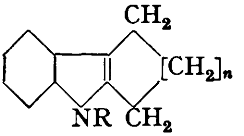
229. *The Action of Nitric Acid on Derivatives of Coumarono(2' : 3' : 3 : 2)indole.*

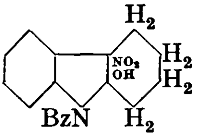
By S. R. Cawley and S. G. P. Plant.

The N-*acyl* derivatives of *coumarono*(2' : 3' : 3 : 2)*indole* (V) on nitration in acetic acid give addition compounds of the type (VI), or less probably (VII), as the main products with small amounts of substitution compounds, whereas the analogous but slightly more complex N-*acyl* derivatives of coumarono(2' : 3' : 1 : 2)-β-naphthindole (X) give exclusively nitro-substitution products. These addition compounds are not degraded to benzene derivatives by alkalis so smoothly as those from related simpler indoles.

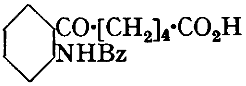
Nitric acid combines additively at the 2 : 3-position with many 1-acyl-2 : 3-dialkylindoles, *e.g.*, 1-benzoyl-2 : 3-dimethylindole, 9-benzoyltetrahydrocarbazole (I; *n* = 2; R = Bz), and various 8-acyldihydropentindoles (I; *n* = 1; R = Ac, Bz, CO_2Et) to give compounds analogous to (II) (Plant and Tomlinson, J., 1933, 955; Perkin and Plant, J., 1923, **123**, 676, 3242; Plant, J., 1929, 2493). In many instances these products have been shown to undergo fission to comparatively simple benzene derivatives on treatment with alkali, as in the conversion of (II) into δ-*o*-benzamidobenzoylvaleric acid (III), but in all the cases so



(I.)



(II.)

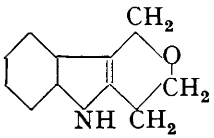


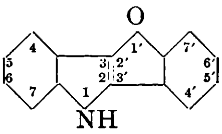
(III.)

far investigated the ring (if any) attached to the indole skeleton at the 2 : 3-position is carbocyclic in character. In view of the importance of compounds which have the indole nucleus fused to a heterocyclic system, as, *e.g.*, in the carbolines, and of the possibility of using the above reactions for degrading them to identifiable derivatives, an investigation has been made of one of the more readily accessible systems of this type with an oxygen-containing ring.

At first attempts were made to prepare the compound (IV) from the phenylhydrazone of tetrahydro-γ-pyrone by Fischer's reaction, but these were unsuccessful, as also were similar attempts made with the p-*nitrophenylhydrazone.* It was possible, however, to prepare *coumarono*(2′ : 3′ : 3 : 2)*indole* (V) from coumaranone and phenylhydrazine, and

(IV.)

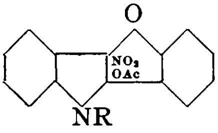


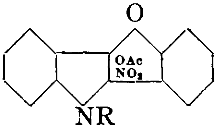


(V.)

this was converted into its 1-*acetyl,* 1-*benzoyl,* 1-*carbethoxy,* and 1-*cinnamoyl* derivatives. All four acyl compounds on nitration in acetic acid solution readily gave as the main products colourless substances formed by addition of NO_2 and OAc, for which the two alternative formulæ (VI) and (VII) are possible. The acetylation of the hydroxyl group

(VI.)





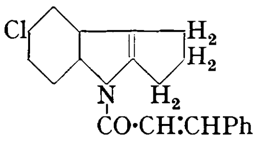
(VII.)

(R = Ac, Bz, CO_2Et, and CHPh:CH·CO.)

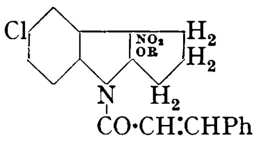
in this reaction is very unusual, but an analogous case exists in 5-chloro-8-cinnamoyldihydropentindole (VIII), which gave both (IX; R = H) and (IX; R = Ac) on nitration (Massey and Plant, J., 1931, 1990).

