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3-ACETYL-1,2,3,3a,4,8b-HEXAHYDRO-1-HYDROXY-1,4,8b-TRIMETHYLCYCLOPENT [*b*] INDOLE

PMR SPECTRUM, AND REACTION WITH HYDROCHLORIC ACID

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Abstract—The structure of 3-acetyl-1,2,3,3a,4,8b-hexahydro-1-hydroxy-1,4,8b-trimethylcyclopent[*b*]-indole (I), the condensation product of 1,3-dimethylindole with hexane-2,5-dione, has been established by analysis of its PMR spectrum. The course of the reaction of I with concentrated hydrochloric acid is also elucidated.

The condensation of 1,3-dimethylindole with hexane-2,5-dione in the presence of aqueous alcoholic hydrogen chloride affords an indoline, $C_{16}H_{21}NO_2$, which was earlier[1,2] formulated as 3-acetyl-1,2,3,3a,4,8b-hexahydro-1-hydroxy-1,4,8b-trimethylcyclopent[*b*]indole (I), on the basis of its UV and IR spectra, and its chemical behaviour (colour reactions, reluctance to form O-acyl derivatives, semicarbazone formation, and positive iodoform reaction). Subsequently, an alternative structure (III) was suggested for this condensation product;[3] however, the formation of such a molecule is mechanistically much less plausible, since it would necessarily involve in its second stage an internal Mannich reaction (path a) on the vinylogous immonium ion intermediate II, rather than the expected conversion of the latter by loss of the C_2 proton (path b) into the 2-substituted indole derivative (IV).

The product of the formally analogous condensation of 1,3-dimethylindole with mesityl oxide was regarded by Robinson *et al.*[2] as the hexahydrocarbazole derivative (V); this was re-formulated[3] as VI. The subsequent proof[4] that structure V is correct lent vicarious support to the constitution I; however, no direct proof of the correctness of I has hitherto been presented. The PMR spectrum allows a clear distinction to be made between I and III, and provides unequivocal evidence in support of I. As far as the uncontroversial features of this condensation product are concerned, the PMR spectrum[5] (in $CDCl_3$) exhibits sharp signals at 8·65 and 8·68τ (3 protons each), attributed to the C_1 and C_{8b} methyl groups (not necessarily respectively) in I, at 7·74τ (3 protons), ascribed to the $COCH_3$ group, at 7·23τ (3 protons), due to the N-methyl group, and a complex pattern of signals (4 protons) at lower fields (2·67–3·64τ), due to the four aromatic protons. The hydroxyl proton appears as a sharp singlet at 8·13τ, shifted to 6·73τ in the presence of trifluoroacetic acid. The critical features of this PMR spectrum, which allow the structure I to be

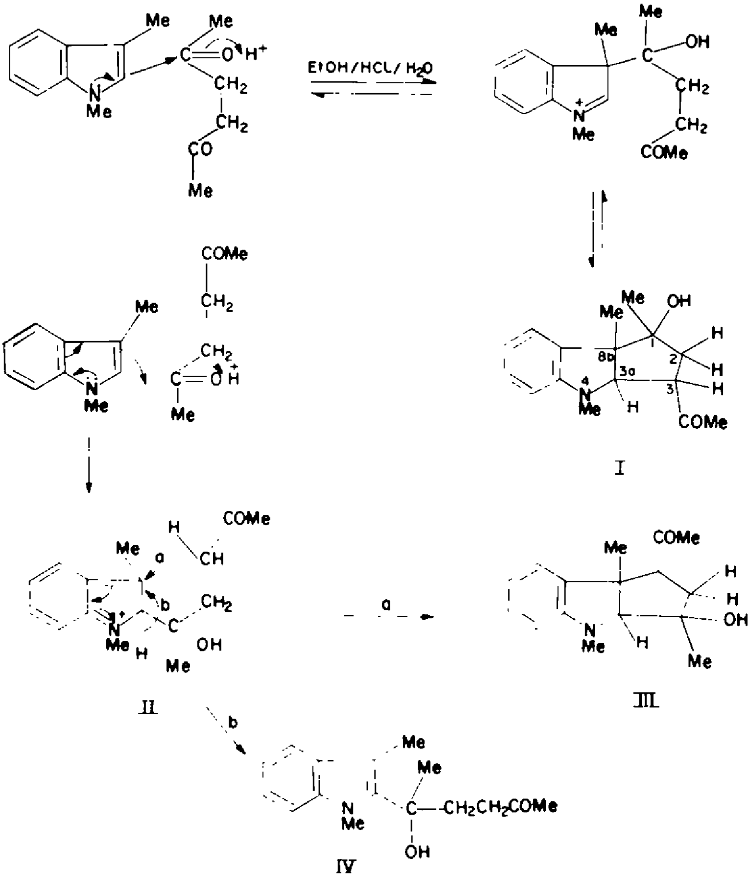
[1] R. Robinson and J. E. Saxton, *J. Chem. Soc.* 2596 (1953).

