884. *Indoles. Part IV.* The Reaction between 1,3-Dimethylindole and Mesityl Oxide.*

By B. Robinson and G. F. Smith.

The carbazole structure (III) proposed for the product of the acid-catalysed interaction of 1,3-dimethylindole and mesityl oxide by Robinson and his co-workers [1] has been confirmed experimentally.

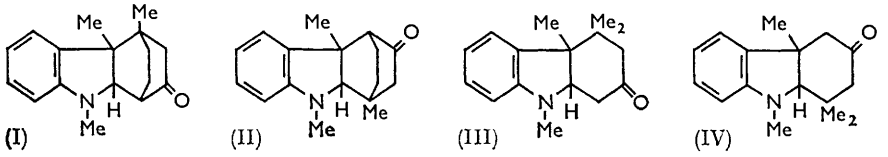
The acid-catalysed reaction of 1,3-dimethylindole with 3-methylcyclohex-2-enone and with mesityl oxide was found by Sir Robert Robinson and his co-workers [1,2] to lead to crystalline products containing an indoline system and a keto-group, to which, without further experimental evidence and mainly on the plausible assumption that the first step in the reaction must be electrophilic addition of the β-carbon atom of the αβ-unsaturated ketone to the β-position of the indole nucleus, they assigned structures (I) and (III) respectively. In a later paper on electrophilic substitution in skatole and its derivatives, Noland and D. N. Robinson [3] put forward the view that, since skatole undergoes electrophilic substitution at the α-position, the first step in the above reactions might well be attack of the αβ-unsaturated ketone at the α-position of the 1,3-dimethylindole, and suggested structures (II) and (IV) for the adducts.

* Part III, *J.*, 1957, 3546.

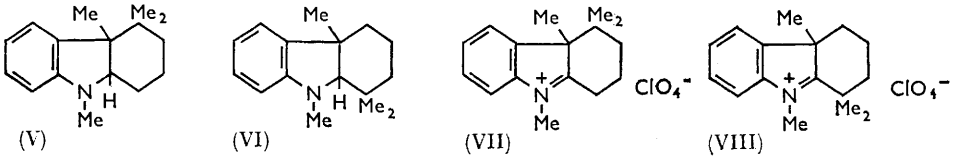
[1] Cockerill, Sir Robert Robinson, and Saxton, *J.*, 1955, 4369.
[2] Sir Robert Robinson and Saxton, *J.*, 1953, 2596.
[3] Noland and D. N. Robinson, *Tetrahedron*, 1958, **3**, 68.

We now present experimental evidence which strongly supports structure (III) for the mesityl oxide product and therefore by analogy structure (I) for the methylcyclohexenone product.

The mesityl oxide product was smoothly reduced by the Huang-Minlon procedure to the oxygen-free base (V) which was shown not to be identical with 1,2,3,4,10,11-hexahydro-1,1,9,11-tetramethylcarbazole (VI), the synthesis of which is described below. In order to

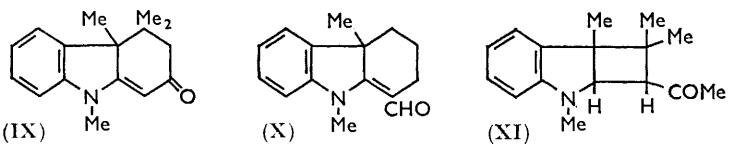


ensure that the non-identity was not simply due to stereoisomerism at the ring-junction, base (V) was dehydrogenated with mercuric acetate in aqueous acetic acid to the 3*H*-indolium salt, isolated as the perchlorate (VII): this was different from the perchlorate (VIII) synthesised from 1,2,3,4-tetrahydro-1,1-dimethylcarbazole (see below). A difference which has a strong bearing on the structural problem is that whereas an alkalinified solution from the latter salt showed ultraviolet absorption expected of an indolinol, with bands at 253 and 302 mμ (ε 8330, 2800), an alkaline solution of the isomer (VII) showed absorption expected of an enamine, with a single intense band at 277 mμ (ε 13,500). This shows that position 1 of the carbazole system in the mesityl oxide product must carry at least one hydrogen atom. This salt (VII) was smoothly reduced back to base (V) by potassium borohydride in methanol, showing that no skeletal rearrangement had occurred in the dehydrogenation. This evidence clearly eliminates structure (IV) for the mesityl oxide adduct.



