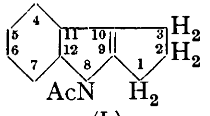
57. *Structural Problems in the Indole Group. Part IV. An Alternative Method for determining the Structure of Nitro-compounds.*

By S. G. P. Plant and W. D. Whitaker.

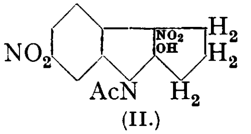
The exact constitutions of the isomeric 4(or 6)- and 6(or 4)-nitrodihydropentindoles could not be determined by the method used in analogous cases (Parts I and II), and an alternative way of attacking this type of problem has been developed. The 8-acetyl derivative of one of them gives a product by the addition of nitric acid at the 9 : 10-position which can be transformed *via* γ-*4-nitro-2 acetamidobenzoylbutyric acid* into the known 4-nitro-2-acetamidobenzoic acid, and it follows that the nitro-group in this isomer is in the 6-position. The constitutions of the two nitro-5-chlorodihydropentindoles obtained from *cyclo*pentanone-4-chloro-3-nitrophenylhydrazone follow from the conversion of the 8-acetyl derivative of one of them by analogous steps into *5-chloro-4-nitro-2-acetamidobenzoic acid* and then into *methyl 5-chloro-4-nitroanthranilate*, which have been synthesised for comparison. A further application of the method has resulted in the characterisation of the 4- and 6-nitro-2 : 3-dimethylindoles.

The ambiguity which exists regarding the structure of indoles obtained by an application of Fischer's reaction to meta-substituted phenylhydrazones has delayed the complete solution of several substitution problems in the indole series. In Parts I and II (J., 1936, 899; 1937, 1125) there is described the exact characterisation of some 4- and 6-nitro-substituted indoles by a method which involved the preparation of the corresponding 7-chloro-4-nitro-derivatives from 2-chloro-5-nitrophenylhydrazine and their reduction to halogen-free amines which were compared with the reduction products of the nitro-indoles themselves. The method is not applicable, however, to all nitro-compounds of this type and an alternative procedure has now been developed.

By the nitration of 8-acetyldihydropentindole (I) two nitro-derivatives, m. p. 195° and 154° [called the " 4(or 6)- " and the " 6(or 4)-nitro- " compound respectively], have been prepared and these on hydrolysis gave nitrodihydropentindoles identical with the two obtained by the elimination of ammonia from *cyclo*pentanone-*m*-nitrophenylhydrazone (Perkin and Plant, J., 1923, **123**, 3242; Plant, J., 1929, 2493), but a more exact determination of their structure was not at the time possible. In an effort to solve this problem along the lines mentioned above, *7-chloro-4-nitrodihydropentindole* has been synthesised, but attempts to reduce it resulted in resinification and recalled the behaviour of dihydropentindole itself under similar conditions. It has now been found, however, that the nitro-8-acetyldihydropentindole of m. p. 195° can be converted on further treatment with nitric acid into *6 : 10-dinitro-9-hydroxy-8-acetyltetrahydropentindole* (II), a reaction typical of this group of compounds. The latter has been degraded with alkali in a manner already observed in analogous cases to give γ-*4-nitro-2-acetamidobenzoylbutyric acid* (III), the structure of which was established by oxidation with aqueous potassium permanganate to 4-nitro-2-acetamidobenzoic acid, identical with the substance described by Wheeler and Barnes (*Amer. Chem. J.*, 1898, **20**, 217). It thus follows that the so-called " 4(or 6)- " and " 6(or 4)-nitro-8-acetyldihydropentindole " are the 6- and the 4-nitro-derivative respectively, and the corresponding 6- and 4-nitrodihydropentindoles obtained on hydrolysis and also synthetically melt at 153° and 199° respectively.



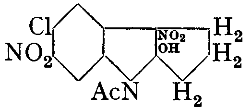
(I.)



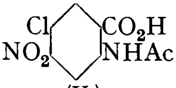
(II.)

(III.)

