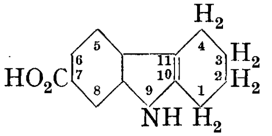
236. *Structural Problems in the Indole Group. Part II.*

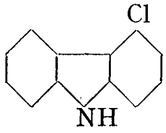
By R. C. G. Moggridge and S. G. P. Plant.

The investigation is a study of methods which might be used to remove the ambiguity attaching to the structures of several indole derivatives from the fact that Fischer's reaction can proceed in two alternative ways when applied to meta-substituted phenylhydrazones, and was undertaken also to obtain a more exact generalisation than has hitherto been possible regarding the course of the substitution reactions observed with 9-acyltetrahydrocarbazoles (numbering given in formula I). The tetrahydrocarbazole-5- and 7-carboxylic acids and the 5- and 7-chlorotetrahydrocarbazoles have been identified by the conversion of one of the isomers in each case into the corresponding 2-substituted carbazole. Nitration products obtained from various 9-acyl derivatives of 6-chloro-, 6-methyl-, and 3-methyl-tetrahydrocarbazole have all been shown to have the nitro-group in the 7-position, which can now be said, therefore, to be the normal position for the substituent in this series.

Reference has been made in Part I (J., 1936, 899) to the ambiguity which exists regarding the constitution of many indole derivatives as a result of the alternative positions which the cyclisation process may involve during their preparation from meta-substituted phenylhydrazones. Recent developments in various fields of carbazole chemistry have made it possible to settle several structural problems of this type in the tetrahydrocarbazole series. Thus two acids, m. p. 287° and 210°, were obtained by Collar and Plant (J., 1926, 808) by the elimination of ammonia from *cyclo*hexanone-*m*-carboxyphenylhydrazone, and it has now been found that the dehydrogenation of the methyl ester of the former with palladised charcoal gives a product from which carbazole-2-carboxylic acid (I. G. Farbenind. Akt.-Ges., D.R.-P. 555,312; Plant and Williams, J., 1934, 1142) was obtained on hydrolysis. It follows that the compound, m. p. 287°, is tetrahydrocarbazole-7-carboxylic acid (I), and its isomer has the carboxyl group in the 5-position. Dehydrogenation of the methyl ester of tetrahydrocarbazole-8-carboxylic acid, obtained from *o*-hydrazinobenzoic acid, gave an almost quantitative yield of methyl carbazole-1-carboxylate, but a similar process applied to the acid itself resulted in simultaneous decarboxylation with the formation of carbazole.



(I.)



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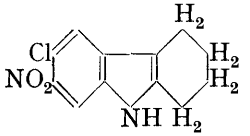
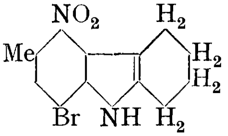


(III.)

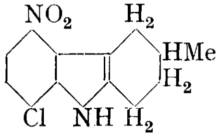
It recently became necessary in connexion with other investigations in this laboratory to obtain a specimen of the hitherto unknown 4-chlorocarbazole (II) and it seemed probable that this could be done by dehydrogenating the products which might result from the application of Fischer's reaction to *cyclo*hexanone-*m*-chlorophenylhydrazone. The mixture obtained from the latter reaction has been found readily to yield 7-*chlorotetrahydrocarbazole* (*acetyl* compound, m. p. 111°), the constitution of which was established by its conversion into the well-known 2-chlorocarbazole (Ullmann, *Annalen*, 1904, **332**, 82) on boiling with sulphur in quinoline. The residue obtained after removal of as much of the 7-chloro-compound as possible gave 5-*chloro*-9-*acetyltetrahydrocarbazole*, m. p. 133°, on acetylation. The 5-chlorotetrahydrocarbazole obtained by hydrolysis of the latter has not been isolated as a solid, but the dehydrogenation of the acetyl derivative has given 4-*chloro*-9-*acetylcarbazole*, m. p. 126°, which was hydrolysed to the required 4-*chlorocarbazole*, m. p. 96°.

