134. *The Nuclear Alkylation of Aromatic Bases. Part II. The Action of Methyl Alcohol on the Hydrochlorides of 2- and 4-Aminodiphenyl.*

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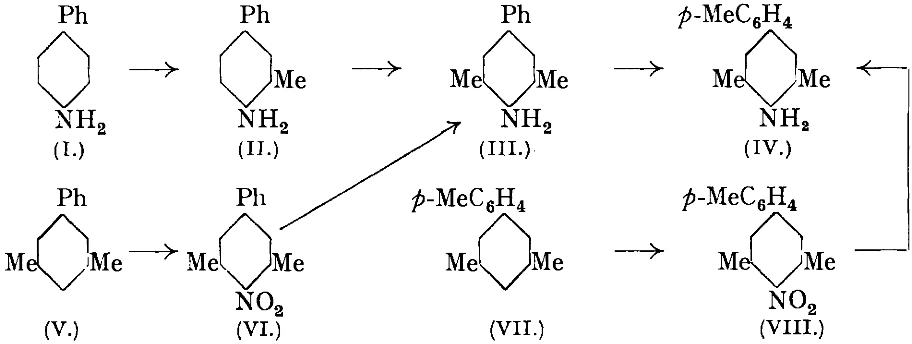
A FEW examples are known which involve the real or the apparent migration of a substituent group from a side chain to the nucleus in the diphenyl series. Scarborough and his co-workers, for example, obtained nuclear-chlorinated acetamidodiphenyls from *N*-chloroacetamidodiphenyls (J., 1926, 557; 1927, 89, 3000; compare also Bell, Kenyon, and Robinson, J., 1926, 1239). In no case, however, has heteronuclear migration to the 4′-position been observed.

The reaction whereby nuclear methylation is effected by heating an amine hydrochloride with methyl alcohol belongs, possibly exclusively, to the intermolecular type of reaction and it therefore seemed likely that this reaction might provide an example of 4′-substitution by " molecular rearrangement," as indeed proved to be the case. Other methods for effecting nuclear alkylation by the rearrangement of arylalkylamines, however, do not necessarily belong to this type, as shown by Hickinbottom and his co-workers (J., 1927, 64; 1930, 1558, 1566; etc.). The molecular rearrangements of the chloroacetamidodiphenyls studied by Scarborough also belong to the intermolecular type, but these reactions are apparently not applicable to successive substitution to the same extent as shown in the methylation reaction here studied, and consequently they never reach a stage at which substitution in the 4′-position becomes possible, since the requirements of at least one of the two ortho-positions have to be satisfied first.

When the hydrochlorides of 2- and 4-aminodiphenyl were heated with various proportions of methyl alcohol in an autoclave at 250—300°, nuclear methylation of 4-aminodiphenyl proceeded readily to give a product consisting largely of primary bases, but the product obtained from 2-aminodiphenyl consisted largely of secondary and tertiary bases, including a derivative of phenanthridine. This result was not unexpected, since Bell (J., 1930, 1071) has shown that 2-aminodiphenyl is much more resistant than 4-aminodiphenyl to *N*-methylation, and *N*-methylation must precede *C*-methylation. Attention has also been recently drawn by Lesslie and Turner (J., 1933, 1588) to the considerable steric effects about the nitrogen atom attached to the 2-position in the diphenyl nucleus. Further, fewer by-products were obtained in the diphenyl than in the benzene series (Part I; J., 1931, 1581) : small quantities of acridine-like bases were obtained, but, apart from traces of alkali-soluble material, there was no evidence of phenol formation. Nevertheless, the liberation of volatile bases on the addition of alkali to the reaction product shows that some separation of the nitrogen atom from the nucleus must have taken place.

