CCCXXXI.—*Derivatives of Dihydropentindole. Part II.*

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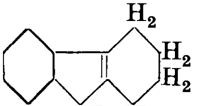
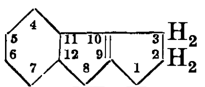
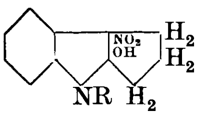
IN view of the varied nature of the addition products formed when nitric acid acts upon the 9-acyltetrahydrocarbazoles (I) (Perkin and Plant, J., 1923, **123**, 676; Manjunath and Plant, J., 1926, 2260; Plant and Rosser, J., 1928, 2454; Plant and Rutherford, this vol., p. 1970) it became of interest to continue in certain directions the investigation of the reactions of derivatives of dihydropentindole (II; R = H), a preliminary study of which has been described (Perkin and Plant, J., 1923, **123**, 3242). In order to identify some of the products formed during the course of this work,



(I.)



(II.)



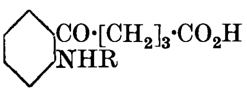
(III.)

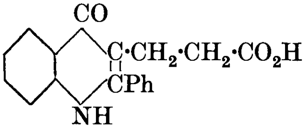
the 4-, 5-, 6-, and 7-*nitrodihydropentindoles* have been prepared. An application of Fischer's indole synthesis to cyclo*pentanone*-o- and -p-*nitrophenylhydrazones* led to the 7- and the 5-nitro-compound, respectively, and a similar procedure with the m-*nitrophenylhydrazone* gave a mixture of the 4- and the 6-nitro-derivative. Since it is not known which of the two alternative positions is occupied by the nitro-group in each of the last two substances, one (m. p. 153°) has been called the 4 (or 6)-, and the other (m. p. 199°) the 6 (or 4)-nitrodihydropentindole. It is interesting to recall that, in the case of *cyclo*hexanone-*m*-nitrophenylhydrazone, the action of dilute sulphuric acid leads to only one of the two possible isomeric nitrotetrahydrocarbazoles (Perkin and Plant, J., 1921, **119**, 1825). It has now been possible to prove, by hydrolysis, that the two nitro-substitution products (m. p.'s 195° and 154°) of 8-acetyldihydropentindole, described in Part I, have the 4 (or 6)- and the 6 (or 4)-configuration, respectively. In addition, 4 (or 6)-*nitro*-8-*benzoyldihydropentindole* has been obtained directly from the corresponding 8-acyl derivative. It thus transpires that, as in the tetrahydrocarbazole series, direct nitration of the 8-acyldihydropentindoles in acetic acid solution results in meta-substitution with respect to the >NR group.

In Part I it has been shown that the action of nitric acid on 8-acetyldihydropentindole yields, not only these substitution products, but also an addition compound (III; R = Ac), and it has been found during the course of the present work that, under similar conditions, the 8-*benzoyl* and 8-*carbethoxy*-derivatives also give exactly analogous products (III ; R = Bz and CO_2Et). These results are both interesting and surprising, because, in the closely related tetrahydrocarbazole series, the benzoyl compound alone gives a substance of this type, whilst the other acyl derivatives so far investigated have all yielded products by the addition of two hydroxyl groups at the double linkage.