Strong support for structure (III) comes from dehydrogenation by mercuric acetate to a product (isolated as the 1 : 1 molecular compound with mercurous acetate) which, because of the intense long-wavelength maximum at 339 mμ (ε 27,700) and the very low value of 1629 cm.$^{-1}$ of the carbonyl stretching frequency [cf. 355 mμ (ε 32,000) and 1670 cm.$^{-1}$ for 1-formyl-2,3,4,11-tetrahydro-9,11-dimethylcarbazole [4] (X)], must contain the carbonyl group in vinylogous conjugation with the nitrogen, and hence have structure (IX). This dehydrogenation product is reduced by zinc dust in methanolic sulphuric acid to the indoline (V). All attempts to isolate an oxygen-containing reduction product failed. The production of base (V) from the ketone (III) by two different routes (reduction under strongly alkaline conditions, and dehydrogenation followed by acidic reduction) indicates that in none of these reactions is a skeletal rearrangement likely to have occurred.

All the above evidence is also consistent with a third mechanistically possible structure

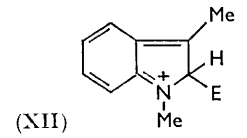


(XI) for the mesityl oxide product. This possibility is eliminated by the failure of the compound to give the iodoform reaction.

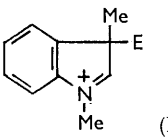
[4] Fritz, *Chem. Ber.*, 1959, **92**, 1809.

It is noteworthy that, although the indoline bases (V) and (VI) are, as would be expected, completely protonated in 0·2N-mineral acid (ultraviolet spectra), the keto-indoline (III) is completely protonated only in 2·5N-acid. The reason for this is rather obscure, for it is not likely to be due to N/C=O interaction [5] in view of the normal stretching frequency (1719 cm.$^{-1}$) of the carbonyl group in this compound. It may be due to steric hindrance to solvation of the cation, although the stereochemistry of (III) is not appreciably different from that of (V). That there is quite considerable crowding around the nitrogen is, however, shown by the failure of both bases (V) and (VI) to react with methyl iodide at 100°, even during very long times.

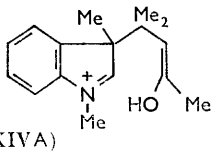
The first step in the formation of the adduct (III), electrophilic attack of the β-position of 1,3-dimethylindole by protonated mesityl oxide, illustrates the point, sometimes overlooked, that the presence of a substituent at a reactive aromatic position does not prevent reversible addition of a reagent at that position. Thus, although the action of a simple electrophilic reagent E^+ on 1,3-dimethylindole leads to the slow formation of a 2-substitution product by way of the intermediate (XII), formation of the more stable cation (XIII) by addition at the β-position occurs very much more frequently than that of (XII).



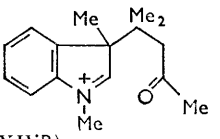
(XII)



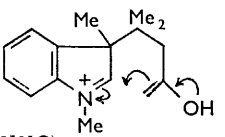
(XIII)



(XIVA)



(XIVB)



(XIVC)

Since cation (XIII) can regain indolic aromaticity only by loss of E^+, no apparent reaction occurs at the β-position. The reaction of mesityl oxide with 1,3-dimethylindole, however, presents a special case, for the immediate product of β-addition, the enol (XIVA) can either dissociate back to the starting materials or ketonise to (XIVB). This keto-cation cannot now as such break down to the starting materials. It can undergo two reversible changes, which are enolisation to (XIVA) which reopens the possibility of dissociation to starting materials; or it can enolise to (XIVC). This now is ideally constituted for cyclisation to (III) by nucleophilic addition of the enol methylene-carbon to the 2-carbon atom of the 3*H*-indolium system. Incidentally, cyclisation of the enol (XIVA) would lead to the cyclobutane structure (XI).

