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ALKALOID STUDIES LI.[1] THE STRUCTURE OF ASPIDODASYCARPINE.[2]

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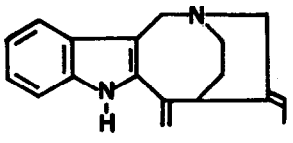
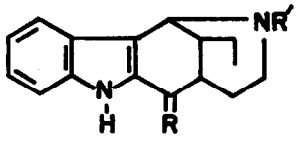
The Brazilian tree Aspidosperma dasycarpon A. DC.[3] has already yielded a number of interesting congeners[4] (II-VI) of uleine (I)[5] as well as the novel alkaloid apparicine (VII).[6] We should now like to record the isolation of still another alkaloid, "aspidodasycarpine," to which we attribute structure VIII. Such a skeleton has not been hitherto encountered among Aspidosperma alkaloids.



VII



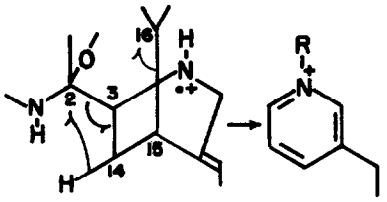
	R	R'
I	CH_2	CH_3
II	CH_2	H
III	O	CH_3
IV	O	H
V		CH_3
VI		CH_3

Aspidodasycarpine exhibited m.p. 207-209°, $[\alpha]_D$ -101° (all rotations in $CHCl_3$), λ_{max}^{EtOH} 240 and 297 mμ (log ε 3.96 and 3.63—typical of dihydroindole), $\lambda_{max}^{CHCl_3}$ 2.90 (m), 5.76 (s) and 6.25 (m) μ and its empirical formula was shown by mass spectrometry and elementary analysis to correspond to $C_{21}H_{26}N_2O_4$. The unsubstituted nature of the four aromatic positions was demonstrated by the n.m.r.

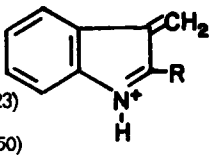
spectrum as was the presence of the methoxycarbonyl group (3H singlet at 3.72 ppm) and the ethylidene side chain (1H quartet at 5.5 ppm (J = 7 cps) and 3H doublet at 1.69 ppm (J = 7 cps)). The secondary nature of N_b as well as the existence of one hydroxyl group was established by the production of an O,N-diacetate (IX) ($C_{25}H_{30}N_2O_6$, m.p. 111-114°, $[\alpha]_D$ -35°, $\lambda_{max}^{CHCl_3}$ 5.77 (s) and 6.18 (s) μ, n.m.r. singlets at 2.16 and 1.92 ppm due to six acetyl protons). Further information on this latter functionality was obtained by base-catalyzed retroaldolization to the amorphous "desformoaspidodasycarpine" (X) ($C_{20}H_{24}N_2O_3$, λ_{max}^{EtOH} 240 and 296 mμ (log ε 3.94 and 3.77), $\lambda_{max}^{CHCl_3}$ 2.95 (m), 5.75 (s) and 6.22 (m) μ), which was characterized as the N_b-acetate XI ($C_{22}H_{26}N_2O_4$, λ_{max}^{EtOH} 240 and 295 mμ (log ε 3.98 and 3.59), $\lambda_{max}^{CHCl_3}$ 2.95 (m), 5.75 (s) and 6.26 (s) μ) and the highly crystalline N_b-hydroxymethyl derivative XII ($C_{21}H_{26}N_2O_4$, m.p. 175-182° (dec.), $[\alpha]_D$ -50°, $\lambda_{max}^{CHCl_3}$ 2.95 (m), 5.75 (s) and 6.20 (m) μ, n.m.r. 1H doublet at 4.15 ppm and 1H doublet at 4.40 ppm (J = 9 cps) due to $N-CH_2-OH$, λ_{max}^{EtOH} 242 and 298 mμ (log ε 3.86 and 3.48) obtained by base-promoted condensation with formaldehyde. The subsequent reactions of XI and XII served to elucidate the ethereal nature of the fourth oxygen for which only negative evidence (lack of infrared absorption and resistance to esterification) had been available. Mild acetic acid treatment of XII regenerated "desformoaspidodasycarpine" (X), while $LiAlH_4$ reduction produced the amorphous N-methyl derivative XIII ($C_{20}H_{28}N_2O_2$). Substitution of $LiAlH_4$ by $LiAlD_4$ effected the introduction of four deuterium atoms (XIV = $C_{20}H_{24}D_4N_2O_2$), thus showing that a carbinolamine ether linkage had been reduced.[7,8] Similar reactions with N-acetyl desformoaspidodasycarpine (XI) led to the N-ethyl analog of XIII.

