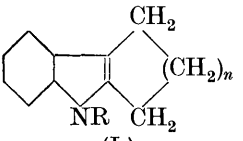
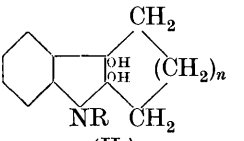
CCLXIX.—*The Action of Nitric Acid on Polycyclic Indole Derivatives. Part X. Further Derivatives of Dihydropentindole.*

By Joseph Paulinus Massey and Sydney Glenn Preston Plant.

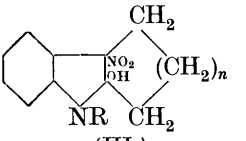
In earlier parts of this series it has been shown that the 9-acyltetrahydrocarbazoles (I; $n = 2$) yield addition products when treated with nitric acid in acetic acid solution. In the majority of cases these products are of the type (II; $n = 2$), but occasionally nitric acid is



(I.)



(II.)

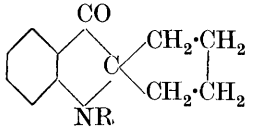


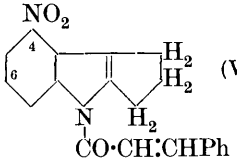
(III.)

added on to the double linkage to give a substance of the formula (III; $n = 2$). It has been shown in Parts III and VIII (J., 1923,

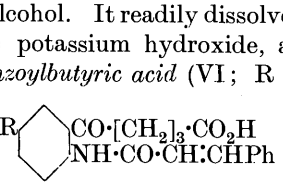
123, 3242; 1929, 2493), however, that 8-acetyl-, 8-benzoyl-, and 8-carbethoxy-dihydropentindole (I; R = Ac, Bz, and CO_2Et; $n = 1$) all yield addition products of the type (III; $n = 1$), and a dihydroxy-compound analogous to (II) has not so far been detected in this series. Moreover, the carbazole derivatives (III; $n = 2$) yield the corresponding dihydroxy-compounds (II; $n = 2$) when their alcoholic solutions are boiled, but the related pentindole derivatives (III; $n = 1$) hitherto studied have all proved to be stable towards boiling alcohol.

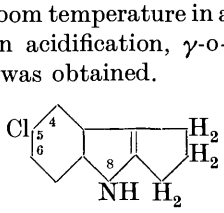
In view of the very interesting transformations which the dihydroxyhexahydrocarbazoles (II; $n = 2$) can undergo, *e.g.*, the facile conversion into the 6-acyl-ψ-indoxyl*spirocyclo*pentanes (IV), it became of interest to extend the study of this reaction with nitric acid to other derivatives of dihydropentindole in the hope that a dihydroxy-compound of the type (II; $n = 1$) might be obtained, either directly or from the nitric acid addition product (III; $n = 1$) by treatment with boiling alcohol. Furthermore, the three compounds of the formula (III; $n = 1$) so far described differ so greatly in their reactions on treatment with alkalis that interest also attaches to a study of further examples from this point of view.

(IV.) 

 (V.)

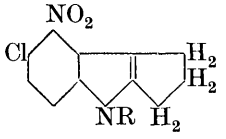
8-*Cinnamoyldihydropentindole* (I; R = CHPh·CH·CO; $n = 1$) has now been prepared by the action of cinnamoyl chloride and potassium hydroxide on dihydropentindole in acetone solution, and, when it was treated with nitric acid under certain conditions (p. 1993), it yielded 4(or 6)-*nitro*-8-*cinnamoyldihydropentindole* (V) and 10-*nitro*-9-*hydroxy*-8-*cinnamoyltetrahydropentindole* (III; R = CHPh·CH·CO; $n = 1$). The latter was, however, unchanged by boiling alcohol. It readily dissolved at room temperature in aqueous-alcoholic potassium hydroxide, and, on acidification, γ-o-*cinnamamidobenzoylbutyric acid* (VI; R = H) was obtained.

(VI.) 

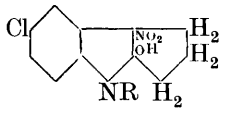
 (VII.)

