Tetrahedron Letters No.1, pp. 77-82, 1970. Pergamon Press. Printed in Great Britain.

Subincanine, a C_{22}- Carbazole Alkaloid

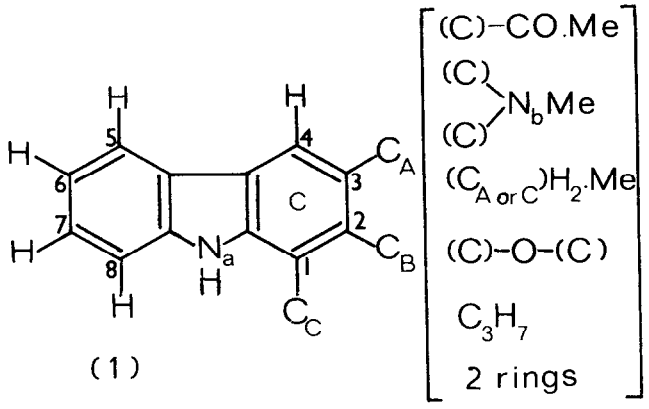
A. J. Gaskell and J. A. Joule

Chemistry Department, University of Manchester, Manchester M13 9PL.

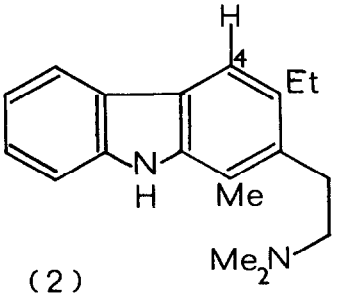
(Received in UK 24 November 1969; accepted for publication 4 December 1969)

Aspidosperma subincanum in four[1,2,3,4] separate investigations has yielded eleven alkaloids,[5] namely ellipticine (and its methosalt), N_b-methyltetrahydroellipticine, olivacine, 1,2-dihydroellipticine (and its methosalt), uleine, dasycarpidone, 3-epi-uleine, 3-epi-dasycarpidone and 1-acetyl-12-hydroxyaspidospermatidine. We report here the isolation and some data on a twelfth alkaloid, subincanine. The very small quantity of the compound isolated has precluded a definitive structural elucidation but our results so far show that this compound is of a new indole alkaloid type which makes publication worthwhile at this stage.

Rings A, B and C. - The spectra and simple reactions of subincanine, m.p. 160-163°, $C_{22}H_{24}N_2O_2$*, clearly show that the molecule has the following features [summarised in part structure (1)]: i) aromatic carbazole system not conjugated to aliphatic nitrogen,



(1)

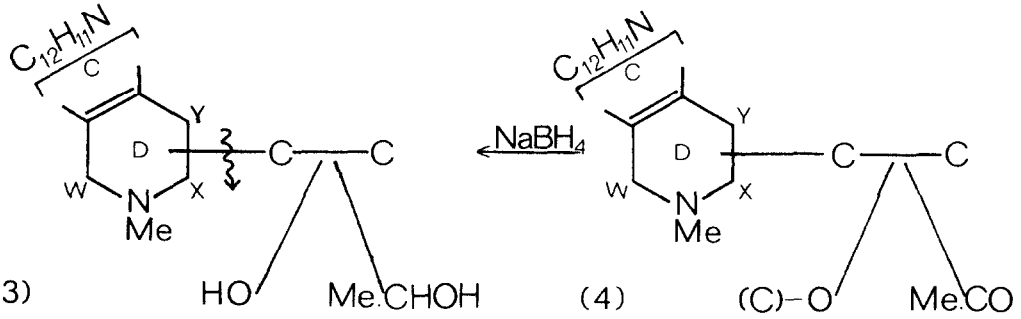


(2)

* All molecular formulae for parent and fragment ions have been confirmed by high resolution mass spectroscopy.

either oxygen or an olefinic unit [λ_{max} 240, 252(sh), 263 (sh), 297, 325, 340 nm; u.v. absorption of alkaloid and reduction products unchanged by acid or base; spectrum overlays that of simpler carbazoles e.g. (2)[5]; ii) N_a-hydrogen [ν_{max}($CHCl_3$) 3460 cm^{-1}; exchange of one hydrogen with D_2O in mass spectrometer; alkaloid not acetylated with Ac_2O/pyridine]; iii) 5 aromatic protons located at C-4, C-5, C-6, C-7 and C-8 [τ ($CDCl_3$) 5H, 1.9-3.2, including 1H, s, 2.25, C-4-H, ((2) has 1H, s, 2.29, C-4-H); 1H, double d, 1.97. (J_{ortho} 7 c/s, J_{meta} 2.5 c/s), C-5-H; 1H, double d, 3.01 (J_{ortho} 7 c/s, J_{meta} 2.5 c/s), C-8-H]; iv) C-acetyl [1720 cm^{-1}; 3H, s, 8.05; m/e 305 (100%), $C_{20}H_{21}N_2O$ ($M-C_2H_3O$); 45 (100%), C_2H_5O in spectrum of dihydrosubincanine (d.h.s.) ($LiAlH_4$)]; v) $C{>}N_b$-methyl [3H, s, 7.43; failure to acetylate]; vi) Ar-ethyl at C-1 or C-3 [3H, t, 8.66 (J 7.5 c/s) and 2H, q, 7.23 (J 7.5 c/s); positioning on ring-C because of existence of a ring across the remaining two stumps]; vii) cyclic ether [failure to acetylate; exchange of only one hydrogen with D_2O in mass spectrometer no;terminal groups available for acyclic ether].

