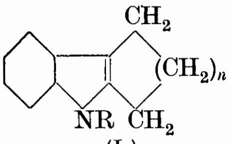
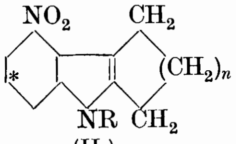
CCCIII.—*The Action of Nitric Acid on Polycyclic Indole Derivatives. Part XI. Combined Addition and Substitution.*

By JOSEPH PAULINUS MASSEY and SYDNEY GLENN PRESTON PLANT.

IN the previous parts of this series the action of a limited amount of nitric acid (little more than one molecular proportion) upon certain *N*-acyl derivatives of dihydropentindole (I; $n = 1$) and tetrahydrocarbazole (I; $n = 2$) has been described. Compounds belonging to the three types (II), (III), and (IV; $n = 2$ only) have been isolated. The nitro-group in the compounds (II) may equally well be in the position indicated by an asterisk, but both of these alternatives are meta-positions with respect to the >NR group. The work now described involves a study of the reactions which take place when some of these acyl compounds are treated with an excess of fuming nitric acid under more vigorous conditions.


(I.)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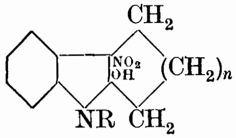
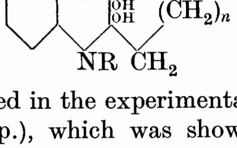
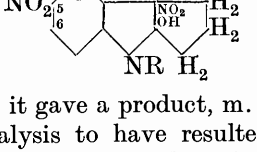

(III.)

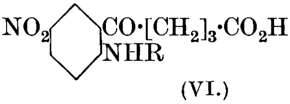
When 8-cinnamoyldihydropentindole (I; R = CHPh:CH·CO; $n = 1$) was acted upon by an excess of nitric acid under conditions described in the experimental section, it gave a product, m. p. 234° (decomp.), which was shown by analysis to have resulted from combined addition (of OH and NO_2) at the double linkage and nitration of the benzenoid part of the molecule. Subsequent investigations proved that the substance was 5 : 10-*dinitro*-9-*hydroxy*-8-*cinnamoyltetrahydropentindole* (V; R = CHPh:CH·CO), so that in the process of its formation addition must have preceded

(IV.)




(V.)

substitution, since simple nitration of the 8-acyldihydropentindoles has already been shown to yield the 4 (or 6)-nitro-compound. The action of alkali under mild conditions has been found to transform this substance into *γ-5-nitro-2-cinnamamidobenzoylbutyric acid*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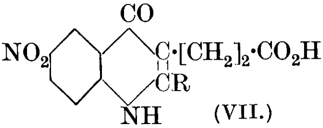
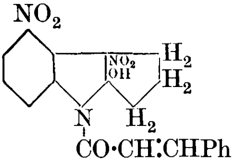
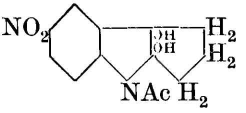

(VII.)

(VI; R = CHPh:CH·CO), which melts sharply at 233—234° and, unlike its precursor, which melts with decomposition, is well suited for direct comparison with specimens derived from other sources. The further action of alkali has converted this acid into *β-6-nitro-2-styryl-4-quinolone-3-propionic acid* (VII; R = CHPh:CH).

The constitution of the substance (V; R = CHPh:CH·CO) was established by treating first 4(or 6)-nitro-8-cinnamoyldihydropentindole and then the isomeric 5-*nitro*-compound with an excess of fuming nitric acid. The former gave an addition product (VIII) which melted with decomposition at 244° and yielded, on treatment with alkali, *γ-2-nitro-6-cinnamamidobenzoylbutyric acid*, m. p. 217°, not identical with the substance (VI; R = CHPh:CH·CO). The latter, however, yielded an addition product which melted with decomposition at 234° and gave an acid, m. p. 233—234°, identical with (VI; R = CHPh:CH·CO), when treated with alkali.

(VIII.)



(IX.)

