probably 3-chloro-5 : 4′-dinitro-4-acetamidodiphenyl, but there is no evidence of the formation of a dibromo-derivative, although the free base, 3-chloro-4′-bromo-4-aminodiphenyl, can be brominated with great ease to yield 3-chloro-5 : 4′-dibromo-4-aminodiphenyl.

3-Nitro-4-acetamidodiphenyl is still less reactive, for it is only partly chlorinated by the prolonged action of dry chlorine in boiling glacial acetic acid solution, whilst bromination with the use of pyridine as a catalyst leads to only a 60% yield of 4′-bromo-3-nitro-4-aminodiphenyl, identical with the product obtained by Le Fèvre and Turner (J., 1926, 2045) by the nitration of 4′-bromo-4-acetamidodiphenyl.

The dinitration of 4-acetamidodiphenyl leads to a quantitative yield of 3 : 4′-dinitro-4-acetamidodiphenyl (I), for which the structure of 3 : 5-dinitro-4-acetamidodiphenyl (II) had previously been suggested by Fichter and Sulzberger (*Ber.*, 1904, **37**, 878) without any proof having been given.

(I.)





(II.)

The corrected structure (I) follows from the fact that the substance can be oxidised to *p*-nitrobenzoic acid.

From an examination of all recorded disubstitution reactions of 4-aminodiphenyl and its derivatives it may be seen that, whereas the free base yields derivatives substituted in the 3- and 5-positions, the acetyl derivative yields derivatives substituted in the 3- and 4′-positions.

This difference in mode of reaction must probably be ascribed to the inhibiting effect of the acetyl group, which decreases the activating power of the amino-group on the adjacent 3- and 5-positions in the same ring to such an extent that the normal ortho-para directive influence of the phenyl group predominates and leads to substitution in the 4′-position.

Although a substituted amino-group normally leads to substitution in the same ring in the first instance, thus showing that the difference in the type of the reaction cannot be solely due to steric hindrance, yet there are recorded instances in which substitution takes place initially in the 4′-position in the opposite ring. Of these, the bromination of 4-acetamidodiphenyl and the nitration of 2-acetamidodiphenyl have already been noted by the authors, and it has been suggested (J., 1926, 557) that these differences may possibly arise in consequence of differences of mechanisms of the substitution reactions. In particular, it has been thought possible that the initial rapid substitution in the same ring as an acetamido-group may be brought about by a mechanism involving an initial attack on the " side chain " followed by a migration reaction (which has been proved to yield the same type of product), and that the far slower substitution in the opposite ring might be due to a direct attack of the substituting group on the aromatic nucleus.

In an attempt to test this hypothesis, an examination of the reactivity towards substitution reagents of diacetyl-4-aminodiphenyl and of 4-phthalimidodiphenyl, which do not contain any hydrogen atom available for indirect attack, has been carried out. In each case it has been found that the reactivity of the molecule was still further decreased by the complete substitution of the amino-group, but unfortunately it has not been possible to isolate any definite substitution products.

4-Diacetylaminodiphenyl could not be attacked under conditions which did not first bring about hydrolysis of at least one of the acetyl groups, whilst 4-phthalimidodiphenyl was found to be too insoluble in the common reagents to be attacked except under conditions which lead to complete decomposition.

It may be noted, however, that the nitration of 4-benzylideneaminodiphenyl (Bell and Kenyon, J., 1926, 2707) and of 4-diphenylyltrimethylammonium nitrate (Vorländer, *Ber.*, 1925, **58**, 1893) in the 4′-position affords direct support for the view that substitution in the 4′-position is a direct reaction which will occur preferentially when indirect substitution is precluded.

As the disubstitution of 4-acetamidodiphenyl would seem to lead generally to substitution in the opposite ring, it would appear that the presence of a substituent group in the adjacent 3-position must also inhibit further substitution in the same ring. In accordance with the statement of Chattaway and Dowden (J., 1924, **125**, 1195) that the migration of a *N*-halogeno-derivative of a substituted acetanilide proceeds less and less readily as the number of substituent groups, especially nitro-groups, is increased, it may be suggested that the observed effect is due to the inhibition of any indirect reactions.

The effect of the nitro-group in 3-nitro-4-acetamidodiphenyl is most marked, for it would seem that not only does it prevent further substitution from taking place in the same ring, but also that it decreases the velocity of substitution in the other ring. This effect is in agreement with the known general effect of the nitro-group in making substitution more difficult to carry out, and it may be used to provide an explanation of the cases of unsymmetrical substitution in the diphenyl series which have been investigated recently.