A study was then made of some acyl derivatives of 5-*chlorodihydropentindole* (VII). The action of nitric acid on the analogous 6-chloro-9-acyltetrahydrocarbazoles has already been examined

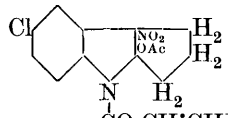
(Part VI; J., 1928, 2454), and it was during the course of these latter investigations that the conversion of the nitric acid addition compounds to the corresponding dihydroxyhexahydrocarbazoles by the action of boiling alcohol was discovered. The indole (VII) was prepared by the application of the Fischer reaction to *cyclo*pentanone-*p*-chlorophenylhydrazone, and it has been converted into its 8-*acetyl*, 8-*carbethoxy*-, and 8-*cinnamoyl* derivatives; attempts to prepare the 8-benzoyl compound have been unsuccessful. In order to establish the structures of some of the nitration products described below, the Fischer reaction was also applied to *cyclo*pentanone-4-chloro-3-nitrophenylhydrazone, and a mixture of the two indoles theoretically possible was obtained. In accordance with the procedure previously adopted in analogous cases, one of these (m. p. 167°) has been called 5-*chloro*-4(or 6)-*nitro*- and the other (m. p. 182°) 5-*chloro*-6(or 4)-*nitro-dihydropentindole*. When these three acyl derivatives of 5-chlorodihydropentindole were treated with nitric acid in acetic acid solution under various conditions (see p. 1995), essentially similar results were obtained in each case. The 4(or 6)-nitro-derivatives (VIII; R = Ac, CO_2Et, and CHPh:CH·CO) and the addition products (IX; R = Ac, CO_2Et, and CHPh:CH·CO) were isolated, but the last three were all stable towards boiling alcohol. The constitutions of the nitro-derivatives (VIII) were established by



(VIII.)



(IX.)



(X.)

hydrolysis, 5-chloro-4(or 6)-nitrodihydropentindole, identical with the synthetic product, being obtained in each case. Of the nitric acid addition compounds (IX), it was found that the cinnamoyl derivative yielded *γ-5-chloro-2-cinnamamidobenzoylbutyric acid* (VI; R = Cl) when its aqueous-alcoholic potassium hydroxide solution was heated, but attempts to obtain crystalline products from the analogous acetyl and carbethoxy-derivatives by treatment with potassium hydroxide under various conditions were unsuccessful. The nitration of 8-cinnamoyldihydropentindole has yielded, in addition, an interesting new type of product. From the ultimate acetic acid mother-liquors, on concentration, there separated a substance which analysis indicated was 5-*chloro*-10-*nitro*-9-*acetoxy*-8-*cinnamoyltetrahydropentindole* (X). This structure was confirmed by the fact that, like the normal addition compound (IX; R = CHPh:CH·CO), this substance gave γ-5-chloro-2-cinnamamidobenzoylbutyric acid when its solution in aqueous-alcoholic potassium

hydroxide was boiled. It was also found to be unaffected by boiling alcohol.

Although the experiments now described have not brought to light a compound of the dihydroxytetrahydropentindole type (II; $n = 1$), they serve to emphasise the remarkable differences which exist between the 8-acyldihydropentindoles (I; $n = 1$) and the 9-acyltetrahydrocarbazoles (I; $n = 2$) in their behaviour towards nitric acid. Thus, the formation of a nitric acid addition product (III; $n = 1$) appears to be the invariable rule with the former derivatives, but, whilst this reaction sometimes occurs with the latter, the more normal course involves the addition of two hydroxyl groups at the double linkage.

In the work hitherto described in this field the procedure has been, in general, to treat the acyl derivative in question with a relatively small amount of nitric acid (very little more than an equimolecular proportion), but experiments are now in progress involving the use of a considerable excess of the reagent. These have brought to light some interesting new compounds which will form the subject of a future communication.

EXPERIMENTAL.

Action of Nitric Acid on 8-Cinnamoyldihydropentindole.—A boiling mixture of dihydropentindole (4 g.), acetone (30 c.c.), and aqueous potassium hydroxide (7 g. of 66%) was treated with a solution of cinnamoyl chloride (6 g.) in acetone (5 c.c.), the whole being well shaken. After dilution with water, the product was crystallised successively from alcohol and acetone, and *8-cinnamoyldihydropentindole* was obtained in yellow plates, m. p. 156° (Found : N, 4·6. $C_{20}H_{17}ON$ requires N, 4·9%).