[2] D. A. Cockerill, R. Robinson and J. E. Saxton, *J. Chem. Soc.* 4369 (1955).

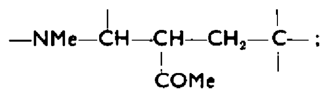
[3] W. E. Noland and D. N. Robinson, *Tetrahedron* 3, 68 (1958).

[4] B. Robinson and G. F. Smith, *J. Chem. Soc.* 4574 (1960).

[5] All PMR spectra were measured using a Varian A-60 spectrometer, with added tetramethylsilane as internal standard.



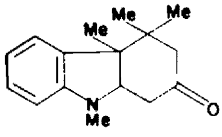
unequivocally assigned to this compound, concern the signals due to the C_2, C_3 and C_{3a} protons. The C_{3a} proton is clearly observed as a doublet centred at 5·97τ (J = 4·5 cs). The C_3 proton and the two non-equivalent protons of the C_2 methylene group constitute an AXY system; accordingly, the C_2 protons appear as two quartets centred at 7·68 and 7·96τ, with J_{XY} = 13·5 cs, J_{AX} = 7·5 cs and J_{AY} = 11·5 cs. The expected quartet due to the A proton (C_3—H) is further split by the C_{3a} proton to give an octet centred at 6·5τ, such that J_{AX} = 7·5 cs, J_{AY} = 11·5 cs and J_{A3a} is 4·5 cs. This evidence conclusively demonstrates the presence in this compound of the part-structure



$$-\mathrm{NMe}-\overset{|}{\mathrm{C}}\mathrm{H}-\underset{\mathrm{COMe}}{\underset{|}{\mathrm{C}}}\mathrm{H}-\mathrm{CH_2}-\underset{|}{\overset{|}{\mathrm{C}}}-\,;$$

structure III is therefore eliminated, and structure I receives convincing support.

One further uncertain feature of the chemistry of I is the course of the dehydration-rearrangement reaction[1] which occurs when it is heated with hydrochloric acid. The product, $C_{16}H_{17}N$, obtained in addition to some 1,3-dimethylindole, exhibits UV absorption which indicates an indole constitution with added conjugated unsaturation (λ_{max} 225, 250, 260, 310 sh, 320, 338, 360, and 386 mμ; $\log_{10} \varepsilon$ 4·2, 4·2, 4·35,



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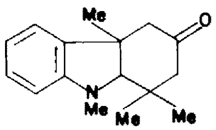

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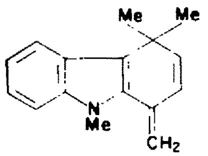

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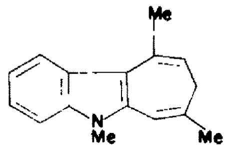

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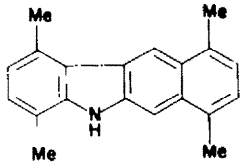

IX

3·25, 3·5, 3·6, 3·95 and 4·0 respectively). The structure VII, which was initially considered,[1] was readily eliminated since the compound gave no formaldehyde on ozonolysis, and did not rearrange to a substituted carbazole when vigorously treated with concentrated acid. The structure VIII (or double bond isomers) advanced in lieu of VII, also seemed unlikely in view of the absence of IR absorption at 770–735 cm^{-1} corresponding to an *ortho*-disubstituted aromatic nucleus. Further, the Ehrlich reaction, although it was obviously atypical, seemed to indicate an indole with a free 2 or 3 position, rather than a 2,3-disubstituted indole. The possibility that condensation of 1,3-dimethylindole with hexane-2,5-dione (or equivalent), generated from I under strongly acidic conditions, might have occurred at positions 4,5 or 5,6 was dismissed by the earlier investigators since no analogies for this type of reaction were available, and in any case the product, $C_{18}H_{17}N$, could not be obtained by direct condensation of the two reagents. However, the recent demonstration[6] that hexane-2,5-dione is capable of condensing with analogous reactive vicinal positions in the carbazole nucleus under similar reaction conditions [cf. formation of 1,4,7,10-tetramethyl-5*H*-benzo[*b*]carbazole (IX) as a by-product in the reaction of indole with hexane-2,5-dione] now makes this an attractive possibility. The two conceivable products from such a reaction are the benzindoles X and XI.

The former (X) is the expected product, if it is accepted that attack first occurs in the 1,3-dimethylindole nucleus *para* to the nitrogen atom, and that cyclization then ensues at the position (i.e. position 6) of greater electron-availability.[7] That this structure, i.e. 1,3,5,8-tetramethyl-1-benz[*f*]indole, is correct, is established by the following evidence. The IR spectrum exhibits absorption at 857 cm^{-1} characteristic of a lone aromatic hydrogen, and at 830 and 809 cm^{-1}, indicative of two adjacent aromatic hydrogen atoms. Attempts to reduce X to the corresponding indoline

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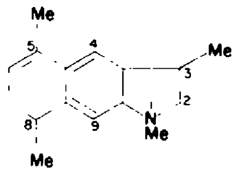
[6] P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.* 3482 (1962).