The action of methyl alcohol on the hydrochloride of 4-aminodiphenyl (I) led to nuclear methylation successively at positions 3, 5, and 4′, as indicated below: it is thus analogous to the bromination of 4-aminodiphenyl (Scarborough and Waters, J., 1926, 561). With $1\frac{1}{2}$ mols. of methyl alcohol, the aminodiphenyl was largely recovered unchanged. With 3 mols. of methyl alcohol, a good yield of primary bases was obtained, from which 4-amino-3 : 5-dimethyldiphenyl (III) and 4-amino-3 : 5 : 4′-trimethyldiphenyl (IV) were isolated (as *acetyl* derivatives): 4-amino-3-methyldiphenyl (II) was not detected, although it must have been an essential intermediate product, and 4-acetamido-3 : 4′-dimethyldiphenyl could not be detected in the acetylated product. With 6 mols. of methyl alcohol, a small quantity of 4-amino-3 : 5 : 4′-trimethyldiphenyl (IV) was isolated as its acetyl derivative, but the major portion of the product consisted of secondary and tertiary bases. This result shows that it is not possible to effect further nuclear methylation, under the conditions mentioned, by increasing the amount of methyl alcohol beyond 3 mols., and higher methylated products can be expected only if an already methylated compound such as 4-dimethylamino-3 : 5 : 4′-trimethyldiphenyl is used as the initial material (compare Part I).



3 : 5-*Dimethyldiphenyl* (V) on nitration gave 4-nitro-3 : 5-dimethyldiphenyl (VI), which on reduction and acetylation gave 4-*acetamido*-3 : 5-*dimethyldiphenyl*. From 3 : 4′-dimethyldiphenyl were similarly obtained 4-nitro-3 : 4′-dimethyldiphenyl and 4-acetamido-3 : 4′-dimethyldiphenyl, while 3 : 5 : 4′-*trimethyldiphenyl* (VII) gave 4-*nitro*-3 : 5 : 4′-*trimethyldiphenyl* (VIII) and 4-*acetamido*-3 : 5 : 4′-*trimethyldiphenyl*. Previous work on the nitration of methyldiphenyls (Grieve and Hey, J., 1932, 1888, 2245; Hey, *ibid.*, p. 2636) indicated that in all three cases mononitration would probably take place at the 4-position, as required, and the identity of the synthetic 4-acetamido-3 : 5-dimethyldiphenyl and 4-acetamido-3 : 5 : 4′-trimethyldiphenyl with the acetylated products obtained from the methylation of 4-aminodiphenyl confirms this view.

Further confirmatory evidence of the identity of the products of the nuclear methylation of 4-aminodiphenyl was obtained by oxidation of the acetylated bases with chromic acid, 4-acetamido-3 : 5 : 4′-trimethyldiphenyl and 4-acetamido-3 : 5-dimethyldiphenyl giving terephthalic and benzoic acid respectively. The acetamidotrimethyldiphenyl was also oxidised with neutral potassium permanganate to give 4-acetamidodiphenyl-3 : 5 : 4′-tricarboxylic acid. The bromometric titration method of Callan and Henderson (*J. Soc. Chem. Ind.*, 1922, **41**, 161T) proved unsuitable as a means of identification (compare also Francis, *J. Amer. Chem. Soc.*, 1926, **48**, 1631; Hey and Grieve, J., 1932, 2246; Hey, *ibid.*, p. 2638).

In the parallel work on 2-aminodiphenyl hydrochloride, 3 and 4 mols. of methyl alcohol were used. The application of the Hinsberg method of separation, as well as treatment with nitrous acid, showed that the products contained mainly tertiary, some secondary, and hardly any primary bases. The tertiary basic portion readily formed a yellow crystalline *methiodide*, which gave a clear colourless solution in hot water. Such behaviour is characteristic of methiodides of the phenanthridine series (Pictet and Hubert, *Ber.*, 1896, **29**, 1182), and the identity of the tertiary base as a dimethylphenanthridine is further supported by the analysis of its methiodide. For comparative purposes the *methiodide* of 2-dimethylaminodiphenyl was prepared and, as anticipated, this showed no yellow colour, whereas the methiodide of 9-methylphenanthridine, prepared by the method of Morgan and Walls (J., 1931, 2447), simulated very closely the behaviour of the above product, which may be 1 : 3-, 3 : 9-, or 1 : 9-dimethylphenanthridine.

EXPERIMENTAL.

