Further Experiments relating to the Condensation of Substituted Indoles with Hexane-2 : 5-dione.

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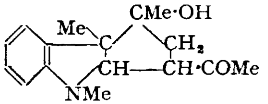
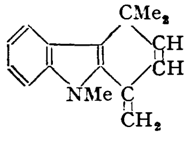
The condensation of 1 : 3-dimethylindole with hexane-2 : 5-dione (Robinson and Saxton, *J.*, 1953, 2596) followed by vigorous treatment of the product with concentrated hydrochloric acid afforded a substance, $C_{16}H_{17}N$, tentatively formulated on the basis of a carbazole skeleton. Attempted synthesis has proved unsuccessful and the failure to find an exocyclic methylene group casts doubt on the suggestion made in 1953. An alternative is that the compound is a derivative of *cyclo*heptane.

The condensation of 1 : 2-dimethylindole and hexane-2 : 5-dione with the help of hydrogen chloride led to the formation of 2 : 5-di-(1′ : 2′-dimethyl-3′-indolyl)hexa-2 : 4-diene. A similar (2 : 1) condensation was realised on using 1 : 2-dimethylindole and 2 : 5-dimethoxytetrahydrofuran.

1 : 3-DIMETHYLINDOLE and hexane-2 : 5-dione condense in aqueous-alcoholic hydrogen chloride with formation of a substance, $C_{16}H_{21}O_2N$, which is very probably (I) (*loc. cit.*). The action on this of concentrated hydrochloric acid at 100° afforded a neutral compound, $C_{16}H_{17}N$ (deeply coloured picrate), thought to be (II) though the possibility of *cyclo*heptatriene formulations was also contemplated.

(I)



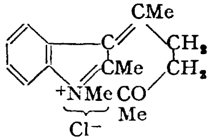


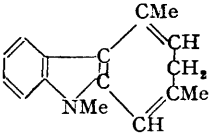
(II)

The dubieties in regard to the structure (II), arising from its infrared spectrum, are much increased by our failure to obtain any trace of formaldehyde after ozonisation.

There is no loss of carbon in the reaction (I → II) and therefore (since $C_{16}H_{17}N$ is certainly an aromatic indole derivative) the 3-methyl group (indole numbering) has probably migrated. The alternative is to break the *cyclo*pentane ring of (I) between the two CMe groups and this greatly increases the difficulty of representing the loss of both oxygen atoms in an acceptable manner. If, however, we assume the intermediate (III) as the result of a migration of methyl from position 3 to position 2 of the indole nucleus, the further change to (IV) is a natural one, and this structure (IV) now becomes our preferred working hypothesis for the constitution of $C_{16}H_{17}N$. There are two obvious variations of (IV) produced by a shift of one or other of the double bonds.

(III)

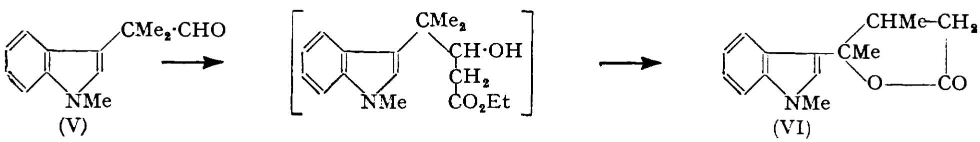




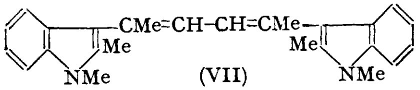
(IV)

This formula agrees with the 2 *C*-Me groups found in $C_{16}H_{17}N$ and its hexahydro-derivative (no sufficient increase for $C{:}CH_2 \longrightarrow {:}CHMe$), as well as the indole character and extended conjugation of the substance (ultraviolet spectrum).