The nitric acid addition compounds (III ; R = Ac, Bz, and CO_2Et) now described are characterised by the remarkable differences displayed in their reactions. The acetyl derivative was found to be readily soluble in cold aqueous potassium hydroxide, and, after the solution had been acidified with acetic acid, a substance was obtained which resulted from the removal of the acetyl group by hydrolysis. The product of this reaction, therefore, appears to be 10-*nitro*-9-*hydroxytetrahydropentindole* (III ; R = H). The benzoyl compound (III ; R = Bz), on the other hand, was found to be both insoluble in, and unchanged by, aqueous potassium hydroxide, but it dissolved gradually in a boiling aqueous-alcoholic solution of this reagent, and, on acidification, γ-o-*benzamidobenzoylbutyric acid* (IV ; R = Bz) was obtained. Further treatment of the latter compound with hot aqueous potassium hydroxide gave as the main product a substance which was derived by the elimination of a molecule of water and was, consequently, probably β-2-*phenyl*-4-*quinolone*-3-*propionic acid* (V). In this series of reactions the benzoyl compound (III ; R = Bz) behaves in a somewhat similar manner to the corresponding tetrahydrocarbazole derivative. The carbethoxy-compound (III ; R = CO_2Et), like the acetyl derivative, readily dissolved in cold aqueous potassium hydroxide, but gave, under these conditions, γ-o-*carbethoxyaminobenzoylbutyric acid* (IV ; R = CO_2Et), from which the corresponding *amino-acid* (IV ; R = H) was obtained by the action of hot aqueous alkali.

(IV.)





(V.)

In the tetrahydrocarbazole series the nitric acid addition products can be converted into the corresponding dihydroxy-compounds (through replacement of NO_2 by OH) by the action of boiling alcohol. The various substances of the type (III) now described were found, on the other hand, to be quite stable under these conditions. The most striking feature of the results recorded in this communication is the remarkable difference observed in so many of the reactions of such closely related compounds.

EXPERIMENTAL.

The Nitrodihydropentindoles.—After a solution of *p*-nitrophenylhydrazine (9 g.) and *cyclo*pentanone (7·5 g.) in alcohol (100 c.c.) had been boiled for 5 minutes and then allowed to cool, cyclo*pentanone*-p-*nitrophenylhydrazone* was obtained in bright yellow plates, m. p. 154° (Found : N, 19·2. $C_{11}H_{13}O_2N_3$ requires N, 19·2%). A mixture of this hydrazone (5 g.), sulphuric acid (100 c.c. of 30%), and *cyclo*pentanone (3 c.c.) was boiled under reflux for 15 minutes, and the ketone was then removed in steam. After cooling, the solid product was treated in boiling alcohol with charcoal, and recovered by treating the filtered solution with water. On crystallisation from alcohol, 5-*nitrodihydropentindole* was obtained in orange-coloured needles, m. p. 165° (Found : N, 13·9. $C_{11}H_{10}O_2N_2$ requires N, 13·8%).

By a similar procedure, *cyclo*pentanone-*o*-nitrophenylhydrazone was obtained in reddish-brown plates, m. p. 72°, and was converted into 7-*nitrodihydropentindole,* which separated from alcohol in red prisms, m. p. 123° (Found : N, 13·8%).

cyclo*Pentanone*-m-*nitrophenylhydrazone* was isolated from alcohol in orange-red prisms, m. p. 120° (Found : N, 19·2%). The crude mixture of solids obtained by heating this hydrazone (5 g.) with sulphuric acid (150 c.c. of 23%) under reflux for 12 minutes was crystallised from alcohol (with charcoal) and 6 (or 4)-*nitrodihydropentindole* was isolated in scarlet plates, m. p. 199° (Found : N, 13·5%). After the mother-liquor had been diluted with water, and the solid again crystallised from alcohol, a small quantity of a mixture of nitro-compounds was obtained, but, when the resulting mother-liquor was once again diluted, and the product crystallised from a still smaller quantity of alcohol, 4 (or 6)-*nitrodihydropentindole* was obtained pure in golden-yellow needles, m. p. 153° (Found : N, 14·2%). The relative quantities of the 6 (or 4)- and 4 (or 6)-derivatives formed in this reaction were in the ratio of approximately 3 : 1.

When the nitro-8-acetyldihydropentindole (m. p. 195°), prepared by Perkin and Plant (*loc. cit.*), was treated for 10 minutes with boiling aqueous-alcoholic potassium hydroxide, the product obtained, recovered by the addition of water, proved to be identical with the 4 (or 6)-nitrodihydropentindole described above, since it separated from chloroform in orange-coloured prisms, m. p. 153° (not depressed by admixture with the synthetical product). The second nitro-substitution product (m. p. 154°) of Perkin and Plant (*loc. cit.*), on similar treatment, yielded 6 (or 4)-nitrodihydropentindole (m. p. 199°), identical in every way with the synthetical compound.