Substitution into the 9-acyltetrahydrocarbazoles presents some interesting features. It has long been known that nitration of several such derivatives involves the introduction of the substituent at either the 5- or the 7-position, both of which can be regarded as meta with respect to the *N*-acyl group, but a more exact generalisation has not been possible. For example, nitration of the 9-acetyl-, 9-benzoyl-, and 9-carbethoxy-derivatives of 6-chlorotetrahydrocarbazole, followed by hydrolysis of the products, has given in each case a substance, m. p. 184°, which was identical with one of the two compounds, m. p. 184° 162°, obtained by removal of ammonia from *cyclo*hexanone-4-chloro-3-nitrophenylhydrazone (Plant and Rosser, J., 1928, 2454). The compound, m. p. 162°, has now been reduced by the prolonged action of tin and alcoholic hydrochloric acid to 5-aminohexahydrocarbazole and then converted into 5-benzamido-9-benzoylhexahydrocarbazole, the preparation of an authentic specimen of which was described in Part I, and it follows that the substance is 6-chloro-5-nitrotetrahydrocarbazole; the isomer, m. p. 184°, resulting from the substitution reactions mentioned above has the nitro-group in the 7-position (III). The latter behaves quite differently on reduction under similar conditions; the chlorine is not removed and the product is 6-*chloro*-7-*aminotetrahydrocarbazole*. The greater stability of the chlorine is readily explained if the double bonds be considered as fixed in the positions shown in (III), but it is more difficult to account for the sluggishness with which the double bond in the 10 : 11-position is reduced. This cannot be entirely attributed to the presence of the chlorine atom, because 6-chlorotetrahydrocarbazole was easily converted by the same reagents into the corresponding *hexahydro*-compound.

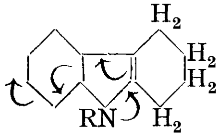
The action of nitric acid on 9-acetyl-6-methyltetrahydrocarbazole has given a product which was converted on hydrolysis into a nitro-6-methyltetrahydrocarbazole, m. p. 181—182° (Manjunath and Plant, J., 1926, 2260). Three positions, the 5-, 7-, and 8-, are possible for the nitro-group. That the compound is not 8-*nitro*-6-*methyltetrahydrocarbazole* has now been shown by the synthesis of this substance, which melts at 210°, from 3-nitro-*p*-tolylhydrazine and *cyclo*hexanone, and the possibility of the 5-position has been eliminated in the following manner. 8-*Bromo*-5-*nitro*-6-*methyltetrahydrocarbazole* (IV) was prepared by an unambiguous route from 5-bromo-2-nitro-*p*-tolylhydrazine and *cyclo*hexanone, and converted by reduction into 5-amino-6-methylhexahydrocarbazole, in which there can be no doubt regarding the position of the amino-group. The latter is an oily base, but it readily gave a characteristic *dibenzoyl* derivative, m. p. 223°. Reduction of the nitro-compound, m. p. 181—182°, under similar conditions gave a different base, m. p. 109°, which must be 7-*amino*-6-*methylhexahydrocarbazole,* the *dibenzoyl* derivative of which melted at 229°. It follows that the nitration process referred to has again resulted in substitution at the 7-position.



(IV.)



(V.)



(VI; R = Acyl.)

Another problem of the same type is presented by 3-methyltetrahydrocarbazole. Nitration of its 9-acetyl, 9-benzoyl, and 9-carbethoxy-derivatives has given compounds which on hydrolysis have all yielded a substance, m. p. 188°, identical with one of the two compounds, m. p. 188° and 175°, obtained synthetically from 4-methyl*cyclo*hexanone-*m*-nitrophenylhydrazone (Plant and Rosser, *loc. cit.*). Substitution must therefore involve either the 5- or the 7-position, and the former has been eliminated by the preparation of 8-*chloro*-5-*nitro*-3-*methyltetrahydrocarbazole* (V) from 2-chloro-5-nitrophenylhydrazine and 4-methyl*cyclo*hexanone and its conversion by reduction during a restricted period into 5-*amino*-3-*methyltetrahydrocarbazole,* m. p. 176°. The substitution product gave an *isomer,* m. p. 107°, under similar conditions and must therefore be the 7-nitro-compound. More prolonged reduction to the corresponding hexahydro-compounds was avoided in this case, since the products would be capable of existing in several stereoisomeric forms (Plant and Rosser, *loc. cit.*). It follows that the 7-position is that generally adopted by the substituent in the 9-acyltetrahydrocarbazole group, the mechanism of the process being explained as in (VI), in which the 10 : 11-double bond forms part of the route involved in the electromeric changes, as first pointed out by Robinson (see J., 1923, **123**, 684).