When 8-acetyldihydropentindole (I; R = Ac; *n* = 1) was treated with an excess of nitric acid, a similar product (V; R = Ac) was obtained, but the nature of the substance subsequently derived from it by the action of alkali could be altered by surprisingly small changes in the experimental conditions. Thus, when a solution of the compound in a mixture of equal volumes of alcohol and aqueous potassium hydroxide (15%) was left for two minutes and then acidified, *γ-5-nitro-2-acetamidobenzoylbutyric acid* (VI; R = Ac) was precipitated, and this could be converted into the *quinolone* (VII; R = Me) by the further action of alkali. When, however, the compound (V; R = Ac) was treated in small quantities with alcohol and a relatively small amount of aqueous potassium hydroxide, the solution yielded, after acidification, a product which appeared, on analysis, to be 5-*nitro*-9 : 10-*dihydroxy*-8-*acetyltetra*-

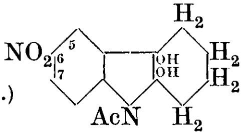
hydropentindole (IX). The constitution of the compound (V; R = Ac) was confirmed by its preparation from 5-*nitro*-8-*acetyldihydropentindole* and the subsequent conversion of this synthetic specimen into the substance (IX), identical with the dihydroxy-compound just described.

The action of nitric acid on ethyl dihydropentindole-8-carboxylate (I; R = CO_2Et; $n = 1$) under similar conditions gave a substance which is undoubtedly the analogous nitrated addition product (V; R = CO_2Et), but attempts to obtain a pure derivative from it by the action of alkali have not been successful. The fact that the formation of the derivatives (V) involves primarily the addition of OH and NO_2 at the double linkage was further confirmed by examining the action of an excess of nitric acid upon 10-nitro-9-hydroxy-8-acetyltetrahydropentindole (III; R = Ac; $n = 1$), previously described in Part VIII (J., 1929, 2493). This reaction resulted in nitration at the 5-position with the formation of (V; R = Ac), the identity of which was established by its conversion into γ-5-nitro-2-acetamidobenzoylbutyric acid (VI; R = Ac).

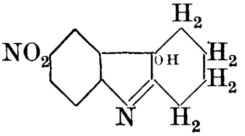
It has been pointed out in Part X (this vol., p. 1990) that special interest attaches to the preparation of dihydroxy-addition products (IV; $n = 1$) in the dihydropentindole series, but, although this type is well known amongst the tetrahydrocarbazole derivatives (IV; $n = 2$), no example in the former series has hitherto been obtained. The formation of the compound (IX) during the course of the present work is, therefore, noteworthy, and it is hoped to make a detailed study of its reactions. Conversion of compounds of the type (III) into those of the type (IV) can sometimes be effected by the action of boiling alcohol, but the derivatives (V) now under investigation were all stable under these conditions.

The results described above made it desirable to study the action of an excess of nitric acid upon the 9-acyltetrahydrocarbazoles (I; $n = 2$), since the earlier work has shown that, of the simple acyl derivatives so far examined, the benzoyl compound alone gives an addition product of the type (III), the more normal mode of addition being such as to yield the compounds (IV; $n = 2$). Furthermore, no instance of combined addition and substitution has been brought to light during the previous work in this field. Since 11-nitro-10-hydroxy-9-benzoylhexahydrocarbazole (III; R = Bz; $n = 2$) is known to be less stable than most of the derivatives of the type (III) and decomposes with evolution of oxides of nitrogen when boiled with glacial acetic acid (Perkin and Plant, J., 1923, **123**, 676), it is not surprising that efforts to prepare a compound analogous to (V) from 9-benzoyltetrahydrocarbazole (I; R = Bz; $n = 2$) were unsuccessful.

When 9-acetyltetrahydrocarbazole (I; R = Ac; $n = 2$) was treated with an excess of nitric acid it yielded a *substance* (X) which obviously results from combined addition (of 2OH) at the double linkage and nitration of the benzene nucleus. The properties of this compound are similar to those previously observed in the case of 10 : 11-dihydroxy-9-acetylhexahydrocarbazole (IV; R = Ac; $n = 2$) itself. Thus, on treatment with alkali it gave 6-*nitro*-11-*hydroxytetrahydrocarbazolenine* (XI), and, on boiling with acetic anhydride and hydrolysis of the product, it yielded 9-nitro-ψ-indoxyl*spirocyclo*pentane (XII), identical with the compound obtained by Perkin and Plant (*loc. cit.*) by boiling ψ-indoxyl*spirocyclo*pentane with dilute nitric acid. The structure assigned by these authors to their product is thus shown to be correct. The constitution of the compound (X) was established by its preparation from 6-nitro-9-acetyltetrahydrocarbazole by the action of an excess of nitric acid. This synthetic product also gave the substance (XI) on treatment with alkali.

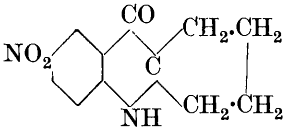


(X.)



(XI.)

