529. *The Condensation of* 1 : 3-*Dimethylindole with Hexane*-2 : 5-*dione and Heptane*-2 : 6-*dione.*

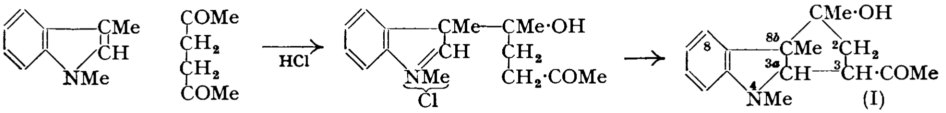
By Sir Robert Robinson and J. E. Saxton.

The diketones named in the title couple with 1 : 3-dimethylindole in the β-position, and the resulting indoleninium salt then undergoes cyclisation between the indole α-carbon atom and the methylene carbon of an appropriately situated oxo-methylene group. This provides a laboratory model for the biosynthesis of strychnine from tryptamine or tryptophan in accordance with the earlier stages of R. B. Woodward's hypothesis.

The αββ-trisubstituted dihydroindole system of strychnine can theoretically be constructed by condensation of a suitable dicarbonyl compound with tryptamine, provided that the β-position is attacked in the first phase of the reaction.

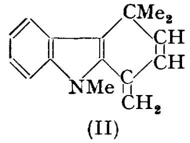
Experiments made in 1949 by Mr. B. P. Moore on the condensation of tryptophan with simple 1 : 5-dioxo-compounds gave unsatisfactory results in most cases, and the reason became clear from the work of the present authors on the similar condensation reactions of skatole (*J.*, 1950, 3136). The 1- and the 2-position were coupled with different carbonyl groups, and substituted benzopyrrocolines resulted. We suspected that the 1 : 2-attack should be attributed to ready coupling with the 1-position in the first place.

Hence it was decided to exclude this possibility by the use of 1 : 3-dimethylindole. Condensation with hexane-2 : 5-dione with the help of hydrogen chloride was not observed in anhydrous media but occurred readily in the presence of 10% of water. The product, $C_{16}H_{21}O_2N$, considered to be (I) is a dihydroindole derivative (ultra-violet spectrum and colour reactions). It contains hydroxyl and carbonyl groups (infra-red spectrum) and is a methyl ketone (iodoform reaction and derivatives). The course of the process is believed to be the following :



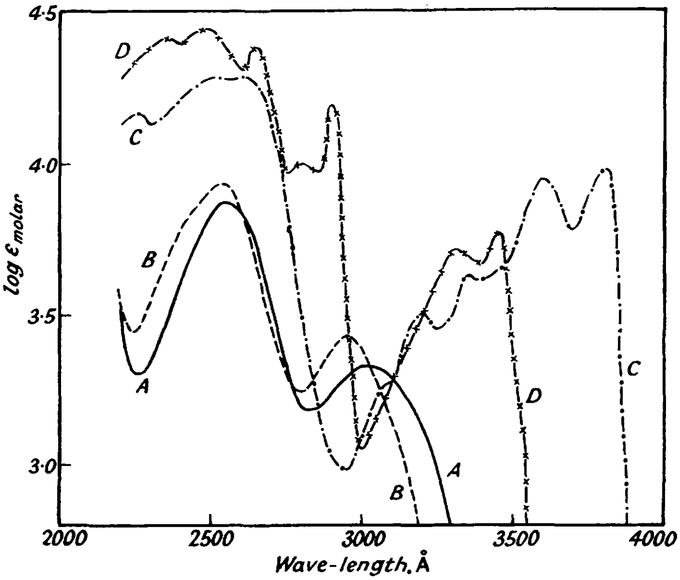
Another product of the reaction, best obtained under slightly varied conditions, was proved to be 1 : 4 : 9-trimethylcarbazole. It was also prepared from 1 : 4-dimethylcarbazole by treatment with sodamide and methyl iodide in liquid ammonia solution. The formation of this carbazole derivative indicates loss of the methyl in the 3-position of the indole nucleus, presumably as methanol or methyl chloride; a normal condensation with loss of two molecules of water completes the process.