An attempted synthesis of (II) was on the following lines. α-3-Indolyl*iso*butyric acid was prepared by the noteworthy method of Erdtman and Jonsonn (*Acta Chem. Scand.*, 1954, **8**, 119) which involves the condensation of indole with acetone and chloroform in presence of alkali. The ester of this acid has been *N*-methylated by Potts and Saxton (*J.*, 1954, 2642) and we have now reduced this derivative to 2-(1-methyl-3-indolyl)-2-methylpropan-1-ol by means of lithium aluminium hydride. The corresponding aldehyde (V) (prepared by the Oppenauer method, using *p*-benzoquinone and aluminium *tert.*-butoxide) gave a variety of complex condensation products with acetone. This aldehyde did not condense with malonic acid under the conditions of the Doebner reaction and it was inactive towards ethyl acetoacetate in presence of piperidine. It condensed, however, with ethyl bromoacetate and zinc under Reformatzky conditions to a product which was not isolated but was converted by hot formic acid into a γ-lactone (infrared band). The formation of a γ-lactone requires the migration of a methyl group and the most probable interpretation leads to the structure (VI).

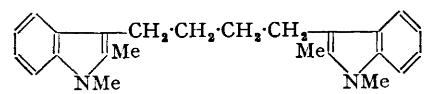

(V) (VI)

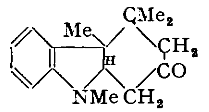
The condensation of 1 : 2-dimethylindole with hexane-2 : 5-dione might have provided an intermediate for synthesis of the heptatriene derivative (IV) but it proceeded (2 : 1), in alcoholic solution containing hydrogen chloride, with formation of the bisindole (VII).


(VII)

On catalytic reduction this product afforded a tetrahydro-derivative, the ultraviolet absorption spectrum and the colour reactions of which were in harmony with its formulation as a 1 : 2 : 3-trisubstituted indole derivative. Attempted reduction with tin and hydrochloric acid gave 2 : 3-dihydro-1 : 2-dimethylindole and fission to 1 : 2-dimethylindole occurred under the influence of hot concentrated hydrochloric acid alone. Analogous condensation of 1 : 2-dimethylindole with 2 : 5-dimethoxytetrahydrofuran gave a lower bis-homologue of (VII) which on catalytic reduction yielded the compound (VIII).

(VIII)




(IX)

The condensation of 1 : 3-dimethylindole with mesityl oxide in aqueous-alcoholic hydrogen chloride parallels the case of methyl*cyclo*hexenone previously described (Robinson and Saxton, *loc. cit.*). The properties of the product are consistent with the structure (IX).

EXPERIMENTAL

Action of Ozone on the Substance, $C_{16}H_{17}N$.—The indole derivative (0·24 g.) was ozonised in carbon tetrachloride solution (30 c.c.) and absorption ceased after 40 min. The issuing gas was passed through a saturated aqueous solution of dimedone but there was no precipitate and the dimedone was all recovered on evaporation. The solid ozonide was added to dilute sulphuric acid (50 c.c.) and the solution distilled, but neither the exit vapours nor the aqueous condensate contained formaldehyde as shown by the failure to obtain any condensation product with dimedone or 2 : 4-dinitrophenylhydrazine.

α-(1-*Methyl*-3-*indolyl*)iso*butyric Acid*.—A mixture of ethyl 1-methyl-3-indolyl*iso*butyrate (3·8 g.) (Potts and Saxton, *loc. cit.*), ethanol (50 c.c.), and 40% aqueous sodium hydroxide (10 c.c.) was refluxed for 4 hr. The *acid*, obtained in the usual way, crystallised from ethanol in colourless plates (2·5 g.), m. p. 181° (Found : C, 71·6; H, 7·0; N, 6·5; NMe, 7·7. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9; N, 6·5; NMe, 13·4%).

2-(1-*Methyl*-3-*indolyl*)-2-*methylpropan*-1-*ol*.—A solution of ethyl α-(1-methyl-3-indolyl)-*iso*butyrate (4·8 g.) in ether (100 c.c.) was added during 15 min. to a stirred suspension of lithium aluminium hydride (10 g.) in ether (100 c.c.), and the whole refluxed for 30 min. After cooling, ethanol, water, and dilute hydrochloric acid were added. The residue, after evaporation of the dried, ethereal layer, crystallised from light petroleum (b. p. 60—80°). 2-(1-*Methyl*-3-*indolyl*)-2-*methylpropan*-1-*ol* (3·4 g.) was obtained as long, colourless prisms, m. p. 86—87° (Found : C, 76·7; H, 8·35; N, 7·2. $C_{13}H_{17}ON$ requires C, 76·85; H, 8·4; N, 6·9%). The *picrate* crystallised from benzene as orange-red needles, m. p. 106—108° (Found : C, 52·9; H, 4·9; N, 12·7. $C_{19}H_{20}O_8N_4$ requires C, 52·8; N, 4·6; N, 13·0%).

