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ALKALOID STUDIES XLII.[1] THE STRUCTURES OF DICHOTAMINE, 1-ACETYL-ASPIDOALBIDINE AND 1-ACETYL-17-HYDROXYASPIDOALBIDINE: THREE NEW ALKALOIDS FROM VALLESIA DICHOTOMA RUIZ ET PAV

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The close botanical relation of the Apocynaceae genera Aspidosperma and Vallesia is also supported by the isolation from Vallesia dichotoma of the typical Aspidosperma alkaloids aspidospermine[3] and vallesin[4] (N-formyl-N-deacetylaspidospermine). A third base accompanying these two known alkaloids, dichotamine, was assigned[4] the empirical formula $C_{21-22}H_{24-26}N_2O_4$. Insufficient material was available for further chemical studies, but infrared spectroscopic measurements suggested the presence of a γ-lactone grouping. While a remarkable variety of different structural types has been isolated[5] from Aspidosperma species, no lactone has as yet

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1 For part XLI see C. Djerassi, Y. Nakagawa, J. M. Wilson, H. Budzikiewicz, B. Gilbert and L. D. Antonaccio, Experientia, in press.

2 National Institutes of Health Postdoctoral Fellow, 1963.

3 V. Deulofeu, J. De Langhe, R. Labriola and V. Carcamo, J. Chem. Soc., 1051 (1940).

4 J. S. E. Holker, M. Cais, F. Hochstein and C. Djerassi, J. Org. Chem., 24, 314 (1959).

5 For pertinent references see B. Gilbert, L. D. Antonaccio and C. Djerassi, J. Org. Chem., 27, 4702 (1962).

been encountered and a new investigation of Vallesia dichotoma leaves was undertaken, using some of the more modern separation techniques and physical methods. We have now noted the presence of at least two dozen alkaloids in addition to aspidospermine, vallesin and the known[6] (+)-akuammidine (compared with an authentic sample by I.R., m.p. and mixture m.p.). At present we are reporting the structure elucidation of the lactonic alkaloid dichotamine (I) and of two new bases (V, VIII) related to aspidoalbine (X).[7]

Dichotamine (m.p. 262-263° (dec.), $[\alpha]_D^{CHCl_3}$ -116°) showed $\lambda_{max}^{CHCl_3}$ 5.72μ (5-membered lactone) and 6.07μ (N-formyl); the ultraviolet spectrum was practically identical with that of vallesin (λ_{max}^{EtOH} 217 (log ε 4.39) and 257 mμ (4.08), λ_{min}^{EtOH} 234 mμ (3.74), λ_{infl}^{EtOH} 286 mμ (3.59)). The n.m.r. spectrum ($CDCl_3$ solution, tetramethylsilane δ=0.00 ppm) showed the presence of an N-formyl group (9.38 δ), three aromatic protons (7.4-6.7 δ), the 2-proton of the indole moiety (quartet at 4.47 δ), an aromatic methoxyl group (3.90 δ), and the grouping $-\overset{|}{\underset{|}{C}}-CH_2-CO-$ (AB doublets, J 16 c.p.s., at 2.42 and 1.98 δ), thus exhibiting considerable similarity (excepting the aromatic protons and methoxyls) to that of the lactone (III) obtained by chromic acid oxidation of O-methyl-N-acetylaspidoalbine (II).[7] The mass spectrum confirmed the empirical formula $C_{21}H_{24}N_2O_4$ (molecular ion at 368) and proved to be very similar to that of the lactone (III): The higher mass range peaks were shifted downward[8] by 74 mass units (difference of CH_2 in N-acyl group and two MeO functions) while the indole-containing ions lacking the N-acyl group were shifted by 60 mass units (=2 MeO). Strong peaks corresponding to M-CH_3, M-CHO, M-CO_2, M-CH_2CO_2, and combinations of these, as well as diagnostic monomethoxy-indole peaks at m/e 160 and 174, were also noted.

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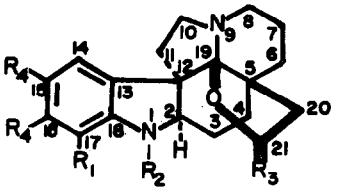
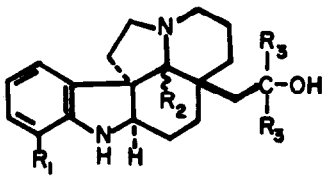
6 J. Levy, J. Le Men and M.-M. Janot, Compt. Rend., 253, 131 (1961).