Reactions of 10-*Nitro*-9-*hydroxy*-8-*acetyltetrahydropentindole.*—This substance, mentioned in the previous communication, was prepared free from the nitro-substitution products by treating a solution of 8-acetyldihydropentindole (10 g.) in glacial acetic acid (40 c.c.) at 65° with fuming nitric acid (3·5 c.c., *d* 1·5). The temperature rose immediately and the solution boiled. On cooling and stirring, the product (3 g.) separated; after being collected and washed with acetic acid, it was obtained pure and colourless. Its solution in alcohol was boiled for 2½ hours, but, on cooling, it separated quantitatively and unchanged.

This addition product (2 g.) dissolved rapidly in aqueous potassium hydroxide (25 c.c. of 20%) at room temperature, and, on dilution of a test portion with water, nothing separated. The main part of the solution, after 3 minutes, was acidified with acetic acid; it then remained clear for a few seconds and subsequently became turbid owing to the separation of an oily product. This solidified on being stirred, and, after crystallisation from alcohol, 10-*nitro*-9-*hydroxytetrahydropentindole* was obtained in colourless plates, m. p. 160° (decomp.) (Found: C, 59·8; H, 5·6; N, 12·4. $C_{11}H_{12}O_3N_2$ requires C, 60·0; H, 5·4; N, 12·7%). After its solution in alcohol had been boiled for 2 hours, and the solvent then distilled off, this substance was recovered unchanged.

Action of Nitric Acid on 8-*Benzoyldihydropentindole.*—A mixture of dihydropentindole (12 g.), acetone (80 c.c.), and aqueous potassium hydroxide (20 c.c. of 66%) was treated gradually with benzoyl chloride (16 c.c.), the whole being vigorously shaken. The product was isolated by dilution with water, and, after crystallisation from alcohol, 8-*benzoyldihydropentindole* was obtained in large colourless plates, m. p. 99° (Found: N, 5·3. $C_{18}H_{15}ON$ requires N, 5·4%). By boiling its solution in aqueous-alcoholic potassium hydroxide for 15 minutes and subsequently adding water, dihydropentindole was obtained.

A solution of the benzoyl compound (31 g.) in glacial acetic acid (120 c.c.) at 65° was treated with nitric acid (12 g., *d* 1·4), dissolved in acetic acid (15 c.c.). The temperature rose rapidly to 90°, and, after cooling and stirring, a mixture (15 g.) of two products separated. When this was crystallised from acetone, 10-*nitro*-9-*hydroxy*-8-*benzoyltetrahydropentindole* separated in colourless plates (6 g.), m. p. 187° (Found: N, 8·6. $C_{18}H_{16}O_4N_2$ requires N, 8·6%). After the acetone mother-liquor had been evaporated, and the solid recrystallised from alcohol, 4 (or 6)-*nitro*-8-*benzoyldihydropentindole* (4·5 g.) was obtained in yellow needles, m. p. 160° (Found: N, 9·0. $C_{18}H_{14}O_3N_2$ requires N, 9·1%). When a solution of this product in aqueous-alcoholic potassium hydroxide was boiled for 5 minutes and then diluted with water, 4 (or 6)-nitrodihydropentindole (m. p.

153°) was obtained and was proved by a mixed m.-p. determination to be identical with the synthetical product.