α-(1-*Methyl*-3-*indolyl*)iso*butyraldehyde* (V).—2-(1-Methyl-3-indolyl)-2-methylpropan-1-ol was unaffected by boiling with aluminium *tert.*-butoxide in acetone, and by chromic acid in *tert.*-butyl alcohol.

A mixture of the alcohol (2 g.), *p*-benzoquinone (4 g.), aluminium *tert.*-butoxide (5 g.), and dry benzene (50 c.c.) was refluxed for 1 hr. The cooled solution was filtered, the solid was washed well with ether, and the combined organic extracts were washed with dilute sulphuric acid and then with aqueous sodium hydroxide until the aqueous extracts were colourless. At this stage emulsions were troublesome and the alkali was added in portions of 25 c.c. and the liquids merely swirled until most of the quinone had been removed. The ether–benzene solution was then dried, the solvent removed, and the residue crystallised from light petroleum (b. p. 40—60°). α-(1-*Methyl*-3-*indolyl*)iso*butyraldehyde* (1·3 g.) was obtained as colourless prisms, m. p. 69—70° (Found : C, 77·8; H, 7·4; N, 7·2. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·4; N, 7·0%). The infrared spectrum shows the presence of an unconjugated carbonyl group (band at 5·84 μ). The *semicarbazone* crystallised from ethanol as colourless rhombs, m. p. 208—209° (Found : C, 65·2; H, 7·1; N, 21·4. $C_{14}H_{18}ON_4$ requires C, 65·1; H, 7·0; N, 21·7%).

β-*Methyl*-γ-(1-*methyl*-3-*indolyl*)-γ-*valerolactone* (VI).—A mixture of methylindolyl*iso*butyraldehyde (3·7 g,). ethyl bromoacetate (4 c.c.), zinc wool (1·5 g.), mercuric chloride (0·1 g.), and benzene (50 c.c.) was heated until a reaction started, which was then allowed to proceed. When the initial reaction had subsided, ethyl bromoacetate (4 c.c.) was added, and the mixture boiled for 5 hr. Acetic acid and water were added after cooling, and the aqueous layer was extracted with ether. The combined organic extracts were washed with dilute aqueous ammonia until the aqueous layer was colourless. The ether–benzene layer was then dried, and the solvent removed. The residue was dissolved in formic acid (25 c.c.) and the solution heated on the steam-bath for 5 hr. The solvent was removed *in vacuo*, the residue dissolved in ether, the ethereal solution washed with dilute aqueous sodium carbonate solution, then dried, and the solvent removed. The residue was dissolved in benzene, and filtered through a column of activated alumina (80 g.). The combined eluates yielded the *lactone* (1·5 g.), which crystallised from benzene as colourless prisms, m. p. 147° (Found : C, 73·8; 74·4, H, 7·1, 6·9; N, 5·9. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·8%). The infrared spectrum shows no peak at 2·87 μ (OH), but a pronounced peak at 5·68 μ (unconjugated γ-lactone CO). When the crude Reformatzky product was treated with iodine (0·2 g.) in boiling toluene, the lactone was again obtained (undepressed mixed m. p. and identical infrared spectrum).

The uncrystallisable oil obtained by filtration of the crude Reformatzky reaction product through alumina showed a hydroxyl band at 2·87 μ, and an ester band at 5·83 μ. The lactone was unchanged when boiled for 6 hr. with red phosphorus and hydrogen iodide in acetic acid.

