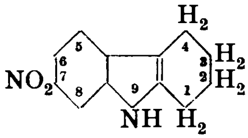
# **205.** *Structural Problems in the Indole Group. 5- and 7-Nitrotetrahydrocarbazoles.*

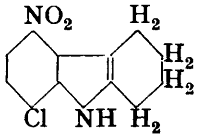
By S. G. P. Plant.

When Fischer's indole synthesis is applied to meta-substituted phenylhydrazones, the removal of ammonia can take place in one, or both, of two alternative ways to give indoles in which it is impossible without further information to say whether the substituent is in the 4- or the 6-position. An outstanding example of this is found in the nitrotetrahydrocarbazoles. A product, m. p. 151—152°, obtained by the action of dilute sulphuric acid on *cyclo*hexanone-*m*-nitrophenylhydrazone has been stated by Borsche, Witte, and Bothe (*Annalen*, 1908, **359**, 49) to be 7-nitrotetrahydrocarbazole (I), although no proof was advanced for the structure. In more recent times this statement has been provisionally accepted as the basis on which the constitutions have been assigned to a considerable number of derivatives of tetra- and hexa-hydrocarbazole. In particular, an apparently isomeric substance, m. p. 172°, obtained by Perkin and Plant (J., 1921, **119**, 1825; 1923, **123**, 676) from various 9-acyltetrahydrocarbazoles by nitration and subsequent hydrolysis has been regarded as 5-nitrotetrahydrocarbazole. It has now been found, however, that the latter is, in reality, 7-nitrotetrahydrocarbazole, while the product from *cyclo*hexanone-*m*-nitrophenylhydrazone is a mixture of the 5- and the 7-nitro-compound in the ratio of approximately 2 : 1.

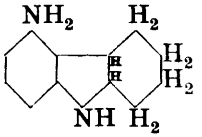
There is no ambiguity regarding the position of the nitro-group in 8-chloro-5-nitrotetrahydrocarbazole (II), since ring closure can take place in one direction only during its synthesis from *cyclo*hexanone-2′-chloro-5′-nitrophenylhydrazone (Perkin and Plant, *loc. cit.*). When this compound was reduced under conditions described in the experimental section, the chlorine was removed and a mixture of authentic *5-aminotetrahydrocarbazole*, m. p. 163°, and 5-aminohexahydrocarbazole (III), an oily base, resulted. The former was converted into a *monoacetyl* compound, and the latter into well-defined *diacetyl* and *dibenzoyl* derivatives. The nitrotetrahydrocarbazole (m. p. 172°) of Perkin and Plant, however, can be reduced to an aminotetrahydrocarbazole, m. p. 101°, and an aminohexahydrocarbazole, m. p. 111° (Edwards and Plant, J., 1923, **123**, 2393; Gurney and Plant,



(I.)



(II.)



(IIII.)

J., 1927, 1314), which are different from the amino-compounds just mentioned. Its nitro-group cannot occupy the 6- or the 8-position because the compound is not identical with either of the substances obtained by removing ammonia from *cyclo*hexanone-*o*- and -*p*-nitrophenylhydrazone respectively, and it must therefore be 7-nitrotetrahydrocarbazole.

On the other hand, when the " 7-nitrotetrahydrocarbazole " obtained as described by Borsche, Witte, and Bothe from *m*-nitrophenylhydrazine was submitted to the prolonged action of tin and alcoholic hydrochloric acid, it gave an oil from which the diacetyl and dibenzoyl derivatives of 5-aminohexahydrocarbazole mentioned above were readily obtained on acylation. A closer investigation, however, has revealed that this nitrotetrahydrocarbazole is not a single substance. Although the crude product has a reasonably sharp melting point which is not greatly altered by recrystallisation from a variety of solvents, acetylation, either before or after crystallisation, gave a product from which 7-nitro-9-acetyltetrahydrocarbazole was isolated in appreciable quantity. A pure specimen of the 5-nitro-compound has not been obtained, but the substance recovered by hydrolysis of the acetylated product after removal of as much of the 7-nitro-derivative as possible readily gave 5-aminotetrahydrocarbazole, identical with the authentic sample, on reduction for a limited period of time.

Reactions similar to those which have now been examined might afford a route to the solution of several analogous structural problems in the indole series. The definite characterisation of 7-nitrotetrahydrocarbazole and of the product described by Borsche, Witte, and Bothe makes it possible, in addition to the compounds described in the present paper, accurately to designate the following substances (J., 1921, **119**, 1825; 1923, **123**, 676, 2393; 1927, 1314; 1929, 1970), the m. p.'s of which are given in parentheses to facilitate reference: the 9-acetyl- (174°), 9-benzoyl- (140°), 9-carbethoxy- (116°), 9-phenylacetyl- (178°), 9-cinnamoyl- (177°), 9-*o*-toluoyl- (154°), 9-*m*-toluoyl- (148°), 9-*p*-toluoyl- (136°), 9-*o*-chlorobenzoyl- (195°), 9-*m*-chlorobenzoyl- (155°), and 9-*p*-chlorobenzoyl- (148°) derivatives of 7-nitrotetrahydrocarbazole (172°); 7-nitrohexahydrocarbazole (69°) and its 9-methyl- (52°), 9-ethyl- (143°), and 9-acetyl- (142°) derivatives; 7-amino- (101°) and 7-acetamido-tetrahydrocarbazole (195°); 7-aminohexahydrocarbazole (111°) and its diacetyl derivative (163°). All these compounds have hitherto been regarded as the corresponding 5-substituted derivatives, although the alternative possibility has been commented upon (J., 1921, **119**, 1828; 1927, 1314).