In the earlier work it has been found that addition compounds are formed far less readily when the indole nucleus is contained in polycyclic systems containing four rings fused together (Oakeshott and Plant, J., 1928, 1840; Bryant and Plant, J., 1931, 93; Plant and Tomlinson, J., 1932, 2192), and the ready formation of the compounds now described is of special interest in this connexion, but all attempts to obtain crystalline substances from them by the action of alkali under various conditions have failed. Although there can be no doubt regarding the structure of the nitric acid addition compounds hitherto described, it is impossible to decide quite so definitely between the alternative structures (VI) and (VII) owing to the doubt which exists concerning the effect upon the double linkage of the attached oxygen atom. Nevertheless it is a significant fact that, as in the series previously studied, an addition product is not formed by the parent indole containing a free >NH group, but only by the *N*-acyl derivatives, and for this reason formula (VI) appears to be much the more probable.

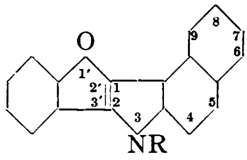
The acetyl-, benzoyl-, and cinnamoyl-coumarono(2′ : 3′ : 3 : 2)indole also gave during the nitration process yellow products which are apparently mixtures of nitro-substitution compounds. In the case of the acetyl and benzoyl derivatives the quantities were insufficient for separation, but from the cinnamoyl compound a pure *mononitro*-derivative has been isolated. The position of the nitro-group is not known, but the substance was found to be different from the *5-nitro-1-cinnamoylcoumarono*(2′ : 3′ : 3 : 2)*indole* synthesised from *coumaranone*-p-*nitrophenylhydrazone* by removal of ammonia and cinnamoylation.



(VIII.)



(IX.)



(R = Ac, Bz)

(X.)

In order to investigate the possibility of obtaining analogous addition compounds from more complex systems of the same type, Fischer's reaction has been applied to coumaranone-β-naphthylhydrazone and the coumarono(2′ : 3′ : 1 : 2)-β-naphthindole has been converted into its 3-*acetyl* and 3-*benzoyl* derivatives (X). Both these compounds on nitration gave almost quantitative yields of a single *mononitro*-substitution product, and it is clear that the course of the reaction with nitric acid is profoundly affected by the presence of the additional benzene nucleus. The position of the nitro-group in these two substances is uncertain, but it must be the same in both cases, since the benzoyl compound was converted into the acetyl by hydrolysis and subsequent acetylation

EXPERIMENTAL.

Tetrahydro-γ-pyrone.—The following conditions for the hydrogenation of γ-pyrone were found to be far more satisfactory than those described by Borsche (*Ber.*, 1915, **48**, 682) and by Cornubert and Robinet (*Bull. Soc. chim.*, 1933, **53**, 565). γ-Pyrone (11 g.) in methyl alcohol (75 c.c.) to which 2% palladised strontium carbonate (12 g.) had been added was shaken while hydrogen was passed in at room temperature under a pressure of 3 atms. Reduction was complete in 15 minutes and after filtration the tetrahydro-γ-pyrone (8 g.) was isolated by fractional distillation. Its p-*nitrophenylhydrazone* separated in orange-brown needles, m. p. 186°, when the ketone (1·4 g.) and *p*-nitrophenylhydrazine (1·2 g.) were mixed in boiling alcohol (5 c.c.) and the solution allowed to cool (Found: C, 56·4; H, 5·7. $C_{11}H_{13}O_3N_3$ requires C, 56·2; H, 5·5%).

Coumarono(2′ : 3′ : 3 : 2)*indole and its* 1-*Acyl Derivatives.*—When a mixture of coumaranone (2·8 g., prepared by the method of Fries and Pfaffendorf, *Ber.*, 1910, **43**, 212) and phenylhydrazine (2·2 g.) had been heated at 120° until almost all the water from the formation of the hydrazone had boiled away, it suddenly effervesced with the evolution of ammonia. The product was immediately cooled, dissolved in boiling alcohol (10 c.c.), treated while hot with a mixture of concentrated hydrochloric acid (2 c.c.) and alcohol (3 c.c.), quickly shaken, and then kept for several hours. The *coumarono*(2′ : 3′ : 3 : 2)*indole* (2·2 g.) which separated was partly purified by dissolution in an excess of hot glacial acetic acid and recovery from the cooled filtered solution by dilution with water; it was then suitable for conversion into its acyl derivatives. It crystallised from alcohol in colourless plates, m. p. 197° (Found: C, 81·1; H, 4·5. $C_{14}H_9ON$ requires C, 81·2; H, 4·3%).

