Tetrahedron Letters No. 22, pp. 1001-1009, 1962. Pergamon Press Ltd. Printed in Great Britain.

MASS SPECTROMETRY IN STRUCTURAL AND STEREOCHEMICAL PROBLEMS.[1] THE STRUCTURE OF THE ASPIDOSPERMA ALKALOID ASPIDOALBINE

Carl Djerassi, L. D. Antonaccio,[2] H. Budzikiewicz and J. M. Wilson

Department of Chemistry, Stanford University, Stanford, California

and

B. Gilbert

Instituto de Quimica Agricola, Ministerio da Agricultura, Rio de Janeiro, Brazil

(Received 13 July 1962)

IN continuation of our studies[3] on the alkaloidal constituents of Brazilian Aspidosperma species, we have investigated the stem bark of Aspidosperma album (Vahl) R. Bent., which was collected in Manaus, Amazonas. The non-phenolic portion yielded the known alkaloid[4] (-)-quebrachamine, while from the phenolic fraction there was isolated a new alkaloid, aspidoalbine, for which we propose structure I, largely on the basis of mass spectral and n.m.r. evidence. Aspidoalbine (I) is the first (dihydro) indole alkaloid in which three of the four aromatic hydrogens are replaced by oxygen functions and it is also the first alkaloid based on an aspidospermine-like skeleton[5] in which the presence of a tetrahydrofuran ring could be demonstrated.

---

[1] Part XVI. For paper XV see H. Budzikiewicz, J. M. Wilson and C. Djerassi, Monatsh. Chem. 93, August (1962).

[2] Recipient of a fellowship from the International Cooperation Administration under a program administered by the U.S. National Academy of Sciences while on leave from the Instituto Nacional de Tecnologia, Rio de Janeiro, Brazil.

[3] For leading references see B. Gilbert, L. D. Antonaccio, A.A.P.G. Archer and C. Djerassi, Experientia 16, 61 (1960) and subsequent papers.

[4] For structure see K. Biemann and G. Spiteller, Tetrahedron Letters 299 (1961).

[5] For a recent list of structural types related to aspidospermine see C. Djerassi, H. W. Brewer, H. Budzikiewicz, O.O. Orazi and R. A. Corral, J. Am. Chem. Soc. 84 (1962) in press.

Aspidoalbine (I) exhibited m.p. 170-172°, $[\alpha]_D$ + 159° (MeOH), + 148° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 6.17 and 6.31 μ (as well as very broad absorption in the 3.1 - 3.5 μ region), λ_{max}^{EtOH} 227 (log ε 4.16) and 267 mμ (3.88), λ_{min}^{EtOH} 215 (4.06) and 250 mμ (3.74), $\lambda_{max}^{EtOH-NaOH}$ 308 mμ (3.64) and $\lambda_{min}^{EtOH-NaOH}$ 288 mμ (3.39) and its elementary analysis indicated the empirical formula $C_{24}H_{32}N_2O_5$ (428). Mass spectrometry verified (molecular ion peak at m/e 428) this conclusion, but also showed the presence of ca. 25% of the lower homolog $C_{23}H_{30}N_2O_5$--an observation which was confirmed by acid hydrolysis and gas phase chromatographic analysis of the volatile acid methyl ester fraction yielding methyl propionate containing some methyl acetate. The alkaloid thus represents a mixture of N-propionyl (Ia) and N-acetyl (Ib) derivatives, reminiscent of the very difficultly separable mixture[6] of aspidospermine and its N-propionyl analog palosine. Of the five oxygen atoms, one is accounted for in terms of the amide grouping, while two are present as aromatic methoxyl groups, as demonstrated by Zeisel determination (calcd. for 2 MeO: 14.48; found: 14.45) and by the n.m.r. signals[7] at 3.86 and 3.85 δ. The fourth oxygen atom is a phenolic group, which must be attached at C-17 because of its strongly hydrogen-bonded nature (infrared spectrum and n.m.r. peak at 11.05 δ). The ethereal nature of the fifth oxygen function was assumed by the absence of any infrared carbonyl bands below 6.0 μ and the inability to effect esterification; its precise mode of attachment is discussed below. The n.m.r. spectrum of aspidoalbine (I) exhibited only a single signal at 6.82 δ, corresponding to one aromatic hydrogen and, in view of the virtually exclusive presence of oxygen functions at positions 15, 16 and 17 (numbering system as in I), but not 14,[8]

