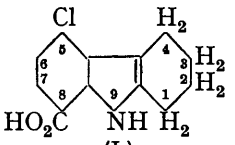
48. *Structural Problems in the Indole Group. Part III. Halogen Compounds.*

By S. G. P. Plant and (Miss) A. E. J. Wilson.

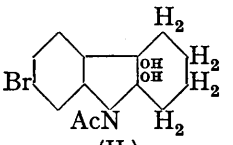
A method is described by which the structures of the two isomeric chloro-indoles obtained by the elimination of ammonia from a *m*-chlorophenylhydrazone may be investigated. In the case of the less stable bromo-compounds from a *m*-bromophenylhydrazone a procedure for correlating them with the analogous chloro-derivatives has been developed by using the dihydroxy-addition compounds obtained from their *N*-acetyl derivatives for the preparation of similarly constituted substances in which the chlorine or bromine is very reactive. Treatment of these compounds with aniline then gives identical products from similarly substituted chloro- and bromo-indoles. The processes have been applied to the complete characterisation of the 5- and 7-*bromotetrahydrocarbazoles*.

Ambiguity must exist regarding the structure of many indoles prepared by an application of Fischer's reaction to meta-substituted phenylhydrazones owing to the alternative positions which the cyclisation process may involve. In Parts I and II (J., 1936, 899; 1937, 1125) a procedure has been described which might be generally applicable to indoles in which the ambiguity relates to the position of a nitro-group, and the present communication indicates a method of approach in the case of substances obtained from *m*-chloro- and *m*-bromo-phenylhydrazones.

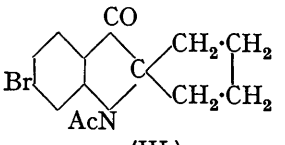
The 5- and 7-chlorotetrahydrocarbazoles have been prepared by the elimination of ammonia from *cyclo*hexanone-*m*-chlorophenylhydrazone and their complete characterisation followed from the fact that the latter was oxidised to 2-chlorocarbazole (Moggridge and Plant, J., 1937, 1125), but this method of determining structure is of limited application and the following more general one has now been developed. 4-Chloroanthranilic acid was converted into the corresponding hydrazine, which was combined with *cyclo*hexanone, and the product transformed by the action of dilute sulphuric acid into 5-*chlorotetrahydrocarbazole*-8-*carboxylic acid* (I), in which there is no doubt about the position of the chlorine. Attempts to decarboxylate this were unsuccessful, but after it had been acetylated it was converted into 5-chloro-9-acetyltetrahydrocarbazole, identical with the substance described by Moggridge and Plant, by heating in quinoline with copper chromite, although the yield was poor.



(I.)



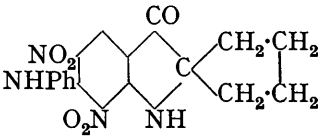
(II.)

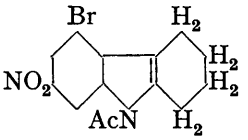


(III.)

Considerable interest attaches to the brominated indoles and it was decided to examine the substances obtained by Fischer's reaction from *cyclo*hexanone-*m*-bromophenylhydrazone. One of these, ultimately shown to be 7-*bromotetrahydrocarbazole*, melted with decomposition at 183° but gave a well-defined *acetyl* derivative, m. p. 123°. The isomeric 5-bromotetrahydrocarbazole has only been obtained as a syrup, but was characterised by its *acetyl* derivative, m. p. 137—139°. The bromo-compounds are often less stable than the chloro-derivatives and would be unlikely to escape complete decomposition in reactions similar to those described above for determining their structures. A study has therefore been made of the possibility of correlating the analogous chloro- and bromo-derivatives. For this purpose advantage was taken of the fact that *N*-acylindoles, when treated with nitric acid in acetic acid solution, readily form products by the addition of OH and OH, or sometimes OH and NO_2, at the 2 : 3-position. In this way the solid bromotetrahydrocarbazole was converted into 7-*bromo*-10 : 11-*dihydroxy*-9-*acetylhexahydrocarbazole* (II), which lost water in the usual way on boiling with acetic anhydride to

give 8-*bromo*-6-*acetyl*-ψ-*indoxyl*spirocyclo*pentane* (III). After removal of the acetyl group the *spiro*-compound was readily nitrated, as is characteristic of this type of substance, with the formation of 8-*bromo*-7 : 9-*dinitro*-ψ-*indoxyl*spirocyclo*pentane*. The bromine in this product was found to be extremely reactive and on treatment with aniline at room temperature 7 : 9-*dinitro*-8-*anilino*-ψ-*indoxyl*spirocyclo*pentane* (IV) was obtained. The same substance was prepared from 7-chloro-9-acetyltetrahydrocarbazole by a similar series of reactions, a result which served to correlate the chloro- and bromo-compounds and led to a definite characterisation of 5- and 7-bromotetrahydrocarbazole.