The apparatus and the general experimental conditions were similar to those described in Part I (*loc. cit.*). The autoclave was of " Monel " metal, electrically heated, and of 250 c.c. capacity. The reaction mixture was contained in a close-fitting open Pyrex vessel within the autoclave. In some experiments the thermometer pocket of the autoclave was dispensed with, the temperature being regulated by the amount of current applied.

The Action of Methyl Alcohol on 4-Aminodiphenyl Hydrochloride.—(A) *With* 1½ *mols. of methyl alcohol.* 4-Aminodiphenyl hydrochloride (50 g.) and methyl alcohol (12 g.) were heated in the autoclave at 250—300° for 12 hours. The product was extracted successively with 50% sulphuric acid, hot water and alkali solution, and the total extract was distilled with steam from strongly acid solution. Even after many hours the distillate contained only 0·5 g. of a colourless nitrogenous oil insoluble in aqueous alkali. The residue was made alkaline with sodium hydroxide (an ammoniacal fishy odour being produced) and subjected to prolonged distillation with steam. Ether extracted from the distillate a colourless oil (5 g.), which on acetylation gave 4-acetamidodiphenyl, m. p. (after crystallisation from dilute alcohol) and mixed m. p. 163—165°. The alkaline liquor was then extracted with benzene, evaporation of which left a red oil (0·5 g.), which partly solidified and after trituration with absolute alcohol and crystallisation from this solvent gave bisdiphenylylamine in nacreous leaflets, m. p. 205° (Found : C, 89·6; H, 5·45. Calc. for $C_{24}H_{19}N$: C, 89·7; H, 5·9%). The total yield of bases in this experiment was poor owing to carbonisation.

(B) *With* 3 *mols. of methyl alcohol.* 4-Aminodiphenyl hydrochloride (50 g.) and methyl alcohol (24 g.) were heated at 250—300° for 12 hours. The product was treated as in (A), a colourless nitrogenous oil (2 g.) being obtained from the acid solution by prolonged distillation with steam. The residual acid solution was made alkaline with sodium hydroxide (ammoniacal fishy odour); the liberated bases were extracted with benzene, since distillation with steam was slow and inefficient. The benzene extract, dried over sodium sulphate, exhibited a green fluorescence, and after removal of the solvent the residue was distilled to give three fractions, b. p.'s 285—290° (5 g.), 290—310° (8 g.), and 310—330° (7 g.), consisting of viscous yellow oils. These were acetylated separately with acetic anhydride and the resulting derivatives were crystallised from alcohol until three main batches, m. p.'s (i) 185—195°, (ii) 200—210°, and (iii) 210—230°, were obtained. Fraction (i) was small, and no material corresponding to 4-acetamido-3-methyldiphenyl (m. p. 166°) could be isolated. Further crystallisation of fraction (ii) gave a product, m. p. 198—200°, not depressed by admixture with 4-acetamido-3 : 5-dimethyldiphenyl (m. p. 200—201°), but pronouncedly depressed by 4-acetamido-3 : 4'-dimethyldiphenyl (m. p. 206°). The absence of a product methylated at the 4'-position in this fraction was confirmed by oxidation with chromic acid as described below. Further crystallisation of fraction (iii) from slightly diluted acetic acid gave a product, m. p. 238—240°, not depressed by 4-acetamido-3 : 5 : 4'-trimethyldiphenyl (m. p. 241°), and confirmation of its identity was obtained by oxidation, as described below.

(C) *With* 6 *mols. of methyl alcohol.* 4-Aminodiphenyl hydrochloride (50 g.) and methyl alcohol (47 g.) were heated at 250—300° for 12 hours. After removal from the autoclave, as previously described, the product was extracted with benzene from strongly acid solution. The aqueous acid layer was then made alkaline (evolution of volatile bases) and again extracted with benzene. The dried benzene extract from the acid solution left, on removal of the solvent, a brown viscous nitrogenous oil (3 g., b. p. *ca.* 360°). Removal of the solvent from the dried benzene extract from the alkaline solution left a residue, which was distilled to give three yellow oily fractions : (i) b. p. 320—330° (10 g.), (ii) 330—340° (5 g.), and (iii) 340—360° (2 g.). Distillation of the residue under reduced pressure gave a little yellow viscous oil, from which on trituration with absolute alcohol a yellow-brown solid, apparently a derivative of acridine, separated. The three main basic fractions, separately acetylated with acetic anhydride, gave small yields of acetylated products, indicating a high percentage of tertiary bases in the oils. From fraction (iii), however, was obtained 4-acetamido-3 : 5 : 4'-trimethyldiphenyl (0·5 g.), m. p. 236—239°, not depressed by an authentic specimen (m. p. 241°). After removal of the solid acetylated products from fractions (i) and (ii), the oily residues were recovered, after boiling with hydrochloric acid, and shown qualitatively to consist largely of tertiary bases together with some secondary bases.