A suspension of 8-cinnamoyldihydropentindole (2 g.) in glacial acetic acid (50 c.c.) at 40° was treated with a solution of nitric acid (0·75 g., *d* 1·42) in acetic acid (3 c.c.), and, after the mixture had been heated to 70°, a clear solution was obtained. On cooling, 4(or 6)-*nitro*-8-*cinnamoyldihydropentindole* separated, and, after crystallisation from acetone, it was isolated in pale yellow prisms, m. p. 230° (Found : N, 8·3. $C_{20}H_{16}O_3N_2$ requires N, 8·4%). When a solution of this product in aqueous-alcoholic potassium hydroxide was boiled for an hour and then diluted with water, a solid was obtained which, after crystallisation from chloroform, melted at 153° and was proved (mixed m. p.) to be identical with the 4(or 6)-nitrodihydropentindole described by Plant (J., 1929, 2495). The alkaline filtrate, on acidification, yielded cinnamic acid.

The same nitro-compound (m. p. 230°) was obtained from the cinnamoyl derivative when the experiment was repeated at 90°

with less acetic acid (25 c.c.), or by the use of fuming nitric acid (0·5 g., *d* 1·5) at 90°. The acetic acid mother-liquors from these experiments were concentrated to a very small volume under reduced pressure. On cooling, the residue set to a sticky brown solid, but, after rubbing with a little acetic acid, a product was collected by filtration. When this had been crystallised from acetic acid containing a small quantity of water, *10-nitro-9-hydroxy-8-cinnamoyltetrahydropentindole* was obtained in colourless needles, m. p. 187° (decomp.) (Found: C, 68·5; H, 5·0; N, 8·5. $C_{20}H_{18}O_4N_2$ requires C, 68·6; H, 5·1; N, 8·0%). When a solution of the latter product in alcohol was boiled for ¾ hour and then cooled, a large proportion of the substance separated unchanged, and the remainder was recovered on dilution with water. When the substance was shaken for a minute at room temperature with equal volumes of alcohol and aqueous potassium hydroxide (15%), an almost clear solution was obtained, and, after filtration and acidification with dilute hydrochloric acid, a solid product soon separated. After being crystallised from glacial acetic acid, *γ-o-cinnamamidobenzoylbutyric acid* was obtained in colourless prisms, m. p. 162° (Found: C, 70·7; H, 5·7. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·6%); this acid was readily soluble in aqueous sodium carbonate, from which it was reprecipitated on acidification.

5-Chlorodihydropentindole and its Nitro-derivatives.—When a solution of *p*-chlorophenylhydrazine (4·5 g.) and *cyclo*pentanone (3·5 g.) in alcohol (20 c.c.) was boiled for 10 minutes and then allowed to cool, *cyclo*pentanone-*p*-chlorophenylhydrazone separated in colourless plates, m. p. 99—100°. After the hydrazone (5 g.) had been treated with water (50 c.c.) and concentrated sulphuric acid (5·5 c.c.), and the mixture warmed on the steam-bath for ½ hour, *5-chlorodihydropentindole* separated. The product was obtained from glacial acetic acid in glistening colourless plates, m. p. 132° (Found: N, 7·3. $C_{11}H_{10}NCl$ requires N, 7·3%).

*cyclo*Pentanone (1·5 g.) was added to a solution of 4-chloro-3-nitrophenylhydrazine (2·5 g.; prepared by the method described by Plant and Rosser, J., 1928, 2461) in the minimum quantity of boiling alcohol, and, after the solution had been boiled for 10 minutes and then cooled, *cyclo*pentanone-4-chloro-3-nitrophenylhydrazone separated in orange-red plates, m. p. 106—107°. A mixture of this hydrazone (13 g.), sulphuric acid (260 c.c. of 30%), and *cyclo*pentanone (8 c.c.) was boiled under reflux for 20 minutes, and the ketone was removed in steam. The solid product was then dissolved in alcohol, and the solution boiled with charcoal for 10 minutes. After being filtered and cooled, the product was recovered by dilution with water. Separation of the two indoles was effected by

crystallisation from benzene; one crystallised first in clusters of yellow needles, and the other later in groups of red prisms. By decanting the solution when the second product started to separate, and recrystallising the first from benzene, *5-chloro-4(or 6)-nitrodihydropentindole* was obtained in yellow needles, m. p. 167° (Found : N, 12·0. $C_{11}H_9O_2N_2Cl$ requires N, 11·8%). The isomeric *5-chloro-6(or 4)-nitrodihydropentindole*, which separated later from the benzene solution, was recrystallised from glacial acetic acid and obtained in red plates, m. p. 182° (Found : N, 11·7%).

cyclo*Pentanone-4-chloro-2-nitrophenylhydrazone* separated when a solution of the corresponding hydrazine (prepared as described by Plant and Rosser, *loc. cit.*) and an excess of *cyclo*pentanone in alcohol was boiled for 15 minutes and then cooled. On recrystallisation from alcohol it was obtained in red needles, m. p. 128° (Found : N, 16·5. $C_{11}H_{12}O_2N_3Cl$ requires N, 16·6%), but attempts to convert it into the corresponding indole have so far been unsuccessful.