A similar problem is associated with 5-chlorodihydropentindole. Two isomeric nitro-derivatives, m. p. 167° and 182°, have been obtained by Massey and Plant (J., 1931, 1990) by applying Fischer's reaction to *cyclo*pentanone-4-chloro-3-nitrophenylhydrazone. One of these, m. p. 167°, was also obtained by nitrating various *N*-acyl derivatives of 5-chlorodihydropentindole and hydrolysing the products. The 8-acetyl derivative of this isomer has now been converted successively into *5-chloro-6 : 10-dinitro-9-hydroxy-8-acetyltetrahydropentindole* (IV), *γ-5-chloro-4-nitro-2-acetamidobenzoylbutyric acid*, and thence by oxidation into *5-chloro-4-nitro-2-acetamidobenzoic acid* (V). The structure of the last substance was established by synthesising a specimen by oxidising the 5-chloro-4-nitro-2-acetamidotoluene described by Kleiderer and Adams (*J. Amer. Chem. Soc.*, 1933, **55**, 4219). As both specimens of the acid (V) melted with decomposition (at 250°) they were converted by the action of methyl-alcoholic hydrogen chloride into *methyl 5-chloro-4-nitroanthranilate* (VI), which melted sharply and was more suitable for direct comparison. The substance, m. p. 167°, is therefore 5-chloro-6-nitrodihydropentindole and it follows that the isomer, m. p. 182°, is the 4-nitro-compound.



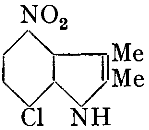
(IV.)



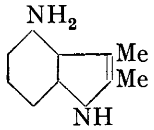
(V.)

(VI.)

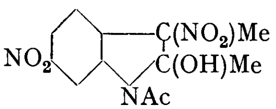
Plant and Tomlinson (J., 1933, 955) found that the nitration of 1-acetyl-2 : 3-dimethylindole gave the 4(or 6)-nitro-derivative, which was hydrolysed to 4(or 6)-nitro-2 : 3-dimethylindole, m. p. 142°, identical with a substance obtained synthetically from the *m*-nitrophenylhydrazone of methyl ethyl ketone. With the object of determining more completely the structure of this substance the 2-chloro-5-nitrophenylhydrazone of methyl ethyl ketone has been converted into *7-chloro-4-nitro-2 : 3-dimethylindole* (VII), which on reduction gave *4-amino-2 : 3-dimethylindole* (VIII), m. p. 163°, with elimination of chlorine. The product of the reduction of 4(or 6)-nitro-2 : 3-dimethylindole under similar conditions was a gum which has not been obtained solid or converted into a satisfactory derivative. Although this suggests that the 4(or 6)-nitro-compound in reality has the nitro-group in the 6-position, the evidence is not conclusive and confirmation was sought by employing the alternative procedure described above. The 4(or 6)-nitro-1-acetyl-2 : 3-dimethylindole readily gave *3 : 6-dinitro-2-hydroxy-1-acetyl-2 : 3-dimethyl-2 : 3-dihydroindole* (IX) on further nitration, and this was degraded with alkali. The product was probably mainly 4-nitro-2-acetamidoacetophenone, analogous to the acids derived from the corresponding dihydropentindole derivatives, but it was difficult to purify and might have contained small amounts of other substances such as 7-nitro-2-methyl-4-quinolone. The crude product, however, gave 4-nitro-2-acetamidobenzoic acid on oxidation, from which it follows that the original 4(or 6)-nitro-compound was in fact the 6-nitro-derivative.



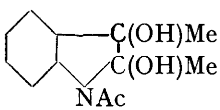
(VII.)



(VIII.)



(IX.)



(X.)

The application of Fischer's reaction to the *m*-nitrophenylhydrazone of methyl ethyl ketone is stated by Plant and Tomlinson to give a mixture of substances, and Bauer and Strauss (*Ber.*, 1932, **65**, 308) have isolated a product, m. p. 126°, which they call 6(4)-nitro-2 : 3-dimethylindole. The observations of Bauer and Strauss have been confirmed, although on further crystallisation from aqueous alcohol the m. p. was raised to 130°, and the product is obviously 4-nitro-2 : 3-dimethylindole, since its m. p. was depressed on admixture with the substance, m. p. 142°, mentioned above.

The results now described confirm the observation already made that the 6-position is the one normally involved during substitution into *N*-acyl-2 : 3-dialkylindoles. The nitration of 1-acetyl-2 : 3-dimethylindole has been found to give *2 : 3-dihydroxy-1-acetyl-2 : 3-dimethyl-2 : 3-dihydroindole* (X) in addition to the 6-nitro-derivative observed by Plant and Tomlinson, which is a further indication of the close similarity between 2 : 3-dimethylindole and tetrahydrocarbazole.

EXPERIMENTAL.