Oxidation Experiments on the Products from Experiment (*B*).—(i) The acetyl derivative (2 g.), m. p. 198—200°, in glacial acetic acid (20 c.c.) was boiled under reflux while a concentrated solution of chromic anhydride in 90% acetic acid was gradually added. After a few hours the product was poured into water, and ether extracted benzoic acid, m. p. and mixed m. p. 120°.

(ii) The acetyl derivative, m. p. 238—240°, was oxidised as described above. The precipitate obtained on dilution with water and also the solid extracted by ether were shown to be terephthalic acid by the preparation of the dimethyl ester (m. p. 139—140°).

(iii) To a boiling suspension of the acetyl derivative (1·5 g.), m. p. 238—240°, in water (20 c.c.) containing magnesium sulphate (3 g.) was added a concentrated solution of potassium permanganate in small portions until the colour persisted (50 hours). The cold solution was then saturated with sulphur dioxide and the white insoluble product (1 g.) was filtered off, washed with water, and precipitated from alkaline solution (Found : C, 56·5; H, 4·2. Calc. for 4-acetamidodiphenyltricarboxylic acid : C, 59·5; H, 3·8%). On titration with *N*/10-alkali and phenolphthalein, 0·10 g. of the acid required 8·8 c.c. The acid (0·5 g.) was esterified in absolute alcohol (30 c.c.) with dry hydrogen chloride, finally on the steam-bath. *Ethyl* 4-*acetamidodiphenyl*-3 : 5 : 4′-*tricarboxylate* crystallised from light petroleum (b. p. 60—80°)-alcohol in white leaflets, m. p. 129—130° (Found : C, 65·0; H, 6·3. $C_{23}H_{25}O_7N$ requires C, 64·65; H, 5·9%).

Synthetical Experiments.—3 : 5-*Dimethyldiphenyl*. A dry ethereal solution of purified *cyclo*hexanone (16 g.) was added gradually to an ethereal solution of 5-*m*-xylylmagnesium bromide (prepared from 30 g. of 5-bromo-*m*-xylene, 3·8 g. of magnesium, and 200 c.c. of ether), and the whole heated on the water-bath for ½ hour. The ice-cooled mixture was decomposed with dilute sulphuric acid, the ethereal layer separated and dried over sodium sulphate, the solvent removed, and the residual liquid distilled under reduced pressure, giving some unchanged *cyclo*hexanone and then 1-(5′-*m*-xylyl)*cyclo*hexanol at 150—160°/20 mm. The latter was dehydrated by formic acid (Sherwood, Short, and Stansfield, J., 1932, 1833) to give 1-(5′-*m*-xylyl)-Δ^1-*cyclo*hexene, b. p. 157—158°/20 mm. The *cyclo*hexene derivative (14 g.) was heated with sulphur (3·8 g.) in an equal volume of quinoline at 250° for 2 hours, the evolution of hydrogen sulphide then ceasing. Dilute sulphuric acid was added to the cold mixture, which was then extracted with ether. The extract was washed with dilute sulphuric acid and with water, dried over sodium sulphate, and evaporated, and the residue distilled under reduced pressure. The almost colourless liquid obtained, b. p. 160—170°/20 mm., was purified by treatment with hydroferrichloric acid (compare Robinson, J., 1925, **127**, 768), and 3 : 5-*dimethyldiphenyl* (8 g.) obtained as a colourless liquid, b. p. 273—276° (Found: C, 92·0; H, 7·5. $C_{14}H_{14}$ requires C, 92·3; H, 7·7%).