For example, in the substitution of 4 : 4′-dichlorodiphenyl (compare Le Fèvre and Turner, J., 1926, 476, 2041) the C_6H_4Cl-group in the first instance has a stronger directive influence than the chlorine atom, and thus substitution occurs in the 2-position, but in the resultant compound the nitro-group has so reduced the directive power of the substituted phenyl group $C_6H_3(NO_2)Cl\cdot$ that the chlorine atom has the predominating directive influence, and in consequence a 3′-substituted derivative is produced.

The unsymmetrical nitration of diphthalylbenzidine may be explained similarly, and it may be noted that here also the phthalyl group plays the part of an inhibitor, in enabling the substituted phenyl group ($-C_6H_4\cdot N\colon Phth$) to have a more powerful directive influence than the substituted amino-group ($-N\colon Phth$) in the first instance (compare Brady, Quick, and Welling, J., 1925, **127**, 2265).

EXPERIMENTAL.

3-*Chloro-5-bromo-4-aminodiphenyl.*—3-Chloro-4-aminodiphenyl (J., 1926, 560), dissolved in cold glacial acetic acid, containing an excess of powdered anhydrous sodium acetate, was treated with bromine (1 mol.) as a 10% solution in the same solvent. The product was separated after 5 minutes by pouring the mixture into water; it crystallised from alcohol in colourless needles, m. p. 107° (Found : 0·1515 g. gave 0·1774 g. of silver halides. Calc. weight, 0·1776 g.). The *benzoyl* derivative crystallised from methyl alcohol in fine needles, m. p. 222° (Found : 0·1633 g. gave 0·1401 g. of silver halides. Calc. weight, 0·1400 g.).

3-*Chloro-5-bromodiphenyl*, obtained from the base by the elimination of the amino-group in the usual manner, formed pale yellow needles, m. p. 29°, b. p. 225°/30 mm. (Found : 0·2283 g. gave 0·2846 g. of silver halides. Calc. weight, 0·2827 g.). On oxidation with chromic anhydride in glacial acetic acid solution, it yielded 3-chloro-5-bromobenzoic acid (m. p. 193°).

3-*Chloro*-5 : 4′-*dibromo*-4-*aminodiphenyl.*—3-Chloro-5-bromo-4-aminodiphenyl was boiled for 3 hours with an excess of bromine in glacial acetic acid solution. The solid which was separated by pouring the mixture into water proved to be partly acetylated, and therefore was hydrolysed by boiling it for 6 hours with alcoholic hydrochloric acid. The pure base then separated, and crystallised from alcohol in long needles, m. p. 129° (Found : 0·2010 g. gave 0·2885 g. of silver halides. Calc. weight, 0·2888 g.). By boiling this base for 8 hours with acetic acid and acetic anhydride, the *diacetyl* derivative was obtained, crystallising from dilute acetic acid in white needles, m. p. 147° (Found : C, 42·9; H, 2·8. Calc.: C, 43·05; H, 2·7%. 0·1716 G. gave 0·2007 g. of silver halides. Calc. weight, 0·2013 g.).

3-*Chloro*-4′-*bromo*-4-*acetamidodiphenyl*.—5 G. of 3-chloro-4-acetamidodiphenyl (*loc. cit.*), 10 g. of anhydrous sodium acetate, and 1 c.c. of pyridine were intimately mixed together, 5 c.c. of bromine were added slowly, and the mixture was heated at 100° for 3 hours. The product was separated from the reaction mixture in 60% yield by repeated crystallisation from methyl alcohol and from dilute acetic acid, and formed white needles, m. p. 185° (Found : 0·1600 g. gave 0·1630 g. of silver halides. Calc. weight, 0·1633 g.). On oxidation with chromic anhydride in glacial acetic acid solution, it yielded *p*-bromobenzoic acid (m. p. 252°). The corresponding *base*, obtained by boiling the acetyl derivative for 4 days with 20% alcoholic hydrochloric acid, crystallised from methyl alcohol in white needles, m. p. 108° (Found : 0·1208 g. gave 0·1421 g. of silver halides. Calc. weight, 0·1417 g.). The base on warming with bromine in acetic acid yielded 3-chloro-5 : 4′-dibromo-4-aminodiphenyl which, alone or mixed with the product obtained by the alternative method, melted at 129°.

3-*Chloro*-4′-*nitro*-4-*acetamidodiphenyl*.—3-Chloro-4-acetamidodiphenyl was gradually dissolved in nitric acid (*d* 1·4) at room temperature, and after ½ hour the solution was poured on ice. The solid produced was washed with dilute ammonia and dissolved in a large volume of alcohol, from which it was deposited, on cooling, in fine yellow needles, m. p. 220·5° (Found: N, 9·4; Cl, 12·1. $C_{14}H_{11}O_3N_2Cl$ requires N, 9·6; Cl, 12·2%). On oxidation with chromic anhydride in glacial acetic acid solution, *p*-nitrobenzoic acid (m. p. 240°) was produced.