7-*Chloro*-4-*nitrodihydropentindole* (By R. C. G. Moggridge).—*cyclo*Pentanone-2-chloro-5-nitrophenylhydrazone separated in yellow needles, m. p. 101°, when a solution of the requisite hydrazine (5 g.) and ketone (5 c.c.) in alcohol (75 c.c.) was boiled for 5 minutes and allowed to cool. It was refluxed for 15 minutes with dilute sulphuric acid (200 c.c. of 25%) and *cyclo*pentanone (2 c.c.), the condenser was then removed, and boiling continued for a further 5 minutes. The solid was crystallised from glacial acetic acid, and 7-*chloro*-4-*nitrodihydropentindole* (1·7 g.) obtained in red needles, m. p. 251° (Found : Cl, 15·0. $C_{11}H_9O_2N_2Cl$ requires Cl, 15·0%).

Conversion of 6-*Nitro*-8-*acetyldihydropentindole into* 4-*Nitro* 2-*acetamidobenzoic Acid.*—When a suspension of 6-nitro-8-acetyldihydropentindole (0·45 g.), m. p. 195° [the " 4(or 6)-nitro-8-acetyldihydropentindole " of Perkin and Plant, *loc. cit,*], in boiling glacial acetic acid (2 c.c.) was treated with nitric acid (0·5 c.c., *d* 1·5) and then left for several hours, 6 : 10-*dinitro*-9-*hydroxy*-8-*acetyltetrahydropentindole* (0·3 g.), which formed colourless prisms, m. p. 215° (decomp.), from acetic acid, separated (Found : N, 13·2. $C_{13}H_{13}O_6N_3$ requires N, 13·7%). A solution of this substance (0·4 g.) in alcohol (6 c.c.) was treated at room temperature with aqueous potassium hydroxide (6 c.c. of 15%), and the whole left for 2 minutes and then acidified with concentrated hydrochloric acid. The resulting solution, which was green at first, rapidly became yellow, and after a few minutes γ-4-*nitro*-2-*acetamidobenzoylbutyric acid*, crystallising in pale yellow prisms, m. p. 165°, from alcohol, separated (Found : C, 53·0; H, 5·0. $C_{13}H_{14}O_6N_2$ requires C, 53·1; H, 4·8%). The acid (0·2 g.) was suspended in water (10 c.c.) containing acetic acid (0·5 c.c.), and the mixture treated gradually at 80° with aqueous potassium permanganate (1%) with constant shaking until a permanent pink colour was imparted to the solution. The whole was decolourised with sulphur dioxide, acidified with concentrated hydrochloric acid, and left for a few hours. The 4-nitro-2-acetamidobenzoic acid which separated was obtained in practically colourless needles, m. p. 215°, from aqueous alcohol, and was found to be identical (mixed m. p.) with a specimen of the acid prepared as described by Wheeler and Barnes (*loc. cit.*).

Synthesis of Methyl 5-*Chloro*-4-*nitroanthranilate and its Preparation from* 5-*Chloro*-6-*nitro*-8-*acetyldihydropentindole.*—5-Chloro-4-nitro-2-acetamidotoluene (Kleiderer and Adams, *loc. cit.*) was suspended in a little water containing a few drops of acetic acid and treated from time to time with aqueous potassium permanganate (1%), the reaction mixture being kept hot by immersion in a boiling water-bath. The oxidation proceeded slowly and most of the water evaporated. The whole was shaken occasionally and, after the addition of a little more than the theoretical amount of permanganate, it was decolourised with sulphur dioxide and acidified with concentrated hydrochloric acid. After the precipitate had been dissolved in dilute aqueous ammonia, the solution filtered, and then acidified with hydrochloric acid, the recovered 5-*chloro*-4-*nitro*-2-*acetamidobenzoic acid* was crystallised from glacial acetic acid and obtained in pale yellow needles, m. p. 250° (decomp.) (Found : N, 10·9. $C_9H_7O_5N_2Cl$ requires N, 10·8%). The acid was then refluxed for 6 hours with methyl-alcoholic hydrogen chloride and the product was obtained by the addition of dilute aqueous sodium carbonate. It was ground with concentrated hydrochloric acid, and the solution filtered; *methyl* 5-*chloro*-4-*nitroanthranilate*, recovered from the filtrate by dilution with water, crystallised from methyl alcohol in red needles, m. p. 140° (Found : C, 41·8; H, 3·1. $C_8H_7O_4N_2Cl$ requires C, 41·6; H, 3·0%).