EXPERIMENTAL.

Dehydrogenation of Methyl Tetrahydrocarbazole-7-*carboxylate.*—The ester, m. p. 155° (Collar and Plant, *loc. cit.*), was mixed with 25% of its weight of palladised charcoal and heated at 280° for 5 hours in an atmosphere of hydrogen. The product was extracted with acetone, precipitated therefrom by the addition of water, and refluxed for 2 hours with aqueous alcoholic potassium hydroxide. When the resulting solution was diluted with water, filtered to remove an insoluble high-melting by-product, and then acidified, carbazole-2-carboxylic acid was precipitated in good yield. It melted at 322° (decomp.) after crystallisation from glacial acetic acid and its identity was confirmed by conversion into its ethyl ester, m. p. and mixed m. p. 184°.

Methyl tetrahydrocarbazole-8-carboxylate, when similarly treated for 14 hours at 300—320°, gave methyl carbazole-1-carboxylate in almost theoretical yield. Carbazole-3-carboxylic acid, identified by mixed m. p. with the acid of Plant and Williams (*loc. cit.*), was obtained in moderate yield, accompanied by a non-acidic high-melting substance, by the hydrolysis of the product obtained similarly from the 6-carboxylate after 5 hours at 280°, but attempts to obtain the unknown carbazole-4-carboxylic acid from methyl tetrahydrocarbazole-5-carboxylate, m. p. 93°, have been unsuccessful.

5- *and* 7-*Chlorotetrahydrocarbazole.*—A mixture of *m*-chlorophenylhydrazine (4 g.) and *cyclo*hexanone (3 c.c.) was heated on the steam-bath for a few minutes and then boiled for 15 minutes with dilute sulphuric acid (16%). Crystallisation of the product from methyl alcohol gave 7-*chlorotetrahydrocarbazole,* which on recrystallisation from alcohol separated in colourless plates, m. p. 181° (Found : Cl, 16·9. $C_{12}H_{12}NCl$ requires Cl, 17·3%). It was converted into 7-*chloro*-9-*acetyltetrahydrocarbazole,* colourless needles, m. p. 111°, from alcohol, by refluxing for an hour with acetic anhydride and then shaking with an excess of water (Found : Cl, 14·2. $C_{14}H_{14}ONCl$ requires Cl, 14·3%). When the methyl-alcoholic mother-liquor was evaporated and the residue crystallised from glacial acetic acid, a further quantity of the 7-chloro-compound was isolated. The oily substance obtained by again evaporating the filtrate was acetylated as above and the product, on recrystallisation three times from alcohol, gave 5-*chloro*-9-*acetyltetrahydrocarbazole* in colourless needles, m. p. 133° (Found : Cl, 14·1%). The 5-chlorotetrahydrocarbazole obtained from this acetyl compound by hydrolysis with either alcoholic hydrogen chloride or aqueous alcoholic potassium hydroxide was an oil which could not be made to crystallise.

2- *and* 4-*Chlorocarbazole.*—A mixture of 7-chlorotetrahydrocarbazole (3·1 g.), sulphur (1 g.), and quinoline (25 c.c.) was refluxed for ½ hour, cooled, and poured into dilute hydrochloric acid. When the precipitate was dried on the steam-bath, distilled under reduced pressure with iron filings, and the distillate crystallised twice from alcohol, 2-chlorocarbazole was isolated in colourless prisms, m. p. 242°. It was identified by mixed m. p. with a specimen obtained from 5-chloro-2-nitrodiphenylamine as described by Ullmann (*loc. cit.*). The latter compound was prepared both by the method of Laubenheimer (*Ber.*, 1876, **9**, 768) from aniline and 3 : 4-dinitrochlorobenzene, and by refluxing 2 : 4-dichloronitrobenzene with an excess of aniline and potassium acetate for an hour, removing the aniline in steam, and crystallising the residue from alcohol. These two alternative methods jointly prove the structure of the product. An attempt to dehydrogenate 7-chlorotetrahydrocarbazole with palladised charcoal in an atmosphere of hydrogen resulted in the elimination of the halogen.