When the main product (I) was vigorously treated with hydrochloric acid it did not afford the trimethylcarbazole but changed to a substance, $C_{16}H_{17}N$, with loss of $2H_2O$. This is clearly an indole derivative and its ultra-violet spectrum (see Figure) discloses further conjugated unsaturation. The colour reactions, and the formation of a deeply coloured picrate, point in the same direction. One possible formula for this substance is (II) and there are two plausible alternatives which are *cyclo*heptatriene derivatives. The problem will be further studied and as the structure is not yet established discussion of the mechanism of its formation must be postponed.



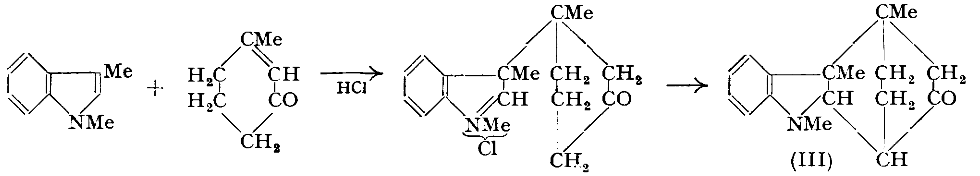
(II)

It was important to extend this type of condensation to the homologous series and for this purpose the condensation of 1 : 3-dimethylindole and heptane-2 : 6-dione was studied. The product was a feeble base, $C_{17}H_{21}ON$, which gave an oxidative colour reaction with ferric chloride very similar to that exhibited by strychnidine. The ultra-violet spectrum and other properties also proclaimed the dihydroindole nature of the substance. The course of the condensation was therefore analogous to that noted in the previous case but, if it were completely similar, the composition would have been $C_{17}H_{23}O_2N$. The new substance contains no hydroxyl group (infra-red spectrum) but it does contain a carbonyl group (infra-red spectrum and derivatives) which is not conjugated with a double bond. We naturally concluded that a substance of type (I) with an extra methylene group in the ring had suffered loss of water with formation of a double bond. However, further work cast doubt on this simple assumption. In the first place a double bond could not be characterised by catalytic reduction and, secondly, the iodoform reaction was either not exhibited or was uncertain. A direct comparison of the compounds $C_{16}H_{21}O_2N$ and $C_{17}H_{21}ON$ in the latter respect was carried out by grinding small specimens with a crystal of iodine, covering them with 10% sodium carbonate solution, and heating them side by side in a shallow bath of boiling water. Visible iodoform was produced from the C_{16} compound but only a doubtful odour from the C_{17} substance. The estimation of *C*-Me gave strong support to the conclusion that a methyl ketone group was absent.



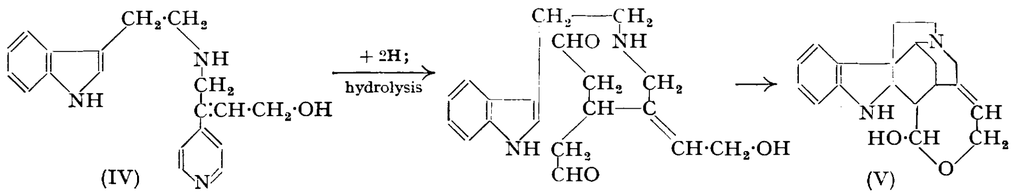
A, 3-*Acetyl*-1 : 2 : 3 : 3a : 4 : 8b-*hexahydro*-1-*hydroxy*-1 : 4 : 8b-*trimethyl*cyclo*pent*[b]*indole in* MeOH.
B, 1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-1 : 9-*dimethylcarbazole in* MeOH.
C, *Indole*, $C_{16}H_{17}N$ (*m. p.* 134°), *in* cyclo*hexane*.
D, 1 : 4 : 9-*Trimethylcarbazole in* MeOH.