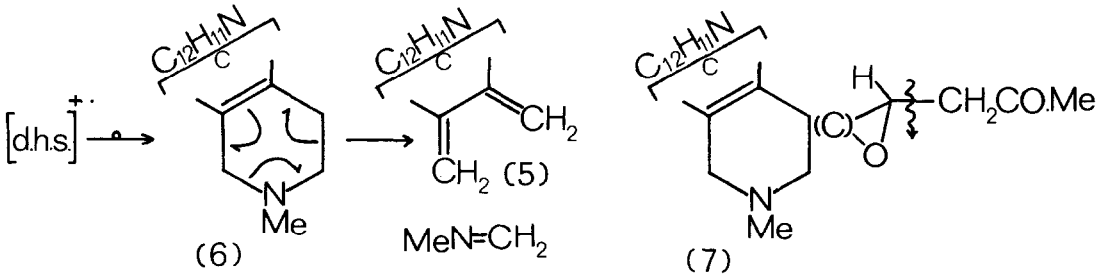
Ring D. - When subincanine was treated with sodium borohydride in hot methanol, tetrahydrosubincanine (t.h.s.) was formed which in turn gave both mono- and di-O-acetates with Ac_2O/pyridine. The mass spectra of these two acetates were in each case dominated by a fragment ion at m/e 263 (100% in each case; 264 only other ion >10%), $C_{18}H_{19}N_2$, corresponding to a loss, in one unit (m^* at 175.5 and 148.7) of $C_6H_{11}O_3$ and $C_8H_{13}O_4$



respectively. It can be seen then that the unit lost (mono- or di-acetylated) comprises the reduced acetyl function attached to one atom of a two carbon unit, one of the carbons of

which also carries the second hydroxyl oxygen (originally present in the alkaloid as an ether). On the basis of this extremely favoured loss one may assign the part structure (3) to t.h.s. and thus (4) to the alkaloid itself. It can be seen that any of the three carbon atoms of ring D would provide a suitable site for attachment of the side chain when measured by their ability to stabilise a positive charge left by cleavage of the side chain (arrow in (3)).

Two further observations serve to confirm the proposed nature of ring D in the alkaloid. Firstly the position of the N-methyl signal, τ 7.43, is very close to the values typical[6] for such groups in N-methyltetrahydroisoquinolines. Secondly the mass spectrum of d.h.s. has a major peak at m/e 221 (90%), $C_{16}H_{15}N$, best represented by part structure (5). This ion

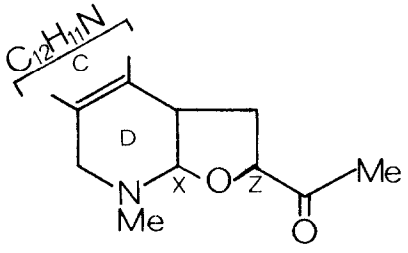


is linked by a metastable ion at 185 to m/e 264 (64%), $C_{18}H_{20}N_2$. D.h.s., obtained by $LiAlH_4$ reduction at 0°, now has the grouping Me.CHOH- as evidenced by the ion at m/e 45 (100%). It seems that a rearrangement from the molecular ion of d.h.s. to an ion at m/e 264, structure (6), allows a subsequent, characteristic[7] retro Diels Alder loss of $Me.N{=}CH_2$ to the ion at m/e 221. An important ion (64%) at m/e 43 corresponding to cleavage with charge retention on the smaller nitrogen fragment was observed in the spectrum of d.h.s. and in the spectra of both mono- and diacetates of t.h.s. (9 and 10% respectively). These data, together with the absence of ions at m/e 221 in the t.h.s. acetates, allow one to state that the side chain attachment to ring D must be at either C-W, or C-Y and not at C-X.