When 5-chloro-9-acetyltetrahydrocarbazole was similarly oxidised with sulphur in quinoline and the product purified as before, 4-*chloro*-9-*acetylcarbazole*, colourless plates, m. p. 126°, from alcohol, was formed (Found : C, 68·9; H, 4·1. $C_{14}H_{10}ONCl$ requires C, 69·0; H, 4·1%). It was refluxed for ½ hour with aqueous alcoholic potassium hydroxide, and the solid obtained on dilution was extracted with hot alcohol. The residue from the evaporation of the filtered solution was crystallised from petroleum (b. p. 60—80°) and 4-*chlorocarbazole* was isolated in colourless needles, m. p. 96° (Found : C, 71·6; H, 4·4. $C_{12}H_8NCl$ requires C, 71·5; H, 4·0%).

Reduction of 6-*Chloro*-7-*nitrotetrahydrocarbazole.*—This substance (2·7 g.), m. p. 184° (Plant and Rosser, *loc. cit.*), was refluxed with granulated tin (27 g.), alcohol (55 c.c.), and concentrated hydrochloric acid (55 c.c.) for 15 hours, a further quantity of tin (13 g.) and hydrochloric acid (25 c.c.) being added after 7 hours. The mixture was made alkaline with sodium hydroxide, the alcohol removed in steam, and the product extracted with ether. After the extract had been dried with potassium carbonate and evaporated, 6-*chloro*-7-*aminotetrahydrocarbazole*, colourless plates, m. p. 166°, from alcohol, remained (Found : C, 65·3; H, 5·9. $C_{12}H_{13}N_2Cl$ requires C, 65·3; H, 5·9%).

The reduction of 6-chlorotetrahydrocarbazole (Borsche, Witte, and Bothe, *Annalen*, 1908, **359**, 53) under similar conditions gave 6-*chlorohexahydrocarbazole*, colourless needles, m. p. 67°, from petroleum (b. p. 60—80°) (Found : C, 69·4; H, 6·7. $C_{12}H_{14}NCl$ requires C, 69·4; H, 6·7%).

Reduction of 6-*Chloro*-5-*nitrotetrahydrocarbazole.*—This compound, m. p. 162° (Plant and Rosser, *loc. cit.*), was reduced with tin and alcoholic hydrochloric acid as above, but the product was an oil which could not be made to crystallise. It was therefore dissolved in acetone containing a little concentrated aqueous potassium hydroxide and shaken with benzoyl chloride. The addition of water then precipitated 5-benzamido-9-benzoylhexahydrocarbazole, colourless needles, m. p. 245°, from alcohol, which was identified by a mixed m. p. with an authentic specimen (Plant, J., 1936, 899).

8-*Nitro*-6-*methyltetrahydrocarbazole.*—After a solution of 3-nitro-*p*-tolylhydrazine (1·75 g.) and *cyclo*hexanone (1·1 c.c.) in alcohol had been boiled for 5 minutes, the corresponding hydrazone, scarlet plates, m. p. 97°, separated on cooling. When this was boiled for 15 minutes with water (200 c.c.) and concentrated sulphuric acid (40 c.c.), 8-*nitro*-6-*methyltetrahydrocarbazole*, brick-red plates, m. p. 210°, from glacial acetic acid, was obtained (Found : N, 12·2. $C_{13}H_{14}O_2N_2$ requires N, 12·2%).