When we realised that the structure (III) for the compound $C_{17}H_{21}ON$ accommodated the facts it seemed probable that the reaction involved dehydration of the diketone to methyl*cyclo*hexenone in the first instance. This hypothesis was confirmed by the formation of the compound $C_{17}H_{21}ON$ from 1 : 3-dimethylindole and 3-methyl*cyclo*hex-2-enone under the usual conditions. The second phase of the process parallels that which occurs in the lower homologous series.



(III)

The investigation now described realises laboratory analogies for two fundamental steps of the biogenesis of strychnine proposed by R. B. Woodward (*Nature*, 1948, **162**, 155) but this has only been achieved by blocking the substitution of hydrogen on the indole nitrogen. Nevertheless a stereochemical device might be used to effect the same purpose. For example a pendent pyridine group could be employed; this by addition of two hydrogen atoms to the pyridine nucleus and hydrolysis would afford a substituted glutardialdehyde of the correct structure. Thus the synthesis of strychnine might be accomplished in an extraordinarily simple fashion. The pyridine derivative (IV) should yield the Wieland–Gumlich aldehyde (V) through the two stages indicated above.



(IV)

(V)

EXPERIMENTAL

Condensaton of 1 : 3-*Dimethylindole with Hexane*-2 : 5-*dione*. (A) 3-*Acetyl*-1 : 2 : 3 : 3a : 4 : 8b-*hexahydro*-1-*hydroxy*-1 : 4 : 8b-*trimethyl*cyclo*pent*[b]*indole* * (I).—A mixture of 1 : 3-dimethylindole (2·9 g.), hexane-2 : 5-dione (2·5 g.), ethanol (9 c.c.), and water (1 c.c.) was cooled in ice, saturated with hydrogen chloride, and kept for 90 min. Water (50 c.c.) was added and the neutral material extracted with ether. The basic product was liberated from the aqueous solution by addition of dilute aqueous sodium hydroxide and isolated by means of ether. The cyclo*pentindole* crystallised from light petroleum (b. p. 60—80°) as massive, colourless rhombs, m. p. 90—92° (3·1 g., 58%) (Found: C, 73·6, 73·8; H, 8·2, 8·4; N, 5·45; active H, 0·82; NMe, 4·12; *C*-Me, 12·0%; *M*, 247. $C_{16}H_{21}O_2N$ requires C, 74·1; H, 8·1; N, 5·4; 2H, 0·77; 1NMe, 11·2; 3*C*-Me, 17·4%; *M*, 259). The *picrate*, prepared in ethanol, separated from acetone as yellow octahedra, m. p. 151° (decomp.) with darkening above 140° (Found: C, 54·2; H, 5·1. $C_{16}H_{21}O_2N,C_6H_3O_7N_3$ requires C, 54·1; H, 4·9%). The *semicarbazone* crystallised from ethanol as long, colourless prisms, m. p. 208—209° (Found: C, 64·4; H, 7·3; N, 18·2. $C_{17}H_{24}O_2N_4$ requires C, 64·6; H, 7·6; N, 17·7%). The base is rapidly degraded by concentrated aqueous hydrochloric acid (see below) but is quite stable to alkalis. It exhibits the properties of a tertiary aromatic amine, and gives a deep orange-red colour with ferric chloride. It gives iodoform with iodine and sodium carbonate solution, condenses with piperonaldehyde to a yellow piperonylidene derivative, and gives a brownish-red colour with sodium nitroprusside in aqueous methanolic sodium hydroxide solution.

The infra-red spectrum shows the presence of an unconjugated carbonyl group with a band at 5·85 μ, and a hydroxyl band at 2·82 μ. However, the base did not react with phenyl *iso*cyanate at room temperature in 72 hr., nor did it react with nitromethane in methanol. Acetic anhydride and pyridine in the cold did not affect the base, but the same reagent at the b. p. led to decomposition, as did the use of toluene-*p*-sulphonyl chloride in pyridine.