Since the mononitration of 9-acetyltetrahydrocarbazole has already been shown to yield the 5-nitro-compound, there can be no doubt that addition precedes substitution during the formation of (X). In confirmation of this, it has been demonstrated during the present investigations that the further action of nitric acid on 10 : 11-dihydroxy-9-acetylhexahydrocarbazole (IV; R = Ac; $n = 2$) also leads to (X), while the nitration of 9-acetylhexahydrocarbazole itself has been shown by Gurney and Plant (J., 1927, 1314) to give the 6-nitro-derivative.



(XII.)

EXPERIMENTAL.

5 : 10-*Dinitro*-9-*hydroxy*-8-*cinnamoyltetrahydropentindole*.—A boiling solution of 8-cinnamoyldihydropentindole (2 g., prepared as described by Massey and Plant, this vol., p. 1993) in glacial acetic acid (15 c.c.) was treated with fuming nitric acid (2 c.c., d 1·5), and, on cooling, a colourless solid separated. After recrystallisation from glacial acetic acid, 5 : 10-*dinitro*-9-*hydroxy*-8-*cinnamoyltetra*-

hydropentindole was obtained in colourless plates, m. p. 234° (decomp.) (Found: C, 60·6; H, 4·3; N, 10·5. $C_{20}H_{17}O_6N_3$ requires C, 60·7; H, 4·3; N, 10·6%). It was recovered unchanged after being boiled with alcohol for an hour. It rapidly dissolved to give a deep red solution when shaken at room temperature with equal volumes of alcohol and aqueous potassium hydroxide (15%), and, after being left for 15 minutes, the addition of dilute hydrochloric acid led to the separation of a sticky brown solid. This crystallised on rubbing with alcohol, and, on recrystallisation twice from glacial acetic acid, γ-5-*nitro*-2-*cinnamamidobenzoylbutyric acid* was obtained in practically colourless plates, m. p. 233—234° (Found: C, 63·4; H, 4·7; N, 7·2. $C_{20}H_{18}O_6N_2$ requires C, 62·8; H, 4·7; N, 7·3%). When a solution of the latter acid (0·3 g.) in aqueous potassium hydroxide (10 c.c. of 15%) was heated on the steam-bath for an hour, cooled, and then acidified with acetic acid, β-6-*nitro*-2-*styryl*-4-*quinolone*-3-*propionic acid* separated, and, after being twice recrystallised from alcohol, it was isolated in yellow needles, m. p. 306° (decomp.) (Found: C, 65·8; H, 4·5. $C_{20}H_{16}O_5N_2$ requires C, 65·9; H, 4·4%).

4 (or 6) : 10-*Dinitro*-9-*hydroxy*-8-*cinnamoyltetrahydropentindole* (VIII).—When a suspension of 4(or 6)-nitro-8-cinnamoyldihydropentindole (3 g., prepared as described by Massey and Plant, *loc. cit.*) in boiling glacial acetic acid (80 c.c.) was treated with fuming nitric acid (4 c.c., *d* 1·5), a clear solution was obtained, but a colourless product rapidly separated on cooling. After the latter had been recrystallised from acetic acid, 4(or 6) : 10-*dinitro*-9-*hydroxy*-8-*cinnamoyltetrahydropentindole* was obtained in colourless needles, m. p. 244° (decomp.) (Found: C, 60·2; H, 4·6. $C_{20}H_{17}O_6N_3$ requires C, 60·7; H, 4·3%). When this dinitro-compound was treated with a mixture of equal volumes of alcohol and aqueous potassium hydroxide, as described above for the 5 : 10-isomeride, and the product was crystallised successively from alcohol and glacial acetic acid, γ-2-*nitro*-6-*cinnamamidobenzoylbutyric acid* was isolated in nearly colourless prisms, m. p. 217° (Found: C, 62·4; H, 4·9. $C_{20}H_{18}O_6N_2$ requires C, 62·8; H, 4·7%).

5-*Nitro*-8-*cinnamoyldihydropentindole and its Nitration.*—A boiling solution of 5-nitrodihydropentindole (1·4 g., prepared as described by Plant, J., 1929, 2493) in a mixture of acetone (20 c.c.) and aqueous potassium hydroxide (3 g. of 66%) was treated gradually with cinnamoyl chloride (2 g.) dissolved in acetone (10 c.c.). After dilution with water, the product was crystallised from acetone, and 5-*nitro*-8-*cinnamoyldihydropentindole* was obtained in yellow prisms, m. p. 231° (Found: N, 8·4. $C_{20}H_{16}O_3N_2$ requires N, 8·4%). The addition of fuming nitric acid (1·5 c.c., *d* 1·5) to a suspension of this substance (1 g.) in boiling glacial acetic acid (15 c.c.) led to a clear solution from which, on cooling, the compound (V; R = CHPh:CH·CO), identical with the nitration product of 8-cinnamoyldihydropentindole, separated. The compound (V; R = CHPh:CH·CO) prepared in this way was converted into γ-5-nitro-2-cinnamamidobenzoylbutyric acid by the procedure described above, and the m. p. of a mixture of the two specimens showed no depression.