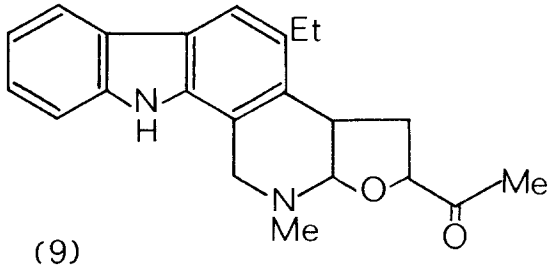
Ether Ring and Point of Attachment of Acetyl Group. - The direct loss of all the side chain (as in the t.h.s. derivatives) was not observed in the mass spectrum of the alkaloid itself. Loss of acetyl radical from the molecular ion (m^{*} 267.4) to give an ion at m/e 305 (100%), $C_{20}H_{21}N_2O$, suggests the presence of a feature capable of stabilising the residual positive charge. The ion at m/e 305 gave rise (m^{*}, 225) to an ion at m/e 262 (80%), a 2:1 doublet of $C_{18}H_{18}N_2$ and $C_{18}H_{16}NO$. These sequential losses strongly suggest that the ether ring is attached to one of the carbon atoms of ring D and that it is only after borohydride cleavage of this attachment that the whole side chain and both oxygens can be lost easily as a unit. There seems to be only one type of special ether which is consistent with all the facts including the lability to borohydride, this is an N_b-C-O-C unit.[8] Epoxide containing structures (7) which might explain the borohydride reductive ether fission seem to be outlawed by the total absence of a cleavage (arrow) of a C_3O-unit in spectra of the alkaloid or any derivative. Oxetane containing structures can be ruled out by the absence of i.r. absorption in the region[9] 980-990 cm^{-1} and of n.m.r. signals in range[9] τ 3.2-6.2.

Any N-C-O ring system envisaged which is not fused to the two adjacent and available carbon atoms of ring D must necessarily have an $\overset{N}{\underset{O}{\diagdown\!\diagup}}$C-hydrogen in an equatorial position, which would be expected[10] to resonate in the range τ 5.2-5.8. The alkaloid does not give signals in this range.

Placing the acetyl residue on carbon also bearing the ether oxygen to explain its ready mass spectral loss, one arrives at the various stereochemical variations on part structure



(8)



(9)

(8). In combination with the rest of the molecule this part structure gives four overall working structures (neglecting stereochemistry) for subincanine. A complex multiplet corresponding to two hydrogens at τ 6.2 in the spectrum of the alkaloid can now be ascribed to overlapping signals from hydrogens at C-X and C-Z.

Remembering the structures of the bases which co-occur with subincanine, all save one of which comprise an indole ring fused to a common C_9-skeleton [as in uleine[5] and (2)] and lack the tryptamine two carbon bridge, we consider that the most reasonable working hypothesis for subincanine at this stage is (9). This formulation contains an indole nucleus in combination with the common skeleton and the "extra" C_4-unit joined to ring D in the orientation derived above.

Noting that subincanine comprises a thirteen carbon atom system fused to an indole nucleus and in the sense that the indole alkaloids are monoterpene derivatives[11], it is tempting to speculate that this new alkaloid may be a sesquiterpene indole alkaloid [having lost one carbon to form the acetyl grouping and a second from C-1 (as in uleine)], though of course other equally reasonable biogenetic derivations can be postulated.

We are indebted to Dr. B. Gilbert for supplying us with plant extract. A.J.G. thanks the S.R.C. for financial support.

References

1. R.B. Woodward, G.A. Jacobucci and F.A. Hochstein, J.Amer.Chem.Soc., 1959 81, 4434.

2. G. Büchi, D.W. Mayo and F.A. Hochstein, Tetrahedron, 1961, 15, 167.

3. B. Gilbert, A.P. Duarte, Y. Nakagawa, J.A. Joule, S.E. Flores, J. Brissolese, J. Campello, E.P. Carazzoni, R.J. Owellen, E.C. Blossey, K.S. Brown and C. Djerassi, Tetrahedron, 1965, 21, 1141.

4. A.J. Gaskell and J.A. Joule, Chem. and Ind., 1967, 1089; A.J. Gaskell, Ph.D. Thesis, Manchester, 1968.

5. B. Gilbert, in "The Alkaloids", Academic Press, New York, 1965, vol. VIII, 469; 1968, vol. IX, 271.

6. Varian Associates, "High Resolution N.M.R. Spectra Catalog.", spectra No. 333, 342 and 347.

7. H. Budzikiewicz, C. Djerassi and D.H. Williams, "Structure Elucidation of Natural Products by Mass spectrometry". Vol. 1 : Alkaloids, Holden Day, San Fransisco, 1964.

8. M.P. Cava, S.K. Talapatra, K. Nomura, J.A. Weisbach, B. Douglas, and E.C.S. Roop, Chem. and Ind., 1963, 1242.

9. A. Weissberger, Ed., "Heterocyclic Compounds with three- and four-membered rings" Part 2, p. 986.

10. T.A. Crabb and R.F. Newton, Tetrahedron, 1968, 24, 1997.

11. "Biosynthesis" in Ann. Reports., 1965 et seq.