The " 5-chloro-4(or 6)-nitro-8-acetyldihydropentindole " of Massey and Plant (*loc. cit.*) was converted into 5-*chloro*-6 : 10-*dinitro*-9-*hydroxy*-8-*acetyltetrahydropentindole*, which formed colourless prisms, m. p. 198° (decomp.), from glacial acetic acid (Found : N, 11·8. $C_{13}H_{12}O_6N_3Cl$ requires N, 12·3%), by a process similar to that described for the chlorine-free analogue except that the nitration was carried out at 100°. It was degraded with alkali as before to γ-5-*chloro*-4-*nitro*-2-*acetamidobenzoylbutyric acid*, which crystallised from alcohol in yellow plates, m. p. 133° (Found : N, 8·3. $C_{13}H_{13}O_6N_2Cl$ requires N, 8·5%). The latter was oxidised with aqueous potassium permanganate as described above to give 5-chloro-4-nitro-2-acetamidobenzoic acid, m. p. 250° (decomp.), identical (mixed m. p.) with the synthetical specimen. Its identity was confirmed by conversion into methyl 5-chloro-4-nitroanthranilate, m. p. 140°.

4-*Amino*-2 : 3-*dimethylindole.*—The 2-chloro-5-nitrophenylhydrazone of methyl ethyl ketone, which crystallised in yellow needles, m. p. 65°, from alcohol, was formed when molecular proportions of the hydrazine and ketone were heated on the steam-bath under reflux for ½ hour. After it had been refluxed for 4 hours with a mixture of equal volumes of glacial acetic acid and concentrated hydrochloric acid, 7-*chloro*-4-*nitro*-2 : 3-*dimethylindole* separated on cooling. It was recrystallised from glacial acetic acid and obtained in orange prisms, m. p. 218° (Found : N, 12·6. $C_{10}H_9O_2N_2Cl$ requires N, 12·5%). This indole (15 g.) was heated on a steam-bath under reflux with a mixture of alcohol (250 c.c.), concentrated hydrochloric acid (250 c.c.), and granulated tin (125 g.) until the yellow colour of the liquid had completely disappeared (about 10 hours). After the whole had been made alkaline with aqueous sodium hydroxide, the alcohol was removed in steam, and the solid collected when cold by filtration. Both the solid and the filtrate were extracted with ether, the united extracts dried with potassium carbonate, and the solvent removed by distillation. The residual brown gum became solid on standing, and was obtained colourless by grinding with a little ether. On crystallisation from chloroform 4-*amino*-2 : 3-*dimethylindole* separated in colourless plates, m. p. 163° (Found : C, 74·7; H, 7·1. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·5%).

Conversion of 6-*Nitro*-1-*acetyl*-2 : 3-*dimethylindole into* 4-*Nitro*-2-*acetamidobenzoic Acid.*—Prepared from 6-nitro-1-acetyl-2 : 3-dimethylindole [the 4(or 6)-nitro-1-acetyl-2 : 3-dimethylindole of Plant and Tomlinson, *loc. cit.*] as described above for the corresponding dihydropentindole derivative, 3 : 6-*dinitro*-2-*hydroxy*-1-*acetyl*-2 : 3-*dimethyl*-2 : 3-*dihydroindole* separated from glacial acetic acid in pale yellow prisms, m. p. 198° (decomp.) (Found : N, 14·6. $C_{12}H_{13}O_6N_3$ requires N, 14·2%). It was treated (0·2 g.) with a mixture of alcohol (3 c.c.) and aqueous potassium hydroxide (3 c.c. of 15%), and the whole boiled for a few minutes. The orange precipitate which was obtained on the addition of an excess of dilute hydrochloric acid, probably mainly 4-nitro-2-acetamidoacetophenone, was converted without further purification into 4-nitro-2-acetamidobenzoic acid, identified by mixed m. p. with an authentic specimen, by oxidation with dilute aqueous permanganate as described above.

2 : 3-*Dihydroxy*-1-*acetyl*-2 : 3-*dimethyl*-2 : 3-*dihydroindole.*—The acetic acid mother-liquor from the preparation of a considerable quantity of 6-nitro-1-acetyl-2 : 3-dimethylindole as described by Plant and Tomlinson (*loc. cit.*) was concentrated under reduced pressure first at room temperature for 3 hours to remove oxides of nitrogen and then at 45° to one-fourth of its original volume. When the solution was then cooled and shaken with an equal volume of ether, 2 : 3-*dihydroxy*-1-*acetyl*-2 : 3-*dimethyl*-2 : 3-*dihydroindole*, crystallising in pale yellow prisms, m. p. 132—134°, from alcohol, was precipitated (Found : C, 65·2; H, 6·8; N, 6·1. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%).

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