5 : 10-*Dinitro*-9-*hydroxy*-8-*acetyltetrahydropentindole* (V; R = Ac).—A boiling solution of 8-acetyldihydropentindole (3 g., prepared as described by Perkin and Plant, J., 1923, **123**, 3242) in glacial acetic acid (15 c.c.) was treated with fuming nitric acid (3 c.c., *d* 1·5), and, on standing for some time, a colourless product separated. After recrystallisation from alcohol, 5 : 10-*dinitro*-9-*hydroxy*-8-*acetyltetrahydropentindole* was obtained in colourless needles, m. p. 187° (decomp.) (Found: C, 50·9; H, 4·5; N, 13·7, 13·5. $C_{13}H_{13}O_6N_3$ requires C, 50·8; H, 4·2; N, 13·7%). This substance separated unchanged from its alcoholic solution after being boiled for an hour. Its solution in equal volumes of alcohol and cold aqueous potassium hydroxide (15%) was left for 2 minutes and then acidified with dilute hydrochloric acid. The γ-5-*nitro*-2-*acetamidobenzoylbutyric acid*, which separated slowly, was recrystallised from alcohol and obtained in colourless plates, m. p. 166° (Found: C, 53·0; H, 4·9; N, 9·6. $C_{13}H_{14}O_6N_2$ requires C, 53·1; H, 4·8; N, 9·5%). When a solution of this acid in equal volumes of alcohol and aqueous potassium hydroxide (15%) was boiled for 25 minutes and then acidified with dilute hydrochloric acid, β-6-*nitro*-2-*methyl*-4-*quinolone*-3-*propionic acid* was precipitated, and, after recrystallisation twice from glacial acetic acid, it was obtained in pale brown prisms, m. p. 213—214° (Found: N, 10·4. $C_{13}H_{12}O_5N_2$ requires N, 10·1%).

The above dinitro-compound (V; R = Ac) (0·1 g.) readily dissolved when treated with alcohol (4 c.c.) and a small quantity (0·5 c.c.) of cold aqueous potassium hydroxide (15%), and, after the solution had been kept for a minute, it was acidified with dilute hydrochloric acid. The solid which slowly separated was twice recrystallised from alcohol and 5-*nitro*-9 : 10-*dihydroxy*-8-*acetyltetrahydropentindole* was isolated in colourless plates, m. p. 111° (Found: C, 55·9; H, 5·3; N, 9·6. $C_{13}H_{14}O_5N_2$ requires C, 56·1; H, 5·0; N, 10·1%).

A solution of 5-nitrodihydropentindole in ten times its weight of acetic anhydride containing a trace of sulphuric acid was boiled for an hour, and, on cooling, 5-*nitro*-8-*acetyldihydropentindole* separated. After recrystallisation from alcohol, it was obtained in pale yellow plates, m. p. 218° (Found: N, 11·4. $C_{13}H_{12}O_3N_2$ requires

N, 11·5%). When a suspension of this derivative (0·45 g.) in boiling glacial acetic acid (2 c.c.) was treated with fuming nitric acid (0·5 c.c., *d* 1·5) and the resulting solution was left for several hours, the dinitro-compound (V; R = Ac) separated. After treatment with alkali under the appropriate conditions (given above), the latter yielded the dihydroxy-compound (IX), which was shown by a mixed m. p. determination to be identical with the specimen obtained by the previous method.

When fuming nitric acid (0·5 c.c., *d* 1·5) was added to a suspension of 10-nitro-9-hydroxy-8-acetyltetrahydropentindole (0·4 g., prepared as described by Plant, *loc. cit.*) in boiling glacial acetic acid (1 c.c.), a vigorous reaction ensued, and a clear solution was obtained. On cooling and stirring, the dinitro-compound (V; R = Ac) separated, and, after being treated with equal volumes of alcohol and aqueous potassium hydroxide (15%) as described above, γ-5-nitro-2-acetamidobenzoylbutyric acid, identical with the earlier specimen, was obtained.