4-*Acetamido*-3 : 5-*dimethyldiphenyl*. To a solution of 3 : 5-dimethyldiphenyl (4 g.) in glacial acetic acid (15 c.c.) was gradually added nitric acid (*d* 1·42; 15 c.c.). After 12 hours, the solution was poured into water and extracted with ether. The washed (aqueous sodium carbonate, water) and dried (calcium chloride) extract was evaporated and the residual oil (3·5 g.) was dissolved in hot alcohol and added in small portions to a boiling solution of stannous chloride (20 g.) in concentrated hydrochloric acid (40 c.c.). This mixture was heated on the steam-bath for 2 hours, then made alkaline, and extracted with ether. Evaporation of the dried extract left a brown oil (3 g.), which was immediately acetylated on the addition of acetic anhydride. 4-*Acetamido*-3 : 5-*dimethyldiphenyl* crystallised from alcohol in fine white needles, m. p. 200—201° (Found : C, 80·4; H, 7·0; N, 5·9. $C_{16}H_{17}ON$ requires C, 80·5; H, 7·2; N, 5·9%).

3 : 4′-*Dimethyldiphenyl*. A solution of 4-methyl*cyclo*hexanone (16·4 g.) in an equal volume of dry ether was added slowly to an ethereal solution of *m*-tolylmagnesium bromide prepared from 25 g. of *m*-bromotoluene, 3·6 g. of magnesium, and 200 c.c. of dry ether. After being heated on the water-bath for ½ hour, the solution was decomposed and then, by the methods described above under 3 : 5-dimethyldiphenyl, 1-*m*-tolyl-4-methyl*cyclo*hexanol (15 g., b. p. 155—165°/20 mm.), the corresponding *cyclo*hexene, and 3 : 4′-dimethyldiphenyl (8 g.) were obtained, the last as a colourless liquid, b. p. 284—287° (Kruber, *Ber*., 1932, **65**, 1382, gives b. p. 288—289°/752 mm.) (Found : C, 92·0; H, 7·4%). Nitration, reduction, and acetylation as described above gave 4-acetamido-3 : 4′-dimethyldiphenyl, m. p. 204–206° (Kliegl and Huber, *Ber*., 1920, **53**, 1655, give m. p. 206°) (Found : C, 79·8; H, 6·7; N, 5·7%).

3 : 5 : 4′-*Trimethyldiphenyl*. From 4-methyl*cyclo*hexanone (18 g.) and 5-*m*-xylylmagnesium bromide (prepared from 30 g. of 5-bromo-*m*-xylene and 3·8 g. of magnesium in 200 c.c. of dry

ether) were prepared, in turn, 1-(5′-*m*-xylyl)-4-methyl*cyclo*hexanol (16 g., b. p. 154—164°/20 mm.), the *cyclo*hexene, and (without quinoline as solvent) 3 : 5 : 4′-*trimethyldiphenyl* (b. p. 175—185°/23 mm.), which formed white needles (7 g.), m. p. 44—45°, after two crystallisations from alcohol (Found : C, 91·9; H, 7·6. $C_{15}H_{16}$ requires C, 91·8; H, 8·2%).

4-*Acetamido*-3 : 5 : 4′-*trimethyldiphenyl.* Nitration of 3 : 5 : 4′-trimethyldiphenyl (2·5 g.) in glacial acetic acid (15 c.c.) with nitric acid (*d* 1·42 ; 15 c.c.) gave, by the process already described, a red oil (2 g.), which slowly solidified. Recrystallisation from aqueous alcohol gave 4-*nitro*-3 : 5 : 4′-*trimethyldiphenyl* in pale yellow needles, m. p. 94—95° (Found : N, 5·9. $C_{15}H_{15}O_2N$ requires N, 5·8%). This was reduced, and the product acetylated, by the methods given above. 4-*Acetamido*-3 : 5 : 4′-*trimethyldiphenyl* crystallised from absolute alcohol in fine white needles, m. p. 241—242° (Found : C, 80·0; H, 7·45; N, 5·2. $C_{17}H_{19}ON$ requires C, 80·6; H, 7·5; N, 5·5%).