[7] H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.* 43, 87 (1947).



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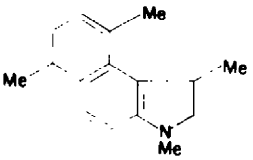

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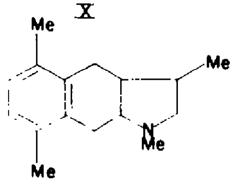

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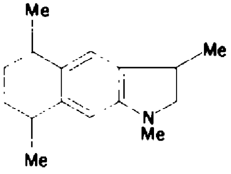

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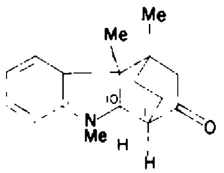
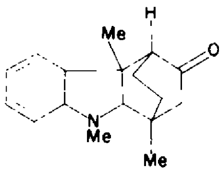


XIV



XV

derivative failed, but hydrogenation using Adams' catalyst gave a basic hexahydro derivative [picrate, m.p. 216–217° (dec)], which exhibits simple aromatic absorption [λ_{max} 200 and 216 (sh) mμ; log ε 4·51 and 3·9], and which is probably XII. In accordance with this, its IR spectrum contains a band at 805 cm^{-1} indicative of two adjacent aromatic hydrogen atoms; the band at 857 cm^{-1} in X, due to the lone aromatic hydrogen atom(s), has disappeared. Hydrogenation of X in the presence of W7 Raney nickel catalyst gave a different basic hexahydro derivative (picrate, m.p. 131–132°), whose spectrum is that of a substituted aniline (λ_{max} 240 and 300 mμ; log ε 4·03 and 3·63); this we formulate as XIII.

The PMR spectrum of 1,3,5,8-tetramethyl-1-benz[*f*]indole (X) in CCl_4 solution is comparatively simple, and consists of eight sharp peaks. The three C-methyl groups give rise to intense singlets (3 protons each) at 7·67τ (C_3-methyl), 7·38 and 7·33τ (C_5 and C_8 methyl groups); these values accord well with observed signals at 7·70 and 7·75τ in the spectra of 3-methylindole (in $CDCl_3$)[8] and 1,3-dimethylindole (in CCl_4),[9] due to the C_3-methyl group, and with values[9] of 7·30 and 7·24τ for the C_7 and C_{10} methyl groups in IX (measured in $CDCl_3$ solution).

The N-methyl group in X is observed as a sharp singlet at 6·44τ [cf. 6·63τ in N-methylindole ($CDCl_3$ solution),[8] 6·24τ in 1,4,9-trimethylcarbazole[9] (CCl_4 solution), and 6·85τ in 1,3-dimethylindole[9] (CCl_4 solution)]. At lower fields the five aromatic protons give rise to four sharp singlets. Of these, the peak at 3·33τ is attributed to the C_2 proton in X; this compares with values of 3·46, 3·65, and 3·70 for the analogous protons in indole, 3-methylindole,[10] and 1,3-dimethylindole[9] respectively, all measured in CCl_4 solution.

The remaining signals in the PMR spectrum of X occur at 2·08, 2·58τ (one proton

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[8] L. A. Cohen, J. W. Daly, H. Kny and B. Witkop, *J. Amer. Chem. Soc.* **82**, 2184 (1960).

[9] Unpublished observations by P. A. Cranwell and J. E. Saxton.

[10] R. V. Jardine and R. K. Brown, *Canad. J. Chem.* **41**, 2067 (1963).

each), and at 3·10τ (two protons). The first two are assigned to the C_9 and C_4 protons respectively, and the last one to the two hydrogens at C_6 and C_7.

The reaction of the cyclopentindole (I) with concentrated hydrochloric acid therefore involves fission to its progenitors, followed by a re-synthesis by condensation at positions 5 and 6 in the 1,3-dimethylindole nucleus. However, attempts to obtain X by direct combination of 1,3-dimethylindole and hexane-2,5-dione have so far failed.

The third condensation product in this series, namely, that obtained from 1,3-dimethylindole and either heptane-2,6-dione or 3-methylcyclohex-2-enone, was formulated by Robinson and Saxton[1] as XIV. This structure is supported by the PMR spectrum of this condensation product (in $CDCl_3$ solution), since the C_{10} proton appears as a doublet centred at 6·6τ (J = 4·5 cs). The spectrum at higher fields is too complex and not sufficiently well resolved to permit detailed analysis of the multiplet signals produced by the three methylene groups and the C_1 proton; however, the appearance of the C_{10} proton as a doublet effectively excludes the alternative structure (XV).[3]

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