1,2,3,4,10,11-Hexahydro-1,1,9,11-tetramethylcarbazole (VI) was synthesised as follows: Fischer cyclisation of the phenylhydrazone of 2,2-dimethylcyclohexanone [6] gave 1,2,3,4-tetrahydro-1,1-dimethylcarbazole which was converted into the Grignard derivative and methylated with methyl iodide in refluxing benzene, to afford 2,3,4,11-tetrahydro-1,1,11-trimethyl-1*H*-carbazole; this base was converted by methyl iodide into the quaternary salt (VIII; I^- instead of ClO_4^-), reduction of which with potassium borohydride gave the desired base (VI).

Experimental

1,2,3,4,10,11 - *Hexahydro* - 4,4,9,11 - *tetramethylcarbazole* (V).—1,2,3,4,10,11 - Hexahydro - 4,4,9,11-tetramethyl-2-oxocarbazole [mesityl oxide product (III)] (1·14 g.), hydrazine hydrate (3·2 c.c.), solid potassium hydroxide (4·4 g.), and diethylene glycol (50 c.c.) were refluxed for 2·5 hr. The mixture was then slowly distilled until the temperature of the liquid reached 210° and refluxing was continued for 4 hr. Water (200 c.c.) was added to the cooled mixture, and

[5] Anet, Bailey, and Sir Robert Robinson, *Chem. and Ind.*, 1953, 944.
[6] King, King, and Topliss, *J.*, 1957' 919.

the whole extracted with ether (3 × 50 c.c.). The dried ether extracts gave a liquid (1·03 g.) which was dissolved in methanol (4 c.c.) containing picric acid (1·32 g.). The crystalline picrate had m. p. 138—140° with slight sintering at 123° (1·63 g., 76%). A further crop, m. p. 136—139° (0·36 g., 17%), was obtained by concentration of the mother-liquor. The pure *picrate* crystallised from methanol as orange prisms, m. p. 139—140° (slight sintering at 124°) (Found: C, 57·4; H, 5·65; N, 12·2. $C_{22}H_{26}N_4O_7$ requires C, 57·6; H, 5·7; N, 12·1%).

The *base*, liberated from the pure picrate, distilled at 70—80° (bath-temp.)/0·3 mm. and slowly became brown in air (Found: C, 83·5; H, 9·95. $C_{16}H_{23}N$ requires C, 83·8; H, 10·1%). It had $\lambda_{max.}$ 256, 300 mμ (ε 8700, 3080 respectively in EtOH), changed to benzenoid absorption by the addition of hydrochloric acid. The infrared spectrum showed no absorption in the carbonyl stretching region.

2,3,4,11-*Tetrahydro*-4,4,9,11-*tetramethyl*-1H-*carbazolium Perchlorate* (VII).—A solution of the base (V) (165 mg.) in 5% aqueous acetic acid (15 c.c.) containing mercuric acetate (1·1 g.) was heated at 75—85° for 3·5 hr. The precipitated mercurous acetate was filtered off, mercuric ions were precipitated by hydrogen sulphide, and the clear solution was treated with saturated aqueous potassium perchlorate (50 c.c.) and left at 5° overnight. The crystals which separated (0·89 g.) were extracted with warm methanol. The extracts gave the crude *perchlorate* (VII), m. p. 232—238° (174 mg., 73·5%), which after two crystallisations from methanol formed feathery needles, m. p. 241—242° (Found: C, 58·75; H, 6·5. $C_{16}H_{22}ClNO_4$ requires C, 58·7; H, 6·7), $\lambda_{max.}$ 236, 239, 275 mμ (ε 4230, 4440, 5930 respectively in EtOH), changing on basification to $\lambda_{max.}$ 277 mμ (ε 13,500).

Reduction of the Perchlorate (VII) *by Potassium Borohydride*.—A solution of the methoperchlorate (VII) (18·3 mg.) in methanol (5 c.c.) was treated with excess of potassium borohydride, and the mixture left at room temperature for 1 hr. The methanol was then boiled off under reduced pressure and the residue partitioned between ether and water. The dried extracts gave a colourless liquid (12·4 mg.) which with picric acid (14·2 mg.) in methanol (1 c.c.) gave a picrate, m. p. 134—138° (18·7 mg.). Recrystallisation from methanol gave orange prisms, m. p. 138—140° (sintering at 123°), undepressed by the picrate of 1,2,3,4,10,11-hexahydro-4,4,9,11-tetramethylcarbazole (V) of the same m. p.