The addition product (III; R = Bz) was completely unchanged after its solution in alcohol had been boiled for 2 hours, being recovered in a pure condition by distillation of the solvent. It was quite insoluble in 20% aqueous potassium hydroxide, even on boiling for a few moments, and was recovered unchanged. When this substance (2 g.) was added to a boiling mixture of alcohol (50 c.c.) and aqueous potassium hydroxide (12 c.c. of 7%), it gradually went into solution during 20 minutes. The whole was then cooled, diluted with water, and acidified with concentrated hydrochloric acid. The product separated as an oil, which rapidly solidified on stirring, and, after recrystallisation from alcohol, *γ-o-benzamidobenzoylbutyric acid* was obtained in colourless prisms, m. p. 170—171° (Found : N, 4·4. $C_{18}H_{17}O_4N$ requires N, 4·5%). This compound dissolves readily in dilute aqueous ammonia.

When a solution of this acid (2 g.) in aqueous potassium hydroxide (35 c.c. of 15%) was heated on the steam-bath for an hour, then diluted with an equal volume of water and acidified with concentrated hydrochloric acid, nothing separated, but, after the solution had been made alkaline again and re-acidified with acetic acid, a colourless product was obtained. This was purified by boiling for a few moments with acetone, in which the main portion was sparingly soluble, and subsequently crystallised from aqueous alcohol, from which β-2-*phenyl*-4-*quinolone*-3-*propionic acid* separated in colourless prisms, m. p. 218—220° (Found : C, 73·3; H, 5·3. $C_{18}H_{15}O_3N$ requires C, 73·7; H, 5·1%).

Action of Nitric Acid on Ethyl Dihydropentindole-8-*carboxylate*.—This *ester* was obtained by a process similar to that employed for the 8-benzoyl derivative, an equal volume of ethyl chloroformate being used instead of benzoyl chloride. It separated from alcohol in colourless prisms, m. p. 84° (Found : N, 6·2. $C_{14}H_{15}O_2N$ requires N, 6·1%), and on hydrolysis with boiling aqueous-alcoholic potassium hydroxide, readily yielded dihydropentindole.

When a solution of the ester (15 g.) in glacial acetic acid (45 c.c.) at 55° was treated with nitric acid (5·5 c.c., *d* 1·4), dissolved in acetic acid (6 c.c.), the temperature rose immediately to 90°, but nothing separated from the cooled solution after standing for 2 days. The solution was then evaporated to small bulk under reduced pressure, and, on cooling and stirring, a product, m. p. 120°, was obtained. After recrystallisation from alcohol, *ethyl* 10-*nitro*-9-*hydroxytetrahydropentindole*-8-*carboxylate* was isolated in colourless prisms, m. p. 128° (Found : N, 9·9. $C_{14}H_{16}O_5N_2$ requires N, 9·6%). No appreciable quantity of a nitro-substitution product was obtained in this experiment. The above addition product was also obtained by the use of fuming nitric acid (*d* 1·5) under similar conditions.

The addition product (1 g.) dissolved slowly in aqueous potassium hydroxide (50 c.c. of 7%) at room temperature, and, after being acidified with glacial acetic acid, the solution remained clear for about 2 minutes and then became turbid. After 24 hours, the product had separated as a colourless solid, m. p. 143—145°. On crystallisation from alcohol, γ-o-*carbethoxyaminobenzoylbutyric acid* was isolated in colourless prisms, m. p. 152° (Found : C, 60·3; H, 6·1; N, 5·2. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1; N, 5·0%). In admixture with 10-nitro-9-hydroxytetrahydropentindole, the substance melted at a much lower temperature.

A solution of this acid (1·2 g.) in aqueous potassium hydroxide (35 c.c. of 15%) was heated for an hour on the steam-bath, cooled, acidified with concentrated hydrochloric acid, and filtered from a very small quantity of solid material. It was then made alkaline with potassium hydroxide and acidified with acetic acid, whereupon the product gradually separated during the course of a few hours. After crystallisation from dilute alcohol, γ-o-*aminobenzoylbutyric acid* was obtained in pale brown plates, m. p. 125—126° (Found : N, 6·9. $C_{11}H_{13}O_3N$ requires N, 6·8%).

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