---

[6] W. I. Taylor, N. Raab, H. Lehner and J. Schmutz, Helv. Chim. Acta 42, 2750 (1959)

[7] All n.m.r. spectra were measured with a 60 mc. (Varian A-60) as well as a 100 mc. (Varian H-100) spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard (δ=0.00). All signals are reported in p.p.m. as δ values (δ = c.p.s./mc).

[8] The only exceptions appear to be the mushroom alkaloids, psilocybine and psilocine and related simple indoles (e.g. bufotenin); see A. Hofmann, R. Heim, A. Brack, H. Kobel, A. Frey, H. Ott, T. Petrzilka and F. Troxler, Helv. Chim. Acta 42, 1557 (1959).

among polycyclic indole alkaloids,[9] we assume a 15,16,17-trioxygenation pattern for aspidoalbine.

Methylation of aspidoalbine (I) with dimethyl sulfate in acetone solution in the presence of anhydrous potassium carbonate (40 hr reflux) provided a 3:1 mixture (determined mass spectrometrically), m.p. 120-122°, $[\alpha]_D^{MeOH}$ + 6° of the methyl ethers IIb and IIc, which were cleaved by heating with aqueous hydrochloric acid to pure N-deacyl-O-methylaspidoalbine (IIa), m.p. 148-149°, $[\alpha]_D^{MeOH}$ -36°, pK'_a (33% DMF) 8.50, λ_{max}^{EtOH} 212 (4.48), 240 (3.85 shoulder) and 305 mμ (3.63) and λ_{min}^{EtOH} 273 mμ (2.96). Propionylation of IIa provided pure O-methylaspidoalbine (II b), m.p. 118-120°, $[\alpha]_D^{MeOH}$ + 8°, while acetylation of IIa yielded N-depropionyl-N-acetyl-O-methylaspidoalbine (IIc), m.p. 177-178°, $[\alpha]_D^{MeOH}$ + 6°, λ_{max}^{KBr} 6.05 μ, λ_{max}^{EtOH} 218 (4.51), 258 (4.15) and 295 mμ (3.58 shoulder) and λ_{min}^{EtOH} 242 mμ (3.95). The n.m.r. spectra of the two N-acyl derivatives IIb and IIc (but not that of IIa) exhibited the typical quartet (corresponding in area to one proton) in the 4.5 δ region, which has been shown earlier[10] to be due to the lone C-2 hydrogen in N-acyldihydroindoles such as aspidospermine (Va) in which there are also present two hydrogens at C-3. Partial structure IV for aspidoalbine can, therefore, be considered to be established.

The nature of the remainder of the molecule and its mode of attachment to moiety IV could be elucidated by mass spectrometry. The mass spectra of aspidoalbine (I) and its derivatives IIa, IIb and IIc all exhibit a substantial M-28 peak[11]--similar to the M-28 peak (first observed by Biemann and collaborators[12] in the aspidospermine (Va) series and associated with the expulsion of ethylene (see arrows in Va) from

[9] N. Neuss, "Physical Data of Indole and Dihydroindole Alkaloids", Eli Lilly and Co., Indianapolis, 1961.

[10] C. Djerassi, A.A.P.G. Archer, T. George, B. Gilbert, J. N. Shoolery and L. F. Johnson, Experientia 16, 532 (1960). Further confirmation for the correctness of this assignment is provided in C-3 substituted aspidospermine derivatives (C. Djerassi, H. W. Brewer, H. Budzikiewicz, O. O. Orazi and R. A. Corral, ibid. 18, 113 (1962)).