2,3,4,11-*Tetrahydro*-4,4,9,11-*tetramethyl*-2-*oxocarbazole* (IX).—A suspension of the mesityl oxide product (III) (325 mg.) in a solution of mercuric acetate (2·2 g.) in 15% aqueous acetic acid (35 c.c.) was heated at 75—85° for 3 hr. The precipitated mercurous acetate was filtered off, and both the solid and the orange filtrate were extracted continuously with ethyl acetate for 3 days. The extract yielded an orange glass (818 mg.) which crystallised on trituration with ethanol to a product, m. p. 224—226°, darkening from 194° (684 mg., 67%). Crystallisation from ethanol yielded 2,3,4,11-*tetrahydro*-4,4,9,11-*tetramethyl*-2-*oxocarbazole mercurous acetate complex* as pale yellow, leaf-shaped plates, m. p. 227—228°, darkening from 194° [Found: C, 31·4; H, 3·2. $C_{16}H_{19}NO,Hg_2(CH_3{\cdot}CO_2)_2$ requires C, 31·6; H, 3·3%], $\lambda_{max.}$ 242, 304, 351 mμ (ε 16,100, 6350, 31,100 in EtOH). The infrared spectrum showed a sharp band at 1629 cm.$^{-1}$.

The above complex (413 mg.) was partitioned between 6N-hydrochloric acid (120 c.c.) and chloroform (100 c.c.). The acid layer was extracted with further quantities of chloroform (2 × 50 c.c.). The combined organic extracts were washed with aqueous sodium carbonate and water and dried. Evaporation of the solvent gave the crude product, m. p. 148—153° (116 mg., 89%). After two crystallisations from light petroleum (b. p. 100—120°) the 2,3,4,11-*tetrahydro*-4,4,9,11-*tetramethyl*-2-*oxocarbazole* was obtained as colourless needles, m. p. 158—159° (Found: C, 78·9, 79·2; H, 7·75, 7·9; N, 5·95. $C_{16}H_{19}NO$ requires C, 79·6; H, 7·9; N, 5·8%), $\lambda_{max.}$ 237, 301, 339 mμ (ε 16,700, 8300, 27,700). The infrared spectrum showed a sharp band at 1629 cm.$^{-1}$.

Reduction of the Ketone (IX) *to the Base* (V).—A solution of the above dehydrogenation product (IX) (38 mg.) in 20% methanolic sulphuric acid (30 c.c.) was treated with zinc dust (24 g.), and the whole heated on the steam-bath with frequent shaking for 6 hr. The mixture was filtered and worked up for ether-soluble basic and neutral material. The former was a colourless oil (37 mg.) which on being passed down an alumina column (grade H) with ether gave a colourless liquid (27 mg., 75%) with an ultraviolet spectrum identical with that of base (V) and gave a picrate, m. p. 138—140° (slight sintering at 125°) undepressed by the picrate of (V). The alumina column was then stripped with the methanol, to give material (7 mg.) the ultraviolet spectrum of which was identical with that of the starting material (IX).

1,2,3,4-*Tetrahydro*-1,1-*dimethylcarbazole*.—A solution of phenylhydrazine (60 g.) and of a

mixture of 2,2- and 2,6-dimethylcyclohexanone (prepared by the method of King, King, and Topliss [6]) (31·5 g.) in glacial acetic acid (125 c.c.) was refluxed for 24 hr. Most of the acetic acid was then distilled off, and the residue partitioned between 5N-hydrochloric acid (200 c.c.) and ether (200 c.c.). The ether layer was washed with acid (2 × 60 c.c.) and water and was dried. Evaporation yielded the crude product which crystallised completely (33·4 g.). Two crystallisations from light petroleum gave 1,2,3,4-*tetrahydro*-1,1-*dimethylcarbazole* as prisms, m. p. 110—111° (27·6 g., 55%) (Found: C, 84·1; H, 8·45. $C_{14}H_{17}N$ requires C, 84·35; H, 8·6%), $\lambda_{max.}$ 229, 283, 290 mμ (ε 35,200, 7080, 6270 respectively in EtOH). The infrared spectrum showed a sharp band at 3505 cm.$^{-1}$ (NH stretching) and twin peaks at 1370 and 1390 cm.$^{-1}$ (*gem*-dimethyl).