Ethyl 5 : 10-*Dinitro*-9-*hydroxytetrahydropentindole*-8-*carboxylate* (V; R = CO_2Et).—When fuming nitric acid (3 c.c., *d* 1·5) was added to a boiling solution of ethyl dihydropentindole-8-carboxylate (3 g., prepared as described by Plant, *loc. cit.*) in glacial acetic acid (15 c.c.), a vigorous reaction ensued, and, on cooling, *ethyl* 5 : 10-*dinitro*-9-*hydroxytetrahydropentindole*-8-*carboxylate* separated. After being twice recrystallised from acetic acid, it was obtained in colourless prisms, m. p. 222° (decomp.) (Found: C, 50·0; H, 4·4; N, 12·1, 12·3. $C_{14}H_{15}O_7N_3$ requires C, 49·8; H, 4·4; N, 12·5%). This substance separated unchanged after its solution in alcohol had been boiled for two hours. It readily dissolved in aqueous-alcoholic potassium hydroxide, but attempts to isolate a pure compound from the product obtained by acidifying the solution have been unsuccessful.

6-*Nitro*-10 : 11-*dihydroxy*-9-*acetylhexahydrocarbazole* (X).—When a boiling solution of 9-acetyltetrahydrocarbazole (2 g.) in glacial acetic acid (5 c.c.) was treated with fuming nitric acid (2 c.c., *d* 1·5) a vigorous reaction occurred and a sticky syrup resulted, but, on stirring, a colourless solid slowly appeared and its separation was aided by the addition of more acetic acid (10 c.c.). The product was purified by boiling it with alcohol, in which it is sparingly soluble, and then recrystallising it twice from glacial acetic acid. 6-*Nitro*-10 : 11-*dihydroxy*-9-*acetylhexahydrocarbazole* was then obtained in colourless prisms, m. p. 238° (decomp.) (Found: C, 57·7; H, 5·6; N, 9·7. $C_{14}H_{16}O_5N_2$ requires C, 57·5; H, 5·5; N, 9·6%). Like the analogous compounds (IX) and (IV; R = Ac, $n = 2$), it readily dissolved in aqueous-alcoholic alkali to give a yellow solution from which it was reprecipitated by the addition of hydrochloric acid, but not by dilution with water. When this product (0·4 g.) was boiled for 25 minutes with a mixture of alcohol (7·5 c.c.) and aqueous potassium hydroxide (15 c.c. of 10%), a deep red solution was obtained, and, on cooling, 6-*nitro*-11-*hydroxytetrahydrocarbazolenine* separated in brownish-yellow plates. After recrystallisation from methyl alcohol, it was obtained in yellow prisms, m. p. 192° (Found : C, 62·2; H, 5·4. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2%).

Fuming nitric acid (1 c.c., *d* 1·5) was added slowly to a boiling suspension of 6-nitro-9-acetyltetrahydrocarbazole (1 g., prepared as described by Perkin and Plant, J., 1921, **119**, 1825) in glacial acetic acid (15 c.c.), and a clear solution resulted. The product which separated on standing for several hours was recrystallised from acetic acid, and the derivative (X) was obtained. When the latter was boiled with aqueous-alcoholic alkali in the manner described above, it yielded 6-nitro-11-hydroxytetrahydrocarbazolenine, which was shown by a mixed m. p. determination to be identical with the substance derived originally from 9-acetyltetrahydrocarbazole.

A solution of the product (X) (0·6 g.) in acetic anhydride (10 c.c.) was boiled for two hours and then shaken with an excess of water. The precipitate was dissolved in equal volumes of alcohol and aqueous potassium hydroxide (15%); the solution was boiled for ½ hour and then acidified with dilute hydrochloric acid. The product which separated was recrystallised twice from alcohol, and 9-nitro-ψ-indoxyl*spirocyclo*pentane was obtained in nearly colourless needles, m. p. 241°, identical (mixed m. p.) with the product of nitration of ψ-indoxyl*spirocyclo*pentane (Perkin and Plant, *loc. cit.*).

The compound (X) separated slowly after fuming nitric acid (0·5 c.c., *d* 1·5) had been added to a boiling solution of 10 : 11-dihydroxy-9-acetylhexahydrocarbazole (1 g., prepared as described by Perkin and Plant, *loc. cit.*) in glacial acetic acid (6 c.c.), and its identity was confirmed by its conversion into the derivative (XI) by the process given above.

THE DYSON PERRINS LABORATORY,
OXFORD.

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