The base peak in the mass spectrum of aspidodasycarpine (VIII) or the desformo derivative X occurs at m/e 108 and can be ascribed[9] to the stable 3-ethylpyridinium ion b produced from the molecular ion a by homolysis of the allylically activated 15-16 bond, fission of the 2-3 linkage with hydrogen transfer from C-14 (see fishhooks[9]

in a) and shift of the double bond into the ring. In accordance with this assignment, the base peak in the N-methyl derivative XIII (or in N-methylaspidodasycarpine) occurs at m/e 122 (c) and in the deuteriated analog XIV at m/e 123 (d). The mass spectra of the acetates IX and XI display two relevant peaks—one at m/e 150 (e) and the other at m/e 108 (b) due to the familiar[9] expulsion of ketene from the N-acetyl moiety.



b R = H (m/e 108)
c R = CH_3 (m/e 122)
d R = $CDCH_2$ (m/e 123)
e R = $COCH_3$ (m/e 150)

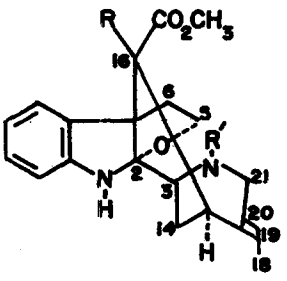


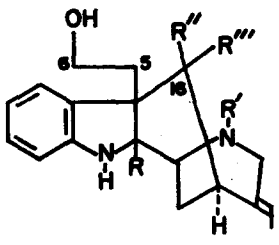
f R = H (m/e 130)
g R = D (m/e 131)

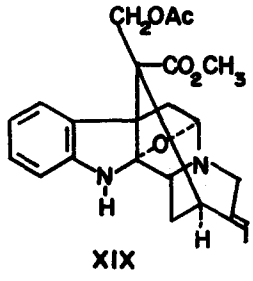
Of equal importance was the observation that the nearly ubiquitous[9] indole peak at m/e 130 (f) is shifted to m/e 131 (g) in the mass spectrum of the $LiAlD_4$ reduction product XIV. This represents prima facie evidence, as demonstrated earlier with Ψ-akuammigine[8,10] and picraline (XIX),[8,11] that one of the termination points of the ether ring (cleaved by $LiAlD_4$) must be at C-2.

Structurally significant information could be derived from the course of the zinc-hydrochloric acid treatment of aspidodasycarpine diacetate (IX) which produced the amorphous dihydro-diacetate XV ($C_{25}H_{32}N_2O_6$) and an indole ($C_{23}H_{28}N_2O_4$, m.p. 196-199°, λ_{max}^{EtOH} 224, 277, 284 and 292 mμ, log ε 4.40, 3.75, 3.79 and 3.73, $\lambda_{max}^{CHCl_3}$ 2.93 (m), 5.85 (s) and 6.17 (s) μ) to which we attribute structure XVII on the following basis. The presence of the grouping $H_2C{=}\overset{|}{C}\text{-}CO_2CH_3$ followed from the bathochromic shift of the infrared carbonyl band, the salient n.m.r. features (1H signal each at 6.20 and 5.63 ppm and 3H singlet at 3.72 ppm) and the chemical structure

($AcOCH_2-\overset{1}{\underset{|}{C}}-CO_2CH_3$) of the progenitor IX. The attachment of a CH_2CH_2OH moiety to the indole double bond is suggested by the broad 2H n.m.r. signal at 3.0 ppm (C-6 protons) and the 2H triplet (J = 7 cps) at 3.85 ppm (C-5 protons) which is shifted to 4.30 ppm (J = 7 cps) in the N,O-diacetate XVIII ($C_{25}H_{30}N_2O_5$, m.p. 186-189°, λ_{max}^{KBr} 2.93 (m), 5.77 (s), 5.83 (s) and 6.15 (s) μ). Other important n.m.r. signals of XVII occur at 8.55 ppm (indole NH), 5.0 ppm (1H multiplet due to C-3 proton), 4.49 ppm (A part of AB system of C-21 protons with J = 13 cps; B part obscured by methoxy signal at 3.72 ppm), 2.20 ppm (1H multiplet due to C-15 proton) and 2.02 ppm (3H singlet of N-acetyl protons).