The ultra-violet absorption of the base was typical of a dihydroindole, with maxima at 2550 ($\log_{10} \varepsilon_{\text{molar}} = 3·97$) and 3000 Å ($\log_{10} \varepsilon_{\text{molar}} = 3·33$), which follows closely the absorption of hexahydro-1 : 9-dimethylcarbazole, which has maxima at 2550 ($\log_{10} \varepsilon_{\text{molar}} = 3·93$) and 2950 Å ($\log_{10} \varepsilon_{\text{molar}} = 3·42$).

3-*Acetyldodecahydro*-1-*hydroxy*-1 : 4 : 8b-*trimethyl*cyclo*pent*[b]*indole*.—The foregoing pentin-

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* Enumeration and name according to Ring Index no. 1418.

dole (1·2 g.) in ethanol (25 c.c.) was hydrogenated at atmospheric pressure and temperature, Adams's catalyst (0·1 g.) being used. After 4 hr. only 100 c.c. of hydrogen had been absorbed, but after perchloric acid (1 drop of 60%) had been added the reduction continued. When absorption ceased 360 c.c. hydrogen had been taken up (336 c.c. for $3H_2$). The resulting solution was filtered, an excess of dilute alkali added, and the ethanol removed. The base was dissolved in ether, the solution dried, and the product obtained by distillation. The *decahydropentindole* (1 g.) was collected at 120—130°/0·05 mm. (Found : C, 72·8; H, 10·4; N, 4·9. $C_{16}H_{27}O_2N$ requires C, 72·5; H, 10·2; N, 5·3%). This base did not exhibit the colour reactions of the parent compound, for example, the oxidative reaction with ferric salts.

1 : 2 : 3 : 3a : 4 : 8b-*Hexahydro*-1-*hydroxy*-1-1′-*hydroxyethyl*-1 : 4 : 8b-*trimethyl*cyclo*pent*[b]-*indole*.—A solution of lithium aluminium hydride (0·3 g.) in ether (25 c.c.) was added dropwise to a solution of the acetylhexahydropentindole (1 g.) in ether (25 c.c.) and the mixture refluxed for an hour. The excess of the reagent was destroyed by addition of moist ether and then water; the ethereal layer was dried and evaporated. The residue was crystallised from benzene, and 1 : 2 : 3 : 3a : 4 : 8b-*hexahydro*-1-*hydroxy*-3-1′-*hydroxyethyl*-1 : 4 : 8b-*trimethyl*cyclo*pent*[b]*indole* (yield almost quantitative) obtained as long, colourless prisms, m. p. 142·5—143·5° (Found : C, 73·3, 73·9; H, 8·5, 8·8; N, 5·3. $C_{16}H_{23}O_2N$ requires C, 73·6; H, 8·8; N, 5·4%). This base is unaffected by boiling concentrated hydrochloric acid (10 min.), conditions under which the parent keto-amine is degraded to a compound $C_{16}H_{17}N$ (see below).

Reaction of 1 : 3-*Dimethylindole with Acetonylacetone* (B).—A solution of 1 : 3-dimethylindole (12 g.) and hexane-2 : 5-dione (10 g.) in ethanol (25 c.c.) was saturated with hydrogen chloride while cooling in ice, then kept at the room temperature for 6 hr., after which it was poured into water (200 c.c.) and extracted with ether. The ethereal solution was dried, the solvent removed, the residue distilled, and the volatile material collected at 140—190°/0·07 mm. (8·4 g.). The distillate was passed in light petroleum (b. p. 60—80°) through an alumina column. Elution with the same solvent gave 1 : 4 : 9-*trimethylcarbazole* (0·5 g.), obtained from methanol–ethanol as colourless needles, m. p. 131—132°, alone or mixed with authentic 1 : 4 : 9-trimethylcarbazole (see below : m. p. 132°) (Found : C, 85·6; H, 7·2; N, 6·7. $C_{15}H_{15}N$ requires C, 86·1; H, 7·2; N, 6·7%). Further elution of the substances adsorbed on the alumina column yielded colourless, uncrystallisable oils, which did not give crystalline picrates and possibly contained tetramethylcarbazoles.