3-*Chloro*-5:4′-*dinitro*-4-*acetamidodiphenyl*.—3-Chloro-4-acetamidodiphenyl was gradually dissolved in nitric acid (*d* 1·5) at room temperature, and after 3 hours the solution was poured on ice. The solid produced was washed with dilute ammonia and extracted with alcohol; the residue crystallised from a large volume of methyl alcohol in fine, pale yellow needles, m. p. 250° (Found: N, 12·7; Cl, 10·55. $C_{14}H_{10}O_5N_3Cl$ requires N, 12·5; Cl, 10·55%). The substance was not oxidised by boiling with chromic anhydride in glacial acetic acid solution. Such stability is characteristic of diphenyl derivatives containing a nitro-group in each ring.

5-Bromo-3-nitro-4-aminodiphenyl.—3-Nitro-4-aminodiphenyl (Fichter and Sulzberger, *loc. cit.*), dissolved in glacial acetic acid at 30–40°, was treated gradually with bromine (1 mol.) as a 10% solution in the same solvent. The product was separated after $\frac{1}{2}$ hour by pouring the mixture into water, and, on attempted crystallisation from any of the common solvents, formed a very flocculent, orange-yellow mass of m. p. 99—101° which could not be freed from traces of more highly brominated substances (Found: Br, 30·1, 29·95. $C_{12}H_9O_2N_2Br$ requires Br, 27·3%). A similar mixture was obtained by the bromination of 3-nitro-4-aminodiphenyl in chloroform solution. An attempt at separation of a pure product by acetylation of the mixture was not successful.

By eliminating the amino-group in the usual manner, *5-bromo-3-nitrodiphenyl* was obtained in a pure form in more than 60% yield. It crystallised from alcohol in pale yellow needles, m. p. 72°, b. p. 240—250°/30 mm. (Found: Br, 28·8. $C_{12}H_8O_2NBr$ requires Br, 28·8%). On oxidation with chromic anhydride in glacial acetic acid solution, it yielded 5-bromo-3-nitrobenzoic acid (m. p. 159—160°).

5 : 4′-Dibromo-3-nitro-4-aminodiphenyl.—5-Bromo-3-nitro-4-aminodiphenyl was heated at 100° for 6 hours with excess of bromine in glacial acetic acid solution, and the product, which was separated by pouring the mixture into water, was recrystallised from dilute acetic acid, forming red needles, m. p. 158° (Found: Br, 42·9. $C_{12}H_8O_2N_2Br_2$ requires Br, 43·0%). On oxidation with chromic anhydride in glacial acetic acid solution, it yielded *p*-bromobenzoic acid (m. p. 253°).

The same product was obtained in poor yield by boiling 3-nitro-4-acetamidodiphenyl for 4 days with a large excess of bromine in glacial acetic acid solution.

4′-Chloro-3-nitro-4-acetamidodiphenyl.—Chlorine was passed for 4 hours into a solution of 10 g. of 3-nitro-4-acetamidodiphenyl and 20 g. of anhydrous sodium acetate in 200 c.c. of boiling glacial acetic acid. After cooling, excess of chlorine was removed with a current of air and water was added; a red gum was then deposited. This was extracted with hot alcohol and yielded 3 g. of bright yellow needles, m. p. 199° (Found: Cl, 12·15. $C_{14}H_{11}O_3N_2Cl$ requires Cl, 12·2%). On oxidation with chromic anhydride in glacial acetic acid solution, it yielded *p*-chlorobenzoic acid (m. p. 240°).

The corresponding *base* was obtained by boiling the acetyl derivative for 4 hours with 20% alcoholic hydrochloric acid, and crystallised from dilute acetone in scarlet needles, m. p. 174° (Found: Cl, 14·4. $C_{12}H_9O_2N_2Cl$ requires Cl, 14·3%).