Action of Nitric Acid on 5-Chloro-8-acetyldihydropentindole.— When a solution of 5-chlorodihydropentindole (3 g.) in acetic anhydride (10 c.c.) was boiled for 6 hours and then allowed to cool, *5-chloro-8-acetyldihydropentindole* separated. After recrystallisation from glacial acetic acid it was obtained in colourless needles, m. p. 142° (Found : N, 6·0. $C_{13}H_{12}ONCl$ requires N, 6·0%).

When a solution of this latter product (4 g.) in glacial acetic acid (50 c.c.) at 69° was treated with nitric acid (2 g., *d* 1·42), dissolved in acetic acid (5 c.c.), the temperature rose to 74°, and, on cooling, a solid separated. After recrystallisation from glacial acetic acid, *5-chloro-4(or 6)-nitro-8-acetyldihydropentindole* was isolated in yellow prisms, m. p. 222° (Found : C, 56·4; H, 3·7. $C_{13}H_{11}O_3N_2Cl$ requires C, 56·0; H, 4·0%). Its constitution was established by boiling its solution in aqueous-alcoholic potassium hydroxide for an hour and then diluting it with water; 5-chloro-4(or 6)-nitrodihydropentindole, identical with the product described above, was obtained. The acetic acid mother-liquor from the above nitration product was concentrated under reduced pressure to one-fourth of its volume, and, on cooling, a colourless substance separated. When this was recrystallised from acetone, *5-chloro-10-nitro-9-hydroxy-8-acetyltetrahydropentindole* was obtained in colourless plates, m. p. 197° (decomp.) (Found : C, 53·2; H, 4·3; N, 9·5, 9·7. $C_{13}H_{13}O_4N_2Cl$ requires C, 52·6; H, 4·4; N, 9·4%). This product, unaccompanied by the above 4(or 6)-nitro-derivative, separated slowly, on standing, after nitric acid (3 g., *d* 1·42) in acetic acid (5 c.c.) had been added to a suspension of the acetyl compound (6 g.) in glacial acetic acid (30 c.c.) at 80°, and this procedure, therefore, constitutes a more convenient method than the former for preparing this addition compound.

A solution of this nitric acid addition compound in alcohol was boiled for an hour, but the product separated unchanged in colourless plates on cooling. No crystalline substance has been obtained by the action of aqueous or aqueous-alcoholic potassium hydroxide on it under various conditions.

Action of Nitric Acid on Ethyl 5-Chlorodihydropentindole-8-carboxylate.—Prepared by a process similar to that used for 5-chloro-8-cinnamoyldihydropentindole, but by the use of ethyl chloroformate instead of cinnamoyl chloride, *ethyl 5-chlorodihydropentindole-8-carboxylate* separated from alcohol in practically colourless needles, m. p. 103—104° (Found: N, 5·4. $C_{14}H_{14}O_2NCl$ requires N, 5·3%). When a solution of the ester (5 g.) in glacial acetic acid (50 c.c.) at 70° was treated with nitric acid (2 c.c., *d* 1·42), dissolved in acetic acid (2 c.c.), *ethyl 5-chloro-4(or 6)-nitrodihydropentindole-8-carboxylate* separated on cooling and standing for several hours. After recrystallisation from alcohol, it was obtained in yellow needles, m. p. 152—153° (Found: N, 9·0. $C_{14}H_{13}O_4N_2Cl$ requires N, 9·1%), and its constitution was established by hydrolysing it to 5-chloro-4(or 6)-nitrodihydropentindole as described above for the analogous derivative from 5-chloro-8-acetyldihydropentindole. When the acetic acid mother-liquor had been concentrated under reduced pressure, *ethyl 5-chloro-10-nitro-9-hydroxytetrahydropentindole-8-carboxylate* separated, and, after recrystallisation from benzene, it was obtained in colourless prisms, m. p. 163—164° (Found: C, 52·0; H, 4·4; N, 8·5, 8·6. $C_{14}H_{15}O_5N_2Cl$ requires C, 51·5; H, 4·6; N, 8·6%). When the above nitration process was repeated, but in a smaller quantity of acetic acid (25 c.c.) and at 85°, this addition compound constituted the only product which separated from the resulting solution on standing for 3 days. A further quantity was then obtained by concentrating the mother-liquor. It was recovered unchanged from its alcoholic solution after boiling for 1½ hours, and no crystalline product has been obtained from it by the action of aqueous-alcoholic potassium hydroxide under various conditions.