Synthesis of 1 : 4 : 9-*Trimethylcarbazole*.—A solution of 1 : 4-dimethylcarbazole (1·1 g.) in liquid ammonia (25 c.c.) was added dropwise to a solution of sodamide (from 0·13 g. of sodium) in liquid ammonia (25 c.c.). The mixture was stirred, and methyl iodide (2 g.) added cautiously. The ammonia was allowed to evaporate, and moist ether was added, followed by water and dilute hydrochloric acid. The ethereal layer was dried and the solvent removed. The residue was crystallised from ethanol. 1 : 4 : 9-Trimethylcarbazole (yield almost quantitative) was obtained as colourless needles, m. p. 132° (Found : C, 86·1; H, 7·2; N, 6·7%). This substance developed a dark green colour in a mixture of concentrated sulphuric and nitric acids. The *picrate* crystallised from benzene in red needles, m. p. 185—186° (Found : C, 57·5; H, 4·3. $C_{15}H_{15}N,C_6H_3O_7N_3$ requires C, 57·5; H, 4·1%). The infra-red spectra of the two specimens of trimethylcarbazole were identical in the region 4—14 μ.

Action of Hydrochloric Acid on 3-*Acetyl*-1 : 2 : 3 : 3a : 4 : 8b-*tetrahydro*-1-*hydroxy*-1 : 4 : 8b-*trimethyl*cyclo*pent*[b]*indole*.—A solution of this pentindole derivative (3 g.) in concentrated hydrochloric acid (30 c.c.) was heated for 30 min. on the steam-bath. The cooled solution was diluted with water (100 c.c.) and extracted with ether. The ethereal solution was dried (K_2CO_3) and the solvent removed. Distillation of the residual oil gave 1 : 3-dimethylindole (picrate m. p. and mixed m. p. 143—144°) and a *product*, b. p. 130—150°/0·025 mm. (1 g.), which solidified on trituration with light petroleum and was obtained as colourless needles, m. p. 134° (mixed m. p. with 1 : 4 : 9-trimethylcarbazole, 110—115°), from methanol (Found : C, 85·7, 86·3; H, 7·7, 7·6; N, 6·3; NMe, 9·4; *C*-Me, 11·9. $C_{16}H_{17}N$ requires C, 86·1; H, 7·6; N, 6·3; 1NMe, 13·0; 2*C*-Me, 13·4%). The *picrate* separated from benzene as black, lustrous needles, decomp. 197° (Found : C, 58·3, 58·6; H, 4·7, 4·7; N, 12·6. $C_{16}H_{17}N,C_6H_3O_7N_3$ requires C, 58·4; H, 4·4; N, 12·4%).

In further preparations this substance was purified by conversion of the crude oil into the picrate and regeneration from this derivative. It gave a very pale yellowish-green colour with Ehrlich's reagent in the cold, which became blue on heating. The colour change was reversible. Excess of hydrochloric acid gave a very deep green colour in the presence of *p*-dimethylaminobenzaldehyde. Its colourless methanolic solution exhibited an intense blue fluorescence which was destroyed by addition of mineral acid.

The infra-red spectrum of this substance has a small peak at 5·80 µ, and a large one at 11·59 µ.

Reduction of the indole $C_{16}H_{17}N$. The indole derivative $C_{16}H_{17}N$ (0·36 g.) was hydrogenated in ethanol solution at the atmospheric temperature and pressure in presence of Raney nickel (W7) as the catalyst. Absorption ceased when 120 c.c. of hydrogen had been absorbed (105 c.c. required for $3H_2$). The solution was filtered, the ethanol removed, and the basic material extracted from the residual oil. The basic *product* was a colourless oil, b. p. 145—150°/0·01 mm. (Found: C, 83·7; H, 9·8; *C*-Me, 14·1. $C_{16}H_{23}N$ requires C, 83·8; H, 10·0; 2*C*-Me, 13·1; 3*C*-Me, 19·6%). The *picrate* crystallised from ethanol as long, yellow needles, m. p. 131—132° (Found: C, 58·0; H, 5·7; N, 12·8. $C_{16}H_{23}N,C_6H_3O_7N_3$ requires C, 57·6; H, 5·7; N, 12·2%).