4′-Bromo-3-nitro-4-acetamidodiphenyl.—5 G. of 3-nitro-4-acetamidodiphenyl, 10 g. of powdered anhydrous sodium acetate, and 1 c.c. of pyridine were intimately mixed together, 5 c.c. of bromine were gradually added, and the mixture was heated at 100° for 8 hours. The brominated product was isolated from the reaction mixture in 60% yield by extraction with acetone, and crystallised from that solvent in fine yellow plates, m. p. 207—208° (Found: Br, 24·0. Calc. for $C_{14}H_{11}O_3N_2Br$: Br, 23·9%). On oxidation with chromic anhydride in glacial acetic acid solution it yielded *p*-bromobenzoic acid (m. p. 253°). On hydrolysis with 20% alcoholic hydrobromic acid, the corresponding base was obtained, crystallising readily from dilute acetone in scarlet needles, m. p. 175° (Found: Br, 27·3. Calc. for $C_{12}H_9O_2N_2Br$: Br, 27·3%). Both the acetyl derivative and the base are obviously identical with the products obtained by Le Fèvre and Turner (J., 1926, 2045) by the nitration of 4′-bromo-4-acetamidodiphenyl.

3 : *4′-Dinitro-4-acetamidodiphenyl.*—10 G. of 3-nitro-4-acetamidodiphenyl, dissolved in a mixture of 20 c.c. of concentrated sulphuric acid and 10 c.c. of glacial acetic acid at 0°, were treated during 2 hours with a mixture of 6 c.c. of fuming nitric acid and 14 c.c. of glacial acetic acid. After 24 hours, the product was poured on ice, and the yellow solid produced crystallised from glacial acetic acid and then from a large volume of acetone. From the latter solvent it formed long, pale yellow needles, m. p. 243—244° (corr.), obviously identical with the dinitro-4-acetamidodiphenyl, m. p. 240—241° (uncorr.), of Fichter and Sulzberger (*loc. cit.*). The same substance could be obtained more easily by dissolving 4-acetamidodiphenyl in cold fuming nitric acid and pouring the solution on ice after 30 minutes.

On prolonged oxidation with chromic anhydride in glacial acetic acid solution, *p*-nitrobenzoic acid (m. p. 240—241°) was produced, showing conclusively that the second nitro-group had entered the 4′- and not the 5-position.

The corresponding *base* was obtained by boiling 5 g. of the acetyl derivative with a mixture of 10 c.c. of concentrated sulphuric acid and 200 c.c. of alcohol for 2 days. It crystallised from a large bulk of alcohol in orange plates, m. p. 233—234°, corresponding exactly in properties with the base of Fichter and Sulzberger.

3 : *4′-Dinitrodiphenyl,* obtained from the base by the elimination of the amino-group in the usual manner, crystallised from acetone in pale yellow needles, m. p. 189° (Found: N, 11·5. Calc.: N, 11·5%). Mention has already been made of the use of this compound for structure determination (this vol., p. 96).

Diacetyl-4-aminodiphenyl was obtained by boiling 4-acetamidodiphenyl (10 g.) with acetic anhydride (50 c.c.) and anhydrous sodium acetate (5 g.) for 6 hours. It crystallised from light petroleum (b. p. 60—80°) in fine, white needles, m. p. 121° (Found: C, 75·55; H, 6·0. $C_{16}H_{15}O_2N$ requires C, 75·85; H, 5·9%).

It was not attacked by chlorine in cold 5% solution, but was hydrolysed on warming in presence of chlorine. There was no action on warming with 1 mol. of bromine in presence of anhydrous sodium acetate and a drop of pyridine, but complete decomposition occurred when a large excess of bromine was used.

On dissolving the diacetyl compound in nitric acid (*d* 1·4) at 0° and pouring the solution into ice and water after 10 minutes, a nitrated mixture was formed from which were separated pure specimens of 3-nitro-4-(mono)acetamidodiphenyl, m. p. 132°, and 3 : 4′-dinitro-4-(mono)acetamidodiphenyl, m. p. 244°; both were identified by mixed melting-point determinations with specimens obtained by the normal methods, and occurred in such quantities as to correspond to more than 70% of the theoretical yield of nitrated products.

4-*Phthalimidodiphenyl* was prepared by heating equivalent quantities of phthalic anhydride and 4-aminodiphenyl at 160° for 6 hours. It was a white powder, m. p. 288°, almost insoluble in all low-boiling solvents, but could be purified by long-continued extraction, in a Soxhlet apparatus, with boiling benzene. For analysis, it was separated twice from a large bulk of toluene and finally from xylene (Found: C, 80·3; H, 4·3. $C_{20}H_{13}O_2N$ requires C, 80·25; H, 4·4%).

The substance was insoluble in fuming nitric acid at room temperature, and was not attacked by bromine in presence of pyridine at 100°. It was decomposed completely by nitration in a large volume of concentrated sulphuric acid.

All the m. p.'s recorded in this paper have been corrected, and where necessary the identity of a substituted benzoic acid has been established by the "mixed m. p." method.

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