Methyl γ-*Hydroxy*-β-*methyl*-γ-(1-*methyl*-3-*indolyl*)-n-*valerate*.—A solution of the above lactone (1 g.) in ethanol (10 c.c.) along with aqueous sodium hydroxide (5 c.c. of 20%) was boiled for 3 hr. and then cooled overnight. *Sodium* γ-*hydroxy*-β-*methyl*-γ-(1-*methyl*-3-*indolyl*)-*valerate* then separated and was recrystallised from acetone–benzene, and so obtained as colourless prisms, m. p. 217°. After drying at 100° for 4 hr., it had m. p. 228—230° (Found : C, 62·0; H, 6·5; N, 5·1; Na, 7·8. $C_{15}H_{18}O_3NNa,\frac{1}{2}H_2O$ requires C, 61·7; H, 6·5; N, 4·8; Na, 7·9%).

The sodium salt (1 g.) was dissolved in acetone (20 c.c.) and methyl iodide (5 c.c.), and the solution boiled for 4 hr. The solvent was removed, the residual oil dissolved in ether, and the solution filtered from sodium iodide, dried, and evaporated. The residue crystallised slowly and recrystallised from light petroleum (b. p. 60—80°). The methyl ester (0·5 g.) was obtained as colourless prisms, m. p. 73—75° (Found : C, 70·2; H, 7·5; N, 5·1. $C_{16}H_{21}O_3N$ requires C, 69·8; H, 7·6; N, 5·1%). The infrared spectrum shows a hydroxyl band at 2·87, and an ester band at 5·82 μ.

γ-*Hydroxy*-β-*methyl*-γ-(1-*methyl*-3-*indolyl*)-n-*valeric Acid*.—The sodium salt (1 g.) was dissolved in the minimum of cold water, and excess of dilute hydrochloric acid added. The precipitated *acid* was collected, washed well with cold water, and dissolved in the minimum of cold acetone. Gradual dilution of this solution with cold water gave colourless needles (0·59 g.), which softened and dehydrated above 59° to a pasty mass, which clarified above 140° (Found : C, 65·0; H, 7·6; N, 5·1. $C_{15}H_{19}O_3N,H_2O$ requires C, 64·5; H, 7·5; N, 5·0%). Slow crystallisation of the hydroxy-acid from acetone–benzene yields the lactone, m. p. and mixed m. p. 147°.

Distillation of the methyl ester of the hydroxy-acid at 160—170°/0·07 mm. (bath) gave a mixture of lactone and unchanged hydroxy-ester.

The lactone was also obtained on boiling a solution of the hydroxy-ester in xylene containing iodine for 2 hr.

2 : 5-*Di*-(1 : 2-*dimethyl*-3-*indolyl*)*hexa*-2 : 4-*diene* (VII).—A slow stream of hydrogen chloride was passed through a solution of hexane-2 : 5-dione (2·5 g.) and 1 : 2-dimethylindole

(5 g.) in ethanol (20 c.c.), at 0°, until no further solid was precipitated (about 20 min.). The product was collected, washed with ethanol, and crystallised from pyridine. The hexadiene (1·5 g., 23%) was obtained as colourless, hexagonal plates, m. p. 235°, raised to 242° by two further crystallisations from the same solvent. The substance was also obtained as long, colourless prisms, m. p. 270°. A mixture of the two forms gave m. p. 228—232° so that they may be geometrical stereoisomers. The ultraviolet spectrum showed maxima at 2300 and 2900 Å as usually observed with indole derivatives; the extinction coefficients at these peaks were however much lower than the corresponding values for simple indoles.

When the di-(dimethylindolyl)hexadiene (7 g.) was heated for 1 hr. on the steam-bath with concentrated hydrochloric acid (80 c.c.), the only isolable product was 1 : 2-dimethylindole (3·9 g.), m. p. 55° [picrate, red needles (from benzene), m. p. and mixed m. p. 121°].