The Action of Methyl Alcohol on 2-Aminodiphenyl Hydrochloride.—The following is a typical case. 2-Aminodiphenyl hydrochloride (50 g.) and methyl alcohol (24 g.) were heated at 250—300° in the autoclave for 12 hours. The product was recovered from the autoclave as in the previously described experiments, and extracted with benzene, first from strongly acid solution and then from alkaline solution. Evaporation of the former extract left a dark viscous nitrogenous residue (5 g.). The latter extract was dried and distilled and three fractions were collected as yellow viscous oils : (i) b. p. 315—335° (6 g.), (ii) b. p. 335—350° (10 g.), and (iii) b. p. above 350° (4 g., collected under reduced pressure). These were heated separately with acetic anhydride, but no solid derivative was obtained. The bases from fractions (i) and (ii) were therefore recovered (15 g.) and shaken with *p*-toluenesulphonyl chloride (27 g.) in the presence of aqueous alkali. Hydrochloric acid was then added until the mixture was only faintly alkaline, but subsequent distillation with steam only gave a very small yield of tertiary base owing to its low volatility. When cold, an insoluble gum was separated from the solution, and on trituration with light petroleum–benzene a small quantity of a crystalline *p*-toluenesulphonyl derivative (m. p. 250°) was obtained from it. Acidification of the alkaline filtrate, followed by extraction with ether and evaporation of the solvent, left a negligible residue. The main bulk of the alkali-insoluble matter, however, appeared to be a viscous tertiary base, which on warming with methyl iodide readily formed a methiodide. The crude methiodide, washed with acetone and twice crystallised from hot water, in which it formed a clear colourless solution, gave a *dimethylphenanthridine methiodide* in deep yellow needles, m. p. 293—295° (decomp.) (Found : C, 54·55, 55·0; H, 4·2, 4·55. $C_{16}H_{16}NI$ requires C, 55·0; H, 4·6%). The *picrate* of the base, prepared in the usual manner, crystallised from absolute alcohol, in which it was only sparingly soluble, in yellow needles, m. p. 241° (decomp.) (Found : N, 12·7. $C_{21}H_{16}O_7N_4$ requires N, 12·85%).

Methylation of 2-Aminodiphenyl.—(a) *With methyl sulphate* (compare Bell, J., 1930, 1076). 2-Aminodiphenyl (10 g.) was added slowly to methyl sulphate (16 g.), the mixture being finally heated at 150° for 2 hours. The cold solidified mixture was broken up with addition of ice-water and, after addition of aqueous sodium hydroxide, was extracted with ether. A considerable amount of the insoluble methosulphate was removed by filtration, and evaporation of the dried extract left a viscous oil (2 g.), which on treatment with methyl iodide gave 2-*dimethylaminodiphenyl methiodide* in greyish-white plates (from aqueous alcohol), m. p. 228° (decomp.) (Found : C, 53·2; H, 5·5. $C_{15}H_{18}NI$ requires C, 53·1; H, 5·3%).

(b) *With methyl iodide.* 2-Aminodiphenyl (8 g.), methyl iodide (15 g.), and an aqueous solution of sodium carbonate (11 g.) were boiled under reflux until all the methyl iodide had been used up. After a further ½ hour's boiling, the cold product was treated with aqueous sodium hydroxide and extracted with ether. A small quantity of 2-dimethylaminodiphenyl methiodide was filtered off (m. p. 228° after recrystallisation), and evaporation of the ether left a dark oil (7·5 g.), which distilled as a colourless viscous liquid, b. p. 280—285°, and consisted of a mixture of about equal parts of 2-methylaminodiphenyl and 2-dimethylaminodiphenyl.

9-Methylphenanthridine (Morgan and Walls, *loc. cit.*) gave on treatment with methyl iodide a methiodide which crystallised from hot water, in which it formed a clear colourless solution, in fine yellow needles, m. p. 260° (decomp.). The picrate of the base melted at 248° (decomp.). Pictet and Hubert (*loc. cit.*) give m. p. 247° and 233° respectively.

The authors acknowledge with thanks the receipt of a grant from the Chemical Society.

THE UNIVERSITY, MANCHESTER. [*Received, February 2nd,* 1934.]