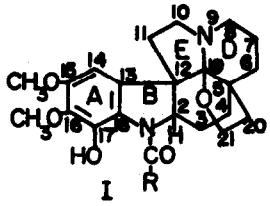
[11] A peak at M-44 (especially noticeable in IIa) is apparently due to the expulsion of the ether bridge in the form of ethylene oxide, acetaldehyde or their equivalents.

ring C--thus suggesting the presence of an unsubstituted two-carbon bridge encompassing C-3 and C-4 in expression I. In contrast to the peak at m/e 124, which represents the strongest one in the aspidospermine (Va) spectrum[12] and is best represented[12] by VI (cleavage of 10-11 bond in M-28 species), the mass spectra of aspidoalbine (Ia) and its relatives (IIa,b,c) do not contain such a peak, but rather show their base peak at m/e 138 (ion VIII). Most importantly, when N-deacyl-O-methylaspidoalbine (IIa) is reduced with lithium aluminum hydride, there is produced N-deacyl-O-methylaspidoalbinol (IIIa), m.p. 175-177°, $[\alpha]_D^{MeOH}$ + 9°, λ_{max}^{EtOH} 300 mμ (3.61) and shoulder at 240 mμ (3.82), λ_{min}^{EtOH} 270 mμ (2.75), the mass spectrum of which now contains the base peak at m/e 140 (ion IXa). A further shift of one mass unit to m/e 141 (ion IXb) is observed in the spectrum of the lithium aluminum deuteride reduction product (IIIb) of IIa. The genesis of peaks VIII and IX is assumed to involve in each instance cleavage of the 10-11 bond in the M-28 (arrows in II) species.

It follows, therefore, that lithium aluminum hydride had effected reductive opening of an oxide ring (involved in a carbinol amine) and that its termination point had to be adjacent to N_b rather than N_a, since the mass spectral indole peaks at m/e 220 (ion VIIa) and m/e 234[13] containing N_a and C-2 were not shifted in the spectra of the $LiAlH_4$ and $LiAlD_4$ reduction products IIIa and IIIb. That the oxide ring had been opened with generation of a primary alcoholic function could be demonstrated by the ready acetylation of the aspidoalbinol derivative IIIa to the N,O-diacetate IIIc (glass, $\lambda_{max}^{capill.}$ 5.76 and 6.0 μ), in which the mass spectral base peak was shifted to m/e 182 (ion IXc) in accordance with the molecular weight increment associated with O-acetylation. The assignment of the m/e 220 (VIIa) and m/e 234 peaks to the indole portion of the molecule could be substantiated by

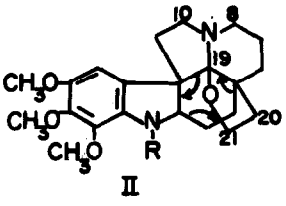
[12] K. Biemann, M. Friedman-Spiteller and G. Spiteller, Tetrahedron Letters 485 (1961).

[13] The m/e 234 peak corresponds to the m/e 220 indole ion (VIIa) containing one additional methylene group.



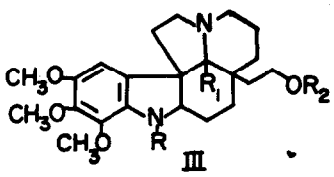
I

a R = C_2H_5
b R = CH_3



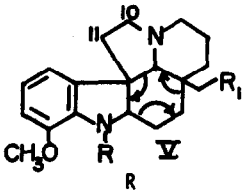
II

a R = H
b R = COC_2H_5
c R = $COCH_3$

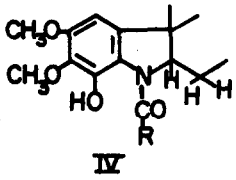


III

	R	R_1	R_2
a	H	H	H
b	H	D	H
c	Ac	H	Ac
d	C_2H_5	H	H
e	CD_2CH_3	H	H

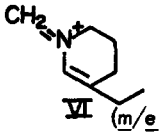


V

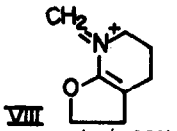


IV

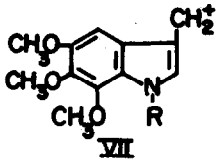
	R	R_1
a	Ac	CH_3
b	$C_6H_5CH{=}CHCO$	CO_2CH_3
c	$C_6H_5CH_2CH_2CO$	CH_2OH
d	H	CH_2OH
e	Ac	CH_2OAc
f	C_2H_5	CH_2OH