After acetyl chloride (1·8 c.c.) had been gradually added to a solution of this indole (0·7 g.) in warm acetone (25 c.c.) containing potassium hydroxide (0·7 g., dissolved in a few drops of water), and the mixture well shaken for a few minutes, the addition of water precipitated 1-*acetylcoumarono*(2′ : 3′ : 3 : 2)*indole* (0·6 g.), which formed colourless needles, m. p. 156°, from alcohol (Found: C, 77·2; H, 4·5. $C_{16}H_{11}O_2N$ requires C, 77·1; H, 4·4%). When the acetyl compound was refluxed for an hour with aqueous-alcoholic potassium hydroxide and the solution left to cool, coumarono(2′ : 3′ : 3 : 2)indole, identified by mixed m. p., separated. 1-*Benzoylcoumarono*-(2′ : 3′ : 3 : 2)*indole*, colourless prisms, m. p. 177°, from glacial acetic acid (Found: N, 4·6. $C_{21}H_{13}O_2N$ requires N, 4·5%), *ethyl coumarono*(2′ : 3′ : 3 : 2)*indole*-1-*carboxylate*, yellowish-brown needles, m. p. 95°, from alcohol (Found: N, 5·0. $C_{17}H_{13}O_3N$ requires N, 5·0%), and 1-*cinnamoylcoumarono*(2′ : 3′ : 3 : 2)*indole*, yellow needles, m. p. 108—112°, from alcohol (Found: N, 4·0. $C_{23}H_{15}O_2N$ requires N, 4·2%), were prepared similarly in good yields with the aid of benzoyl chloride, ethyl chloroformate, and cinnamoyl chloride respectively.

Nitration of the 1-*Acylcoumarono*(2′ : 3′ : 3 : 2)*indoles.*—(a) *Acetyl derivative.* When a suspension of the acetyl compound (0·85 g.) in glacial acetic acid (10 c.c.) was treated with nitric acid (0·34 g., *d* 1·42, in a little acetic acid) and the whole warmed to 60°, a clear solution resulted, from which a small quantity of a feathery lemon-yellow solid separated on cooling and standing for a few hours. After this product, m. p. 205—230°, which could not be purified and was probably a mixture of nitro-derivatives, had been removed by filtration, the solution was concentrated to small bulk under reduced pressure at 70° and left for a few hours; 3(or 2)-*nitro*-2(or 3)-*acetoxy*-1-*acetyl*-2 : 3-*dihydrocoumarono*(2′ : 3′ : 3 : 2)*indole* (0·2 g.), colourless prisms, m. p. 142°, from glacial acetic acid, separated (Found: C, 61·3; H, 4·0; N, 8·0. $C_{18}H_{14}O_6N_2$ requires C, 61·0; H, 4·0; N, 7·9%).

(b) *Benzoyl derivative.* The reaction was carried out as above, but the mixture was warmed to 80° before complete solution occurred. On cooling, a small quantity of a feathery yellow product again separated, but the 3(or 2)-*nitro*-2(or 3)-*acetoxy*-1-*benzoyl*-2 : 3-*dihydrocoumarono*-(2′ : 3′ : 3 : 2)*indole*, colourless prisms, m. p. 185°, from aqueous acetic acid, remained in supersaturated solution and was obtained by filtration and rubbing (Found: C, 66·4; H, 4·0; N, 6·3. $C_{23}H_{16}O_6N_2$ requires C, 66·3; H, 3·8; N, 6·7%).

(c) *Carbethoxy derivative.* The procedure was similar to that used for the acetyl compound, but no yellow substitution product was obtained on this occasion. The *ethyl* 3(or 2)-*nitro*-2(or 3)-*acetoxy*-2 : 3-*dihydrocoumarono*(2′ : 3′ : 3 : 2)*indole*-1-*carboxylate*, which separated from the solution, after being concentrated at 70°, in colourless plates, m. p. 120°, was washed with a very small quantity of ether (Found: N, 7·3. $C_{19}H_{16}O_7N_2$ requires N, 7·3%). It was too soluble in alcohol and acetic acid for satisfactory recrystallisation.

(d) *Cinnamoyl derivative.* The nitration was carried out as before, the temperature being raised to 90°, and, after the solution had been cooled, a yellow product separated, which gave a *mononitro*-1-*cinnamoylcoumarono*(2′ : 3′ : 3 : 2)*indole* as yellow needles, m. p. 243—247°, on recrystallisation from benzene (Found: N, 7·6. $C_{23}H_{14}O_4N_2$ requires N, 7·3%). When the acetic acid filtrate was then concentrated at 70° under reduced pressure, it yielded, as the main product of the reaction, 3(or 2)-*nitro*-2(or 3)-*acetoxy*-1-*cinnamoyl*-2 : 3-*dihydrocoumarono*-(2′ : 3′ : 3 : 2)*indole*, which formed colourless plates, m. p. 157—159°, from alcohol (Found: N, 6·3. $C_{25}H_{18}O_6N_2$ requires N, 6·3%).