2 : 3-*Dihydro*-1 : 2-*dimethylindole*.—(*A*) A mixture of 1 : 2-dimethylindole (4 g,), ethanol (50 c.c.), concentrated hydrochloric acid (50 c.c.), and granulated tin (15 g.) was refluxed for 7 hr. The basic product (3·5 g.) was obtained as a colourless oil, b. p. 103—104°/18 mm., affording a *picrate*, yellow plates (from ethanol), m. p. 131—133° (decomp.) (Found : C, 51·1; H, 4·2; N, 15·1. $C_{10}H_{13}N,C_6H_3O_7N_3$ requires C, 51·1 ; H, 4·3; N, 14·9%).

(*B*) A mixture of the di-(dimethylindolyl)hexadiene (6 g.), concentrated hydrochloric acid (40 c.c.), and tin (15 g.) was boiled for 3 hr. The base isolated in the known manner was purified by distillation. 2 : 3-Dihydro-1 : 2-dimethylindole (4·2 g.) was collected as a colourless oil, b. p. 101—102°/17 mm., n_D^{23} 1·5394 (Found : C, 81·2; H, 9·1; N, 9·5. Calc. for $C_{10}H_{13}N$: C, 81·6; H, 8·8; N, 9·6%). The picrate crystallised from ethanol as yellow plates, m. p. and mixed m. p. 131—133° (Found : C, 51·1, 51·4; H, 4·2, 4·4; N, 15·2%).

2 : 5-*Di*-(1 : 3-*dimethyl*-3-*indolyl*)*hexane*.—The hexadiene (1·8 g.) in pure dioxan (100 c.c.) was hydrogenated in the presence of Raney nickel at 130°/100 atm. for 7 hr. The solution was filtered, and the solvent removed under reduced pressure. The residue was triturated with ethanol, and crystallised twice from the same solvent. 2 : 5-*Di*-(1 : 2-*dimethyl*-3-*indolyl*)*hexane* (1·5 g.) was obtained as colourless prisms, m. p. 157—160° [Found : C, 84·2; H, 8·4; N, 7·3% ; *M* (cryoscopic in camphor), 301. $C_{26}H_{32}N_2$ requires C, 83·9; H, 8·6; N, 7·5% ; *M*, 372]. This substance gives a blue-grey colour when warmed with Ehrlich's reagent; on cooling the colour disappears, an alternation which can be repeated *ad libitum*. The *dipicrate* was prepared in benzene solution, and crystallised from ethanol as brown needles, m. p. 191—192° (Found : C, 55·1; H, 4·9; N, 13·4. $C_{26}H_{32}N_2,2C_6H_3O_7N_3$ requires C, 54·9; H, 4·9; N, 13·5%). This tetrahydro-derivative of (VII) showed normal indole absorption in the ultraviolet region.

An attempted reduction in dioxan using Adams catalyst at the room temperature and pressure did not succeed.

Attempted Reaction of 2 : 5-*Di*-(1 : 2-*dimethyl*-3-*indolyl*)*hexa*-2 : 4-*diene with Maleic Anhydride*.—A solution of the hexadiene (2 g.), maleic anhydride (1·5 g.), and trichloroacetic acid (0·01 g.) in xylene (100 c.c.) was refluxed for 7 hr. The solvent was removed by distillation under reduced pressure, and the residue warmed with dilute sodium hydroxide solution. The solid was collected and crystallised from pyridine. Unchanged hexadiene was recovered as colourless plates, m. p. and mixed m. p. 241°.

Other examples of the non-reactivity of inner units of long conjugated systems have been reported (cf. Weizmann, Bergmann, and Haskelberg, *J.*, 1939, 391; Dilthey, Schommer, and Trösken, *Ber.*, 1933, **66**, 1627).

1 : 4-*Di*-(1 : 2-*dimethyl*-3-*indolyl*)*butadiene*.—Hydrogen chloride was slowly passed through an ice-cooled mixture of 1 : 2-dimethylindole (2 g.), tetrahydro-2 : 5-dimethoxyfuran (4 g.), ethanol (5 c.c.), and water (0·5 c.c.). The stirred mixture was kept at 0° until crystallisation was complete; then the solid was collected, washed well with ethanol, and crystallised twice from pyridine. 1 : 4-*Di*-(1 : 2-*dimethyl*-3-*indolyl*)*butadiene* (0·5 g., 21%) was obtained as colourless, hexagonal plates, m. p. 292—294°, with softening above 275° (Found : C, 84·6; H, 7·3; N, 8·5; *C*-Me, 6·5. $C_{24}H_{24}N_2$ requires C, 84·7; H, 7·1; N, 8·3; 2*C*-Me, 8·8%). The properties of this substance closely resembled those of the hexadiene derivative (VII) described above.