VI (m/e 124)

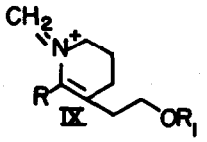


VIII (m/e 138)



VII

a R = H (m/e 220)
b R = C_2H_5 (m/e 248)
c R = CD_2CH_3 (m/e 250)



IX

a R = R_1 = H (m/e 140)
b R = D; R_1 = H (m/e 141)
c R = H; R_1 = Ac (m/e 182)

lithium aluminum hydride reduction of the O,N-diacetate IIIc, which provided the N-ethylaspidoalbinol derivative IIId, in which the m/e 220 and 234 peaks were shifted to m/e 248 (VIIb) and 262, while the base peak remained at m/e 140 (IXa). When the reduction of IIIc was performed with lithium aluminum deuteride, then a further shift of the indole peaks to m/e 250 (VIIc) and 264 was observed in the spectrum of IIIe.

The mass spectral indole peaks (ion VII)--corresponding to partial structure IV of the parent alkaloid--together with the peaks of the hydroaromatic portion (ions VIII and IX) and ethylene[14] account for all of the carbon atoms and the above mass spectral and n.m.r. data strongly suggest an aspidospermine (Va)-like skeleton in which the angular ethyl group is involved in an ether ring terminating adjacent to N_b. Of the three possibilities (C-8, 10 or 19), attachment at C-8 or C-10 would be readily recognizable by n.m.r. measurements, since the resulting hydrogen (at C-8 or C-10) would now be flanked by both oxygen and nitrogen and would thus exhibit a signal in a region somewhere downfield of ca. 4.0 δ. In point of fact, careful quantitative n.m.r. measurements (of IIa,b and c) with a 100 mc. instrument together with appropriate decoupling experiments[15] have shown unambiguously that the only signal in that region--a four-line pattern centered around 4.02 δ--corresponds to the two protons attached to C-21 and that they possess only two neighbors on a carbon atom (C-20) which terminates at a tertiary center. Further confirmation is obtained by comparing the 100 mc. spectrum of N-deacyl-O-methylaspidoalbinol (IIIa) with that of its deuterated analog IIIb. The two spectra are superimposable except for the disappearance in the latter of a sharp signal at 2.17 δ, which is ob-

---

[14] The actual formation of ions VIII or IX from the M-28 species could be verified in each case by the recognition of a metastable peak corresponding to that transition.

[15] Details, together with a reproduction of the n.m.r. spectrum of IIa, are being published separately: J. N. Shoolery, Faraday Soc. Disc. "High Resolution Nuclear Magnetic Resonance", Sept. 1962, in press.

served in the spectrum of IIIa and which occurs at precisely the region where the corresponding C-19 hydrogen signal in aspidospermine (Va) has been assigned.[10]

Chemical evidence for a five-membered ring E--and hence additional evidence for the existence of an aspidospermine skeleton--was provided by chromium trioxide-pyridine oxidation of N-depropionyl-N-acetyl-O-methylaspidoalbine (IIc), which yielded a five-membered lactam (IIc with carbonyl group at C-10), m.p. 214-218°, $[\alpha]_D^{MeOH}$ +22°, of empirical formula $C_{24}H_{30}O_6N_2$ (confirmed mass spectrometrically) exhibiting λ_{max}^{KBr} 5.88 and 6.08 μ, as well as a five-membered lactone (IIc with carbonyl group at C-21), m.p. 225-226°, $[\alpha]_D^{CHCl_3}$ -114°, in which the 4.02 δ n.m.r. signal associated with the two C-21 protons has disappeared. We conclude, therefore, that all of the presently adduced evidence is uniquely consistent with expression I for aspidoalbine.