Action of Nitric Acid on 5-Chloro-8-cinnamoyldihydropentindole.—Prepared from 5-chlorodihydropentindole by a method analogous to that described for 8-cinnamoyldihydropentindole, *5-chloro-8-cinnamoyldihydropentindole* was isolated from acetone in pale yellow plates, m. p. 185° (Found: N, 4·3. $C_{20}H_{16}ONCl$ requires N, 4·4%). A suspension of this product (4 g.) in glacial acetic acid (100 c.c.) at 70° was treated with nitric acid (2 g., *d* 1·42), and, after warming to 90°, a clear solution was obtained. On standing, a solid, m. p. 200—210°, separated, and, after crystallisation from acetone, its m. p. was 220—232°. Although further purification was not effected, this product was proved by hydrolysis to contain 5-chloro-

4(or 6)-nitro-8-cinnamoyldihydropentindole: the solid obtained when its solution in aqueous-alcoholic potassium hydroxide was boiled for ¾-hour and then diluted with water was extracted with hot benzene, from which, after filtration, 5-chloro-4(or 6)-nitrodihydropentindole, identical with the synthetical product, was isolated.

When the above experiment was repeated with a smaller quantity (50 c.c.) of acetic acid at 105°, the resulting solution deposited first a similar product, m. p. 205—215°, and then a colourless solid, m. p. 212° (decomp.). This was recrystallised twice from glacial acetic acid, and *5-chloro-10-nitro-9-hydroxy-8-cinnamoyltetrahydropentindole* was obtained in colourless needles, m. p. 221° (decomp.) (Found: C, 61·8; H, 4·4; N, 7·4, 7·7. $C_{20}H_{17}O_4N_2Cl$ requires C, 62·4; H, 4·4; N, 7·3%). Similar results were obtained under experimental conditions analogous to the latter, but employing fuming nitric acid (1·9 g., *d* 1·5). When the various acetic acid mother-liquors in the above experiments were concentrated under reduced pressure, further quantities of the addition compound were obtained in every case. Finally, the ultimate mother-liquors were united and concentrated still further, and, after standing for 24 hours, a considerable quantity of a brown solid, m. p. 158—167°, separated. When this was twice recrystallised from alcohol, it yielded *5-chloro-10-nitro-9-acetoxy-8-cinnamoyltetrahydropentindole* in colourless needles, m. p. 169° (Found: C, 62·2; H, 4·5; N, 6·6, 6·5. $C_{22}H_{19}O_5N_2Cl$ requires C, 61·9; H, 4·5; N, 6·6%).

5-Chloro-10-nitro-9-hydroxy-8-cinnamoyltetrahydropentindole was recovered unchanged from its solution in alcohol after being boiled for 2 hours. When treated with a mixture of equal volumes of alcohol and aqueous potassium hydroxide (15%), it dissolved to give a red solution, and, after this had been heated on the steam-bath for a minute, allowed to stand for 5 minutes, and then acidified with dilute hydrochloric acid, a sticky brown product was obtained. After recrystallisation twice from alcohol, *γ-5-chloro-2-cinnamamidobenzoylbutyric acid* was isolated in colourless prisms, m. p. 164—165° (Found: N, 4·1. $C_{20}H_{18}O_4NCl$ requires N, 3·8%). 5-Chloro-10-nitro-9-acetoxy-8-cinnamoyltetrahydropentindole, which separated quantitatively and unchanged from its solution in alcohol after being boiled for an hour, also gave this butyric acid derivative when its solution in equal volumes of alcohol and aqueous potassium hydroxide (15%) was boiled for 15 minutes and then acidified with dilute hydrochloric acid.

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