The acidic extracts were basified and extracted with ether, giving the basic 3*H*-indole fraction as a red-brown liquid which partially crystallised (27·2 g.): it was not investigated further.

2,3,4,11-*Tetrahydro*-1,1,11-*trimethyl*-1H-*carbazole*.—Finely powdered 1,2,3,4-tetrahydro-1,1-dimethylcarbazole (4·00 g.) was added to an ether solution of methylmagnesium iodide (from 0·75 g. of magnesium and 4·5 g. of methyl iodide). After the vigorous evolution of methane had subsided, the solution was refluxed for 20 min. and the ether allowed to distil off. Dry benzene (12 c.c.) was added and the solution refluxed whilst methyl iodide (18 c.c.) was added dropwise during 1 hr. Refluxing was then continued for 3 hr. Ether (60 c.c.) was next added, followed by ice and dilute acetic acid. The ether layer was extracted with 3N-hydrochloric acid, and the combined acid extracts were basified with aqueous sodium hydroxide and extracted with ether (2 × 50 c.c.). The ether extract yielded pale yellow crystals (3·55 g., 83%), m. p. 51—55°. Two sublimations at 45—55° (bath-temp.)/0·01 mm. yielded pure 2,3,4,11-*tetrahydro*-1,1,11-*trimethyl*-1H-*carbazole* as prisms, m. p. 58—59° (Found: C, 84·15; H, 8·75. $C_{15}H_{19}N$ requires C, 84·45; H, 9·0%), $\lambda_{max.}$ 258 mμ (ε 6970 in EtOH), $\nu_{max.}$ 1565 cm.$^{-1}$ (C=N).

The *picrate* crystallised from ethanol as yellow needles, m. p. 151—153° (sintering from 136°) (Found: C, 57·2; H, 4·7. $C_{21}H_{22}N_4O_7$ requires C, 57·0; H, 5·0%). The *methiodide* was prepared by heating the base (3·78 g.) in methyl iodide (15 c.c.) in a sealed tube for 4 hr. at 100°. The product (5·96 g., 94·5%) was crystallised once from methanol, to give pale yellow prisms, m. p. 176—177° (Found: C, 54·35; H, 6·2. $C_{16}H_{22}IN$ requires C, 54·1; H, 6·2%), $\lambda_{max.}$ 284 mμ, $\lambda_{infl.}$ 240 mμ (ε 6470, 6330 respectively in EtOH). The *methoperchlorate* (VIII) was obtained by adding 60% perchloric acid to a solution of the methiodide (190 mg.) in water (2 c.c.). Crystallisation from methanol yielded needles, m. p. 161—162° (Found: C, 58·4; H, 6·6. $C_{16}H_{22}ClNO_4$ requires C, 58·7; H, 6·7%), $\lambda_{max.}$ 235, 241, 284 mμ (ε 5250, 5330, 5830 respectively in EtOH) which changed on basification to $\lambda_{max.}$ 253, 302 mμ (ε 8330, 2800 respectively).

1,2,3,4,10,11-*Hexahydro*-1,1,9,11-*tetramethylcarbazole* (VI).—The above methiodide (3·80 g.) in methanol (75 c.c.) was treated with potassium borohydride (1·5 g.). After 1 hr. at room temperature, water (50 c.c.) was added and the methanol boiled off. Ether-extraction of the aqueous phase yielded the crude base as a colourless liquid (2·42 g., 99%). A solution of this in methanol was treated with picric acid (2·90 g.) in methanol (10 c.c.), and the crystalline picrate filtered off. Crystallisation from methanol gave the *picrate*, yellow cubes, m. p. 185—187° (slow decomp. from 164°) (Found: C, 58·2; H, 5·8. $C_{22}H_{25}N_4O_7$ requires C, 57·8; H, 5·7%), of base (VI). This gave the *base* (VI), b. p. 60—70° (bath-temp.)/0·01 mm., slowly becoming brown in air (Found: C, 83·7; H, 9·95. $C_{16}H_{23}N$ requires C, 83·8; H, 10·1%), $\lambda_{max.}$ 251, 293 mμ (ε 8730, 2750 respectively in EtOH), changed to benzenoid absorption by the addition of hydrochloric acid.

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