The presence of three oxygen atoms in the aromatic ring of aspidoalbine precludes simple interrelation with a known aspidospermine relative. Nevertheless, we have carried out a further series of experiments which affords additional mass spectrometric support for structure I. The only known aspidospermine-like alkaloids with an oxygen function on the angular substituent are cylindrocarpine (Vb)[16] and cylindrocarpidine.[16] The former had already been reduced to dihydrocylindrocarpol (Vc) and acid hydrolysis now yielded N-decinnamoylcylindrocarpol (Vd, m.p. 145-147°, $[\alpha]_D^{MeOH}$ + 2°) and upon acetylation the corresponding O,N-diacetate Ve, m.p. 148-150° ($\lambda_{max}^{CHCl_3}$ 5.78 and 6.15 μ). Finally, reduction of the O,N-diacetate Ve with lithium aluminum hydride led to N-decinnamoyl-N-ethylcylindrocarpol (Vf) (glass, but homogeneous on thin-layer chromatography), thus affording three derivatives which were structurally identical with the aspidoalbinol derivatives IIIa, IIIc and IIId and differed only in the aromatic portion of the molecule. It was thus possible to apply to these three pairs (Vd vs. IIIa; Ve vs. IIIc; Vf vs. IIId) the mass

[16] C. Djerassi, A.A.P.G. Archer, T. George, B. Gilbert and L. D. Antonaccio, Tetrahedron 16, 212 (1961).

spectrometric comparison approach first developed by Biemann and collaborators[17] and subsequently also employed in our laboratories.[18] Indeed, a comparison of the mass spectra of these three pairs showed that they were virtually identical in the lower mass range encompassing the fragments from the hydroaromatic portion of the molecule, but differed in the higher mass range (peaks containing the intact aromatic nucleus) by sixty mass units corresponding to the two additional methoxyl groups in the aspidoalbinol series (III). The only noticeable difference in the three pairs resided in the intensity of the M-28 peak. The mass spectra of the cylindrocarpol derivatives Vd, e and f showed a M-28 peak of intensity comparable to that observed in aspidoalbine (I) and its O-methyl derivatives IIa, b and c or in aspidospermine (Va).[12] The spectra of the aspidoalbinol derivatives III, however, contained only a very small or negligible M-28 peak, the mechanistic importance of which was always demonstrable by an appropriate metastable peak.[14] This divergence in intensity is not unreasonable because lithium aluminum hydride reduction of IIa obviously must cause inversion at C-19 to yield the aspidoalbinol series (III), the difference in intensity of the M-28 peaks thus being a reflection of the altered C-19 stereochemistry.[19] We believe, therefore, that aspidoalbine (I) possesses the same relative stereochemistry as cylindrocarpine (Vb) and aspidospermine (Va) (with which Vb has been related chemically[16]), while the aspidoalbinol derivatives III represent the 19-epimers.

Acknowledgment: We are indebted to Dr. J. N. Shoolery and Mr. L. F. Johnson of Varian Associates for the 100 mc. n.m.r. spectra and to Dr. Lois J. Durham for the 60 mc. spectra. The plant collection and identification was

---

[17] See K. Biemann, Angew. Chem. 74, 102 (1962), for references.

[18] Inter al. B. Gilbert, J. M. Ferreira, R. J. Owellen, C.E. Swanholm, H. Budzikiewicz, L. J. Durham and C. Djerassi, Tetrahedron Letters 59 (1962); C. Djerassi, T. George, N. Finch, H. Lodish, H. Budzikiewicz and B. Gilbert., J. Amer. Chem. Soc. 84, 1499 (1962).

[19] This is also observed in the n.m.r. spectra in terms of a pronounced upfield shift of the signal corresponding to the lone aromatic hydrogen: e.g. 6.90δ in IIa vs. 6.47 δ in IIIa.

performed by Dr. William Rodriguez of the Instituto Nacional de Pesquisas do Amazonas and Dr. Aparicio Duarte of the Rio de Janeiro Botanical Garden. Financial assistance was provided by the National Institutes of Health of the U.S. Public Health Service (grant No. A-4257) and by the Rockefeller Foundation.