1 : 4-*Ethylene*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*-4 : 9 : 11-*trimethyl*-2-*oxocarbazole* (III).—(*a*) A solution of 1 : 3-dimethylindole (4 g.), heptane-2 : 6-dione (6 g.), and water (4 c.c.) in ethanol (20 c.c.) was cooled in ice, and saturated with hydrogen chloride. The mixture was kept for 2 days, then diluted with water (100 c.c.) and extracted with ether. The ethereal layer was dried and evaporated, leaving a pale brown viscous oil (7·9 g.). A solution of this oil in light petroleum (b. p. 60—80°) was passed through a column of alumina, and eluent collected in 20-c.c. fractions. The fractions yielding a crystalline solid on evaporation were combined, and the product recrystallised from light petroleum (b. p. 60—80°). 1 : 4-*Ethylene*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro*-4 : 9 : 11-*trimethyl*-2-*oxocarbazole* (2·5 g., 35%) was obtained as long, colourless prisms, m. p. 120—122° (Found: C, 80·2; H, 8·4; N, 5·4; *C*-Me, 5·27. $C_{17}H_{21}ON$ requires C, 80·0; H, 8·2; N, 5·5; 1*C*-Me, 5·97%).

(*b*) An ice-cold solution of 1 : 3-dimethylindole (2·5 g.) and 3-methyl*cyclo*hex-2-enone (2·5 g.) in ethanol (10 c.c.) and water (2 c.c.) was saturated with hydrogen chloride. After being kept overnight at the room temperature, the mixture was poured into water (100 c.c.) and extracted with ether. The dried ethereal extract yielded on evaporation 1 : 4-ethylene-1 : 2 : 3 : 4 : 10 : 11-hexahydro-4 : 9 : 11-trimethyl-2-oxocarbazole, which crystallised spontaneously on cooling. Recrystallisation from light petroleum (b. p. 60—80°) gave prisms (1·9 g., 50%), m. p. 120—122°, alone and when mixed with the product from 1 : 3-dimethylindole and heptane-2 : 6-dione (Found: C, 79·8; H, 8·3%). The *semicarbazone* separated from ethanol in rhombs, m. p. 205° (Found: C, 68·9; H, 8·0. $C_{18}H_{24}ON_4$ requires C, 69·2; H, 7·7%).

This substance is a weak base, which behaves in all respects like a dihydroindole. The ferric chloride oxidative colour reaction is intense carmine, while the Ehrlich reagent gives an emerald-green colour which slowly becomes deep blue. The base couples with diazonium salts to azo-dyes and gives a yellow 2 : 4-dinitrophenylhydrazone. It is soluble in an excess of 1% hydrochloric acid, sparingly so in 2% acid, and does not afford a picrate under the usual conditions.

In the infra-red region there is an absorption maximum at 5·82 µ, indicating an unconjugated carbonyl group; there is no band due to hydroxyl, nor any indication of an olefinic double bond.

The substance was not reduced at atmospheric temperature and pressure at palladised strontium carbonate or Raney nickel. It was reduced slowly in the presence of Adams's catalyst and ethanolic perchloric acid but, when absorption of hydrogen ceased, 25% of the base was recovered unchanged. The remaining fraction, which was strongly basic, was an uncrystallisable oil, which showed no absorption in the carbonyl region, and two small peaks in the hydroxyl region at 3·0 and 3·1 µ. The colour reactions of the product indicated that it still contained a dihydroindole system, and the absorption of hydrogen could be accounted for on the assumption that reduction of an oxo-group was the only reaction.

The ultra-violet spectrum of the parent substance, $C_{17}H_{21}ON$, was normal for a dihydroindole, the absorption showing maxima at 2550 ($\log_{10} \varepsilon = 3{\cdot}89$) and 3030 Å ($\log_{10} \varepsilon = 3{\cdot}48$).

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