During earlier experiments which had for their object a solution of this structural problem 7-nitrotetrahydrocarbazole was converted into its 9-*methyl* derivative. On reduction, the latter gave 7-*amino*-9-*methylhexahydrocarbazole*, which was also prepared by the electrolytic reduction of the substance (m. p. 52°) obtained by Gurney and Plant (*loc. cit.*) by the nitration of 9-methylhexahydrocarbazole. 7-*Benzamido*-9-*benzoylhexahydrocarbazole*, from the benzoylation of the corresponding base, was found readily to give a *monochloro*-derivative, in which the new substituent undoubtedly occupies the 6-position.

## EXPERIMENTAL.

*Reduction of* 8-*Chloro*-5-*nitrotetrahydrocarbazole*.—A mixture of this compound (12·3 g.), alcohol (250 c.c.), concentrated hydrochloric acid (250 c.c.), and granulated tin (125 g.) was refluxed for 15 hours, a further quantity (50 c.c.) of hydrochloric acid being added after 8 hours. After filtration, the solution was made alkaline with sodium hydroxide (200 g. in water), and the alcohol removed in steam. This procedure effected coagulation of the precipitate and facilitated the subsequent extraction of the product with ether. After the ethereal extract had been dried with potassium carbonate and the solvent removed, the residue was crystallised from benzene, from which 5-*aminotetrahydrocarbazole* (3·2 g.) separated in colourless prisms, m. p. 163° (Found: C, 77·5; H, 7·5. $C_{12}H_{14}N_2$ requires C, 77·4; H, 7·5%). 5-*Acetamidotetrahydrocarbazole*, colourless prisms, m. p. 198°, from alcohol, resulted when this base (1·5 g.) was shaken in acetone with potassium hydroxide (1·5 g. in 50% aqueous solution) and acetyl chloride (2·5 c.c.), the product being precipitated with water (Found: N, 12·5. $C_{14}H_{16}ON_2$ requires N, 12·3%). The benzene filtrate from the above base was mixed with ether and the basic material present was extracted with very dilute hydrochloric acid. The product which was liberated when the extract was made alkaline with ammonia was taken up in ether and dried with potassium carbonate. When the oily residue obtained on evaporation was acetylated with potassium hydroxide (6 g.) and acetyl chloride (10 c.c.) in acetone as above, 5-*acetamido*-9-*acetylhexahydrocarbazole*, colourless needles, m. p. 264°, from alcohol, resulted (Found: C, 70·5; H, 7·5; N, 10·3. $C_{16}H_{20}O_2N_2$ requires C, 70·6; H, 7·4; N, 10·3%). 5-*Benzamido*-9-*benzoylhexahydrocarbazole*, obtained similarly from the oily residue with benzoyl chloride, separated from alcohol in colourless needles, m. p. 245° (Found: N, 7·2. $C_{26}H_{24}O_2N_2$ requires N, 7·1%). The diacetyl compound of m. p. 264° was hydrolysed by boiling with concentrated hydrochloric acid for 1½ hours. The base obtained from the resulting solution with ice–ammonia remained as an oil, and was converted into the above dibenzoyl compound, m. p. 245° (mixed m. p.), on benzoylation.

The 5-aminotetrahydrocarbazole mentioned above was reduced to 5-aminohexahydrocarbazole by refluxing with tin and alcoholic hydrochloric acid for 19 hours. The oily product, which was isolated as before and could not be made to crystallise, was acetylated, the diacetyl compound obtained, m. p. 264°, being identified by mixed m. p. with the authentic specimen.