1 : 4-*Di*-(1 : 2-*dimethyl*-3-*indolyl*)*butane* (VIII).—The butadiene (1·4 g.) in pure dioxan (100 c.c.) was hydrogenated in the presence of Raney nickel at 150°/100 atm. for 8 hr. After filtration the solvent was removed under reduced pressure and the residue triturated with light petroleum (b. p. 40—60°) and crystallised twice from benzene. 1 : 4-*Di*-(1 : 2-*dimethyl*-3-*indolyl*)*butane* (1·0 g.) was obtained as colourless rhombs, m. p. 174—176° (Found : C, 84·0; H, 7·9; N, 8·1. $C_{24}H_{28}N_2$ requires C, 83·7; H, 8·1; N, 8·1%). This substance gave a pale pink colour on warming with Ehrlich's reagent; the colour disappeared on cooling, and the usual alternation was possible.

1 : 2 : 3 : 4 : 10 : 11-*Hexahydro*-4 : 4 : 9 : 11-*tetramethyl*-2-*oxocarbazole* (IX).—A solution of 1 : 3-dimethylindole (2·7 g.) in ethanol (10 c.c.) and water (2 c.c.) was saturated with hydrogen chloride, mesityl oxide (3 g.) added, and the mixture kept for 2 hr. Water was added, and the solution extracted with ether. The ethereal solution was dried and evaporated, and the residue triturated with benzene until crystallisation was complete. The solid was collected and recrystallised from aqueous ethanol. The *tetramethyl*-2-*oxocarbazole* (2·5 g.) was obtained as colourless needles, m. p. 96—97° (Found: C, 78·8; H, 8·7. $C_{16}H_{21}ON$ requires C, 79·0; H, 8·6%).

This weak base closely resembles 1 : 4-ethylene-1 : 2 : 3 : 4 : 10 : 11-hexahydro-4 : 9 : 11-trimethyl-2-oxocarbazole (Robinson and Saxton, *loc. cit.*) in its properties. It gives a deep red colour with weakly acid ferric chloride, an indicator azo-compound with diazobenzenesulphonic acid, and a deep carmine-red colour with a mixture of sulphuric and nitric acid.

Succinoylbis-1 : 2-*dimethylindole*.—An intimate mixture of 1 : 2-dimethylindole (5 g.), succinic anhydride (1·8 g.), and powdered zinc chloride (2·5 g.) was heated on a steam-bath for 2 hr. The liquid became deep red and viscous, and on cooling set to a red glass. Water (60 c.c.) was added and the mixture boiled for 5 min., cooled, and kept overnight in the refrigerator. The deep red solid was collected, triturated with ethanol, and crystallised from 2-methoxyethanol. The product (2 g., 31%) was obtained as elongated, colourless prisms, m. p. 215—224° (decomp.) dependent on the rate of heating (Found: C, 77·1; H, 6·7. $C_{24}H_{24}O_2N_2$ requires C, 77·4; H, 6·5%). This *substance* gives a deep reddish-magenta colour with mineral acids. The infrared spectrum shows pronounced peaks at 5·87 and 6·11 μ. This suggests an unsymmetrical constitution or that the substance is a mixture. One of the carbonyl groups is doubtless in position 3 of an indole nucleus because 3-acetyl-1 : 2-dimethylindole (Borsche and Groth, *Annalen*, 1941, **549**, 238, give m. p. 103—104° for this substance but, after three crystallisations from benzene and drying at 80°/15 mm., we find m. p. 110°) has been examined for comparison and found to show a strong band at 6·08 μ. The band at 5·87 μ indicates a carbonyl group attached to an aromatic nucleus.

The reduction of the succinoylbisdimethylindole gave several products which could not be identified.

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