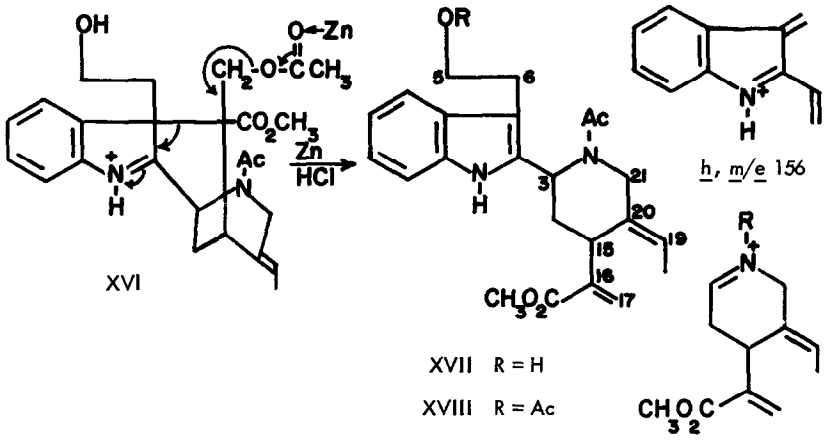


XIX

	R	R'
VIII	CH_2OH	H
IX	CH_2OAc	Ac
X	H	H
XI	H	Ac
XII	H	CH_2OH

	R	R'	R''	R'''
XIII	H	CH_3	H	CH_2OH
XIV	D	CDH_2	H	CD_2OH
XV	H	Ac	CH_2OAc	CO_2CH_3

The mass spectrum was equally consistent with structure XVII. The attachment of the CH_2CH_2OH group to the indole nucleus was supported by the occurrence of the base peak at m/e 365 (M-31 due to fission of 5-6 bond) and by an m/e 351 ion (loss of entire CH_2CH_2OH chain) which is even more pronounced in the mass spectrum of the diacetate XVIII. Both XVII and XVIII display in their mass spectra substantial peaks at m/e 130 (f) and 144, typical[9] of indole alkaloids, m/e 156 (h), m/e 194 and m/e 236. These last two peaks are attributed to ions i and j produced by fission of the 2-3 bond with and without ketene loss from the N-acetyl group, a conclusion which is supported by the 4 mass unit shift to m/e 198 and m/e 240 in the mass spectrum of the tetrahydro derivative of XVII (16-17 and 19-20 double bonds reduced). Barring some skeletal rearrangement, all of the above-summarized results are best accommodated in terms of structure XVII for the indole—a plausible mechanism being shown in XVI which simply represents the protonated open form of aspidodasycarpine diacetate (IX).



XVI

XVII R = H

XVIII R = Ac

h, m/e 156

i R = H (m/e 194)

j R = Ac (m/e 236)

Aspidodasycarpine, for which expression VIII is herewith proposed, bears a close resemblance to picraline (XIX), whose structure[11] and absolute configuration[12] was recently established. In point of fact, a direct correlation between the two alkaloids has now been effected by showing (through direct comparison, including rotation, of the respective crystalline N-hydroxymethyl derivatives XII) that desformo-aspidodasycarpine (X) and the potassium borohydride reduction product[12] of picraline (XIX)[13] are identical.

The empirical formulas of all substances described in this communication are supported by mass spectrometric molecular weight determinations and in many instances also by elementary analysis. We are indebted to Dr. H. Budzikiewicz and Mr. John Smith for several mass spectra, to Dr. Lois J. Durham for the n.m.r. spectra and to Mr. E. Meier for the microanalyses. Prof. Jean LeMen and Mlle. Louisette Olivier (Reims, France) provided a generous sample of picraline from which the authentic comparison compound was prepared.

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(2) Financial support in the form of Fulbright travel grants (to M.O. and J.A.J.) and a research grant (No. GM-11309) from the National Institutes of Health of the U.S. Public Health Service is gratefully acknowledged.

(3) Collected by Dr. B. Gilbert and Mr. Apparicio Duarte in the Facenda da Mãe Dágua, Várzea da Palma Valley, Minas Gerais, Brazil.

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(13) The reductive fission of the C-5 - N_b bond is accompanied by loss of the CH_2OAc substituent through retroaldolization in the strongly basic medium.