*The Nitrotetrahydrocarbazole from* m-*Nitrophenylhydrazine.*—After a solution of *m*-nitrophenylhydrazine (10·2 g.) and *cyclo*hexanone (12 c.c.) in alcohol had been boiled and diluted with water, the hydrazone obtained was boiled for a short time with a mixture of concentrated sulphuric acid (20 c.c.) and water (180 c.c.). The solid product (10·4 g.) was refluxed for 2 hours with acetic anhydride (120 c.c.) containing 8 drops of concentrated sulphuric acid, and the mixture (11·5 g.) obtained by shaking with an excess of water was crystallised from alcohol (3 l.); 7-nitro-9-acetyltetrahydrocarbazole (3·6 g., identified by mixed m. p. with the substance obtained by the nitration of 9-acetyltetrahydrocarbazole as described by Perkin and Plant, *loc. cit.*) separated in a practically pure condition. It was obtained pure by recrystallisation from glacial acetic acid. A similar result was obtained when the nitrotetrahydrocarbazole was crystallised from methyl alcohol before acetylation. The alcoholic mother-liquors were concentrated to about 400 c.c. and then boiled for ½ hour with the addition of potassium hydroxide (12 g.). The solid obtained by dilution with dilute hydrochloric acid was submitted to reduction for 3½ hours with tin and alcoholic hydrochloric acid as described for the 8-chloro-5-nitro-compound. When the product, isolated as before, was crystallised from benzene, 5-aminotetrahydrocarbazole, m. p. 163° (identified by mixed m. p.), was obtained in good yield.

When the crude mixture of nitrotetrahydrocarbazoles obtained from *m*-nitrophenylhydrazine as described above was similarly reduced during 16 hours without previous separation or purification, an oily product was obtained which, on acetylation and benzoylation as before, readily gave 5-acetamido-9-acetylhexahydrocarbazole (mixed m. p.) and the corresponding dibenzoyl compound (mixed m. p.) respectively.

*7-Amino-9-methylhexahydrocarbazole.*—After a solution of 7-nitrotetrahydrocarbazole (1·5 g., prepared by the nitration of 9-acetyltetrahydrocarbazole) in acetone (25 c.c.) containing potassium hydroxide (1·5 g. in a little water) had been shaken with methyl sulphate (1·5 c.c.), the addition of water precipitated *7-nitro-9-methyltetrahydrocarbazole*, which crystallised in yellow needles, m. p. 162°, from alcohol (Found: N, 12·6. $C_{13}H_{14}O_2N_2$ requires N, 12·2%). This compound was reduced by refluxing with tin and alcoholic hydrochloric acid for 5 hours as described above. The resulting *7-amino-9-methylhexahydrocarbazole* was extracted from its ethereal solution with dilute sulphuric acid, recovered by the addition of alkali, and crystallised from alcohol, colourless needles, m. p. 87—89°, being obtained (Found: C, 77·8; H, 9·0. $C_{13}H_{18}N_2$ requires C, 77·2; H, 8·9%). The same base (11·5 g.) was obtained when a solution of 7-nitro-9-methylhexahydrocarbazole (15 g., prepared by the nitration of 9-methylhexahydrocarbazole as described by Gurney and Plant, *loc. cit.*) in sulphuric acid (250 c.c. of 50%) was reduced for 15 hours at room temperature in the cathode compartment of an electrolytic cell, lead electrodes and a current of 0·02 amp. per sq. cm. of cathode being used; it was isolated by diluting the solution with water, filtering, and adding ice–ammonia.

An intense red solution resulted when this base was boiled with acetic anhydride for 15 minutes. The product obtained by subsequently shaking with water was purified by boiling with charcoal in alcohol and recovered by the addition of water to the filtered solution. On crystallisation from methyl alcohol, *7-diacetylamino-9-methylhexahydrocarbazole* separated in colourless plates, m. p. 106° (Found: C, 71·2, 71·5; H, 7·4, 7·3. $C_{17}H_{22}O_2N_2$ requires C, 71·3; H, 7·7%). After this diacetyl derivative had been hydrolysed by boiling its solution in concentrated hydrochloric acid for 25 minutes, the original base, m. p. 87—89°, identified by mixed m. p., was isolated from the cold solution on the addition of ammonia.

*Derivatives of 7-Aminohexahydrocarbazole.*—The amino-compound was obtained from hexahydrocarbazole by nitration and reduction as described by Gurney and Plant (*loc. cit.*). *7-Benzamido-9-benzoylhexahydrocarbazole*, obtained from it by the action of benzoyl chloride and alkali in acetone as described above for the isomeric compound, separated from glacial acetic acid in very small, colourless prisms, m. p. 199° (Found: N, 6·8. $C_{26}H_{24}O_2N_2$ requires N, 7·1%). A solution of this dibenzoyl derivative (2 g.) in glacial acetic acid (30 c.c.) was treated gradually with chlorine (0·71 g.) dissolved in carbon tetrachloride (1 c.c. of solution contained 0·115 g. of chlorine), and, after an hour, poured into water. The carbon tetrachloride mixture was extracted with ether, and the extract washed with aqueous sodium carbonate, dried with potassium carbonate, and evaporated. After the residue had been crystallised from alcohol, the product was dried during 2 hours at 130°, and then recrystallised from benzene; 6-*chloro*-7-*benzamido*-9-*benzoylhexahydrocarbazole* separated in colourless prisms, m. p. 182° (Found: Cl, 8·4. $C_{26}H_{23}O_2N_2Cl$ requires Cl, 8·2%).

THE DYSON PERRINS LABORATORY, OXFORD.

[*Received, May* 15*th*, 1936.]