(IV.) 

 (V.)

When 9-acetyltetrahydrocarbazole is treated with nitric acid in acetic acid solution, a mixture of 7-nitro-9-acetyltetrahydrocarbazole and 10 : 11-dihydroxy-9-acetylhexahydrocarbazole is obtained (Perkin and Plant, J., 1923, **123**, 676; Plant, J., 1936, 899). It is therefore not surprising that during the nitration of the above products in which the 7-position is already occupied by halogen the dihydroxy-compounds are more readily produced. In fact confirmation of the structures of the bromo-compounds was obtained by nitrating the isomeric 5-bromo-9-acetyltetrahydrocarbazole; the only product isolated was a mononitro-derivative which was undoubtedly 5-*bromo*-7-*nitro*-9-*acetyltetrahydrocarbazole* (V).

Experimental.

5-*Chlorotetrahydrocarbazole*-8-*carboxylic Acid and the Decarboxylation of its* 9-*Acetyl Derivative*.—4-Chloroanthranilic acid (4 g., prepared by the method of Hunn, *J. Amer. Chem. Soc.*, 1923, **45**, 1024), suspended in hydrochloric acid (30 c.c. of 23%), was diazotised below 0°, and the filtered solution added to sodium sulphite (11 g.) in a little water. The whole was then treated with glacial acetic acid (10 c.c.) and warmed to 65° while zinc dust was gradually added. After the solution had been filtered, it was saturated with hydrogen chloride at room temperature; the hydrochloride of 4-chloro-2-hydrazinobenzoic acid was precipitated in colourless plates. This was added to water (50 c.c.) containing *cyclo*hexanone (2·5 c.c.), and the mixture boiled and treated with an excess of sodium acetate. After the addition of concentrated sulphuric acid (11 c.c.) the whole was again boiled for ½ hour, and when the solid product was crystallised from glacial acetic acid, 5-*chlorotetrahydrocarbazole*-8-*carboxylic acid* was obtained in pale green prisms, m. p. 245° (decomp.) (Found: N, 5·5. $C_{13}H_{12}O_2NCl$ requires N, 5·6%). The acid was acetylated by refluxing for 15 minutes with acetic anhydride and the product obtained by pouring the solution into water was dissolved in quinoline and heated with a little copper chromite (compare Kinney and Langlois, *J. Amer. Chem. Soc.*, 1931, **53**, 2189; Reichstein, Grüssner, and Zschokke, *Helv. Chim. Acta*, 1932, **15**, 1067; Taylor and Crawford, J., 1934, 1130) at 215° until evolution of carbon dioxide ceased (about 2 hours). When the liquid was then filtered and poured into an excess of dilute hydrochloric acid, 5-chloro-9-acetyltetrahydrocarbazole, colourless needles, m. p. 131°, after two crystallisations fom alcohol, was obtained. Its m. p. was not depressed by admixture with an authentic specimen (Moggridge and Plant, *loc. cit.*).

The 5- *and* 7-*Bromotetrahydrocarbazoles and their* 9-*Acetyl Derivatives*.—A mixture of *m*-bromophenylhydrazine (10·8 g.) and *cyclo*hexanone (7·2 g.) was heated for a few minutes on the steam-bath and then boiled for 5 minutes with dilute sulphuric acid (18%). The product was crystallised from the minimum quantity of boiling alcohol, and 7-*bromotetrahydrocarbazole* obtained in colourless plates, m. p. 183° (decomp.) (Found: C, 57·3; H, 5·0. $C_{12}H_{12}NBr$ requires C, 57·6; H, 4·8%). After this compound had been refluxed for ½ hour with a little acetic anhydride containing a drop of concentrated sulphuric acid, 7-*bromo*-9-*acetyltetrahydrocarbazole* separated, on cooling, in colourless needles, m. p. 123° (Found: C, 57·4; H, 4·9. $C_{14}H_{14}ONBr$ requires C, 57·5; H, 4·8%). A further quantity of the acetyl derivative was obtained by pouring the acetic anhydride filtrate into water and crystallising the precipitate from alcohol. A pure specimen of 7-bromotetrahydrocarbazole, m. p. 183° (decomp.), was prepared by refluxing the acetyl compound for ½ hour with equal volumes of alcohol and

concentrated hydrochloric acid, pouring the mixture into water, and crystallising the product from alcohol.

The alcoholic mother-liquor from the crystallisation of the original product was evaporated under reduced pressure below 60°, but the oily residue could not be made to solidify. It was acetylated as above, and when the substance which separated from the acetic anhydride on cooling was recrystallised from alcohol, *5-bromo-9-acetyltetrahydrocarbazole* was obtained in almost colourless needles, m. p. 137—139° (Found: C, 57·3; H, 5·0%). When hydrolysed like the 7-bromo-compound, the 5-bromotetrahydrocarbazole remained as a syrup which has not been obtained crystalline.