5-*Amino*-6-*methylhexahydrocarbazole.*—5-Bromo-2-nitro-*p*-tolylhydrazine was prepared from the corresponding amine by diazotisation in concentrated hydrochloric acid and reduction with stannous chloride. The precipitate was shaken with much hot water, and the hydrazine isolated from the filtered solution by the addition of sodium acetate; it separated from alcohol in orange needles, m. p. 160°. After the hydrazine (9·6 g.) and *cyclo*hexanone (4·4 c.c.) had been boiled in alcohol for 5 minutes, the mixture treated with water (250 c.c.) and concentrated sulphuric acid (50 c.c.), and boiled again for 20 minutes, 8-*bromo*-5-*nitro*-6-*methyltetrahydrocarbazole*, orange prisms, m. p. 199°, from glacial acetic acid, was obtained (Found : Br, 26·0.

$C_{13}H_{13}O_2N_2Br$ requires Br, 25·9%). This (5·6 g.) was then reduced with tin and alcoholic hydrochloric acid, and the product isolated as described in the case of 6-chloro-7-nitrotetrahydrocarbazole. As the base could not be obtained crystalline, it was shaken in acetone with concentrated aqueous potassium hydroxide and benzoyl chloride (3·8 c.c.), and 5-*benzamido*-9-*benzoyl*-6-*methylhexahydrocarbazole*, colourless needles, m. p. 223°, after crystallisation from benzene and then from alcohol, was isolated by precipitation with water (Found: C, 79·0; H, 6·4. $C_{27}H_{26}O_2N_2$ requires C, 79·0; H, 6·3%).

7-*Amino*-6-*methylhexahydrocarbazole*.—When the nitro-compound, m. p. 182°, described by Manjunath and Plant (*loc. cit.*) was reduced with tin and alcoholic hydrochloric acid as described above, 7-*amino*-6-*methylhexahydrocarbazole*, colourless plates, m. p. 109°, from alcohol, was obtained (Found: C, 77·0; H, 8·8. $C_{13}H_{18}N_2$ requires C, 77·2; H, 8·9%). It was converted by benzoylation as before into 7-*benzamido*-9-*benzoyl*-6-*methylhexahydrocarbazole*, diamond-shaped plates, m. p. 229°, after crystallisation from glacial acetic acid and then from *cyclo*hexanone (Found: C, 79·0; H, 6·4%). A mixed m. p. with the isomeric 5-benzamido-compound showed considerable depression.

When the reduction of the nitro-compound was suspended after ½ hour and the product isolated as before, 7-*amino*-6-*methyltetrahydrocarbazole*, colourless plates, m. p. 175° (after softening at 169°), from alcohol, was obtained (Found: C, 77·8; H, 7·9. $C_{13}H_{16}N_2$ requires C, 78·0; H, 8·0%).

5- *and* 7-*Amino*-3-*methyltetrahydrocarbazole*.—When a mixture of 2-chloro-5-nitrophenylhydrazine (10 g.), 4-methyl*cyclo*hexanone (7·5 g.), and alcohol (25 c.c.) was boiled for 5 minutes, treated with aqueous sulphuric acid (250 c.c. of 27%), and boiled for a further 15 minutes, 8-*chloro*-5-*nitro*-3-*methyltetrahydrocarbazole*, orange plates (4·0 g.), m. p. 195°, after crystallisation from glacial acetic acid and then from alcohol, was obtained (Found: Cl, 13·0. $C_{13}H_{13}O_2N_2Cl$ requires Cl, 13·4%). After this compound had been refluxed for ½ hour with tin and alcoholic hydrochloric acid and the mixture treated as in the analogous cases cited above, 5-*amino*-3-*methyltetrahydrocarbazole*, colourless plates, m. p. 176°, from alcohol, was isolated (Found: C, 77·7; H, 8·0. $C_{13}H_{16}N_2$ requires C, 78·0; H, 8·0%).

When the "5(or 7)-nitro-3-methyltetrahydrocarbazole," m. p. 188°, of Plant and Rosser (*loc. cit.*) was similarly reduced during 20 minutes and the mixture treated as before, 7-*amino*-3-*methyltetrahydrocarbazole*, colourless plates, m. p. 107°, from benzene–petroleum, was obtained (Found: C, 78·1; H, 8·0%).

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

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