5-*Nitro*-1-*cinnamoylcoumarono*(2′ : 3′ : 3 : 2)*indole.*—*Coumaranone*-p-*nitrophenylhydrazone* (0·7 g.) separated in red needles, m. p. 192—194°, when solutions of coumaranone (0·5 g.) and *p*-nitrophenylhydrazine (0·6 g.) in aqueous acetic acid (67%) were mixed and left for a few hours (Found: N, 15·7. $C_{14}H_{11}O_3N_3$ requires N, 15·6%). By refluxing for ½ hour with hydrochloric acid (22%), it was converted into 5-*nitrocoumarono*(2′ : 3′ : 3 : 2)*indole*, which formed feathery brownish-yellow needles, m. p. 270—275°, from alcohol (Found: N, 11·3. $C_{14}H_8O_3N_2$ requires N, 11·1%). When the latter was cinnamoylated by a process similar to that used for coumarono-(2′ : 3′ : 3 : 2)indole itself, 5-*nitro*-1-*cinnamoylcoumarono*(2′ : 3′ : 3 : 2)*indole*, lemon-yellow needles, m. p. 220°, from benzene, was obtained (Found: N, 7·2%).

The m-*nitrophenylhydrazone*, red needles, m. p. 168—169° (Found: N, 15·3%), and o-*nitrophenylhydrazone*, red needles, m. p. 179—181° (Found: N, 15·5%), of coumaranone were similarly prepared, but attempts to convert them into the corresponding indoles were unsuccessful.

Nitration of 3-*Acetyl- and* 3-*Benzoyl-coumarono*(2′ : 3′ : 1 : 2)-β-*naphthindole.*—Coumaranone (2 g.) and β-naphthylhydrazine (2·4 g.) were heated together at about 130° until evolution of ammonia had ceased. The product was dissolved in boiling alcohol (25 c.c.) containing concentrated hydrochloric acid (2 c.c.) and the coumarono(2′ : 3′ : 1 : 2)-β-naphthindole which separated on cooling was purified somewhat by dissolution in hot glacial acetic acid and precipitation by the addition of water. This solid (1·5 g.) in acetone (45 c.c.) containing potassium hydroxide (3 g. in a little water) was well shaken with acetyl chloride (6 c.c.), and the crystalline precipitate was collected and washed successively with acetone and water. The 3-*acetylcoumarono*(2′ : 3′ : 1 : 2)-β-*naphthindole* so obtained crystallised from alcohol in colourless needles, m. p. 169° (Found: N, 4·8. $C_{20}H_{13}O_2N$ requires N, 4·7%). When this acetyl compound (0·5 g.) was heated gradually to 70° in glacial acetic acid (10 c.c.) containing nitric acid (0·17 g., *d* 1·42), a *mononitro*-3-*acetylcoumarono*(2′ : 3′ : 1 : 2)-β-*naphthindole* separated in almost theoretical yield as a red flocculent solid. On recrystallisation from glacial acetic acid it was obtained in red needles, m. p. 234—236° (Found: C, 69·7; H, 3·5. $C_{20}H_{12}O_4N_2$ requires C, 69·8; H, 3·5%).

3-*Benzoylcoumarono*(2′ : 3′ : 1 : 2)-β-*naphthindole*, pale yellow needles, m. p. 201°, from alcohol (Found: N, 3·9. $C_{25}H_{15}O_2N$ requires N, 3·9%), was prepared similarly with the aid of benzoyl chloride, and on nitration as above gave a *mononitro*-derivative, orange-yellow needles, m. p. 241—242°, from glacial acetic acid, in very good yield (Found: C, 73·8; H, 3·6. $C_{25}H_{14}O_4N_2$ requires C, 73·9; H, 3·4%). The latter was refluxed for an hour with aqueous-alcoholic potassium hydroxide and the product obtained by the addition of dilute hydrochloric acid was acetylated by shaking in acetone as before with alkali and acetyl chloride. The mononitro-3-acetylcoumarono(2′ : 3′ : 1 : 2)-β-naphthindole so obtained separated from glacial acetic acid in red needles, m. p. 233—235°, and was shown by a mixed m. p. to be identical with the substance described above.

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