*Conversion of 7-Bromo- and 7-Chloro-9-acetyltetrahydrocarbazole into 7 : 9-Dinitro-8-anilino-ψ-indoxyl*spirocyclo*pentane.*—7-Bromo-9-acetyltetrahydrocarbazole (1 g.) in glacial acetic acid (5 c.c.) at 80° was treated with concentrated nitric acid (0·35 g.) in acetic acid (2·5 c.c.). Effervescence occurred with evolution of oxides of nitrogen, and when the colourless substance which separated on cooling was crystallised from alcohol, *7-bromo-10 : 11-dihydroxy-9-acetylhexahydrocarbazole* was obtained in colourless needles, m. p. 217° (decomp.) (Found: N, 4·4. $C_{14}H_{16}O_3NBr$ requires N, 4·3%). The yield was good, but was diminished when the process was carried out with greater quantities. After this substance had been refluxed for 6 hours with acetic anhydride, and the solution poured into water, *8-bromo-6-acetyl-ψ-indoxyl*spirocyclo*pentane* was obtained, which formed colourless needles, m. p. 107—108°, from alcohol (twice) (Found: N, 4·7. $C_{14}H_{14}O_2NBr$ requires N, 4·5%). This (1 g.) was hydrolysed by boiling with a mixture of water (10 c.c.), potassium hydroxide (3 g.), and alcohol (15 c.c.) for ½ hour, and the 8-bromo-ψ-indoxyl*spirocyclo*pentane (colourless prisms, m. p. 169°, from alcohol) which separated on dilution with water was nitrated by adding it to an excess of nitric acid (*d* 1·5) at room temperature. *8-Bromo-7 : 9-dinitro-ψ-indoxyl*spirocyclo*pentane* was then obtained by pouring the solution into water; it formed pale yellow prisms, m. p. 202°, from alcohol (Found: N, 11·7. $C_{12}H_{10}O_5N_3Br$ requires N, 11·8%). When this compound was added to an excess of aniline at room tmperature, the mixture treated with dilute hydrochloric acid, and the solid crystallised from alcohol, *7 : 9-dinitro-8-anilino-ψ-indoxyl*spirocyclo*pentane* was obtained in orange needles, m. p. 235° (Found: C, 58·8; H, 4·3. $C_{18}H_{16}O_5N_4$ requires C, 58·7; H, 4·3%).

When 7-chloro-9-acetyltetrahydrocarbazole was intimately mixed with twice its weight of glacial acetic acid and treated at 40° with concentrated nitric acid (1 mol.) in a little acetic acid, evolution of oxides of nitrogen occurred; a crystalline product separated on cooling. Recrystallisation from glacial acetic acid gave *7-chloro-10 : 11-dihydroxy-9-acetylhexahydrocarbazole* in colourless plates, m. p. 205—206° (Found: N, 5·2. $C_{14}H_{16}O_3NCl$ requires N, 5·0%), but the first product contained some 7-chloro-11-nitro-10-hydroxy-9-acetylhexahydrocarbazole. This was indicated by the fact that it melted with decomposition (at 185°) and evolved oxides of nitrogen on warming with glacial acetic acid, properties which are characteristic of the nitric acid addition compounds (Perkin and Plant, *loc. cit.*), and was confirmed by its high nitrogen content (Found: N, 5·9%). The dihydroxy-compound was converted successively into 8-chloro-6-acetyl-ψ-indoxyl*spirocyclo*pentane (colourless needles, m. p. 106°, from alcohol), 8-chloro-ψ-indoxyl*spirocyclo*pentane (colourless prisms, m. p. 145°, from alcohol), 8-chloro-7 : 9-dinitro-ψ-indoxyl*spirocyclo*pentane (pale yellow plates, m. p. 196°, from alcohol), and finally into 7 : 9-dinitro-8-anilino-ψ-indoxyl*spirocyclo*pentane, identical (mixed m. p.) with the substance described above, by reactions similar to those used for the analogous bromo-compounds, except that during the nitration of the *spiro*-compound the reaction mixture was warmed to about 60°.

5-Bromo-7-nitro-9-acetyltetrahydrocarbazole.—When 5-bromo-9-acetyltetrahydrocarbazole was treated with nitric acid under conditions similar to those described for the isomeric 7-bromo-compound, there was no effervescence, but the solution turned yellow and *5-bromo-7-nitro-9-acetyltetrahydrocarbazole* separated, on cooling, in yellow needles, m. p. 217° (Found: N, 8·4. $C_{14}H_{13}O_3N_2Br$ requires N, 8·3%). The yield was small, but no further crystalline material could be isolated even after the solution had been concentrated under reduced pressure and left for 3 weeks.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, November 18th,* 1938.]