7 C. Djerassi, L. D. Antonaccio, H. Budzikiewicz, J. M. Wilson and B. Gilbert, Tetrahedron Letters, 1001 (1962).

8 For basis of this mass spectrometric shift technique see K. Biemann, "Mass Spectrometry" McGraw-Hill Book Co., 1962, chapter 8.

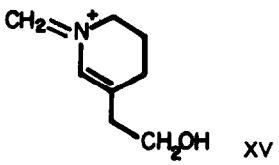




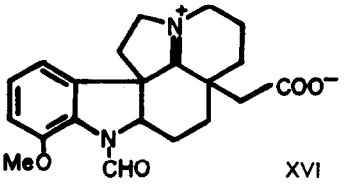
	R_1	R_2	R_3	R_4
I	MeO	CHO	O	H
II	MeO	COMe	H_2	MeO
III	MeO	COMe	O	MeO
IV	MeO	H	O	H
V	OH	COMe	H_2	H
VI	MeO	COMe	H_2	H
VII	MeO	H	H_2	H
VIII	H	COMe	H_2	H
IX	H	H	H_2	H
X	MeO	COEt	H_2	MeO

	R_1	R_2	R_3
XI	MeO	H	H
XII	MeO	D	D
XIII	H	H	H
XIV	H	D	H

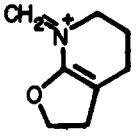
a = $R_2\alpha$; b = $R_2\beta$



XV



XVI



XVII

Acid hydrolysis of (I) led to deformyldichotamine (IV), m.p. 197-198°, the mass spectrum of which showed a similar pattern to those of I and III (m/e 340). Lithium aluminum hydride reduction of IV, followed by partition chromatography,[9] gave equal amounts of the known[7] deacylcylindrocarpol (XIb), m.p. and mixture m.p. 146-148°, and an amorphous, more mobile isomer with the same molecular ion (=$C_{20}H_{28}N_2O_2$), but strikingly different peak intensities in the mass spectrum:

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[9] K. S. Brown, Jr. and S. M. Kupchan, J. Chromatography, 9, 71 (1962).

a strong M-1 peak, but negligible M-18, M-28, or M-59 peaks (all strong in the spectrum of XIb) and a much lower m/e 140 peak (ion XV);[7] all suggesting primary fragmentation of the molecule (XIa) by loss of the C-19 hydrogen atom, assisted by the trans electron pair on the adjacent nitrogen atom. This in turn suggests that the two isomers differ in stereochemistry at C-19, which is mechanistically feasible via the intermediate XVI. Reduction of IV with lithium aluminum deuteride gave two isomers (XII a and b) which showed the expected shifts of all mass spectral peaks predicted to contain no, one, or three deuterium atoms; in particular, a strong M-2 peak was present in the spectrum of XIIa, suggesting loss of C-19 deuterium. Dichotamine may therefore be represented by structure I, the first lactone alkaloid of the aspidospermine group.

Also isolated from the least polar alkaloid fraction were two new compounds with mass spectral base peaks at m/e 138 (XVII), and strong M-44 peaks, suggesting that they fall into the aspidoalbine (X) group.[7,10] The infrared spectrum of the amorphous alkaloid V gave evidence of a phenolic hydroxyl, hydrogen-bonded to an acetyl group, in the 2.8 - 4.3 μ and 6.0 - 6.5 μ regions. The U.V. spectrum was almost identical with that of the known alkaloid with such a system, spegazzinine:[11] λ_{max}^{EtOH} 219 (log ε 4.45), 257 (3.94) and 290 mμ (3.59), λ_{min}^{EtOH} 242 (3.84) and 282 mμ (3.58). The n.m.r. spectrum confirmed the presence of the hydrogen-bonded hydroxyl (10.70 δ), three adjacent aromatic protons, the N-acetyl group (2.30 δ), the 2-proton of the indole portion, and the rigid grouping $-CH_2-CH_2-O-R$ (4.30-3.55 δ). The mass spectrum showed a pattern similar to that of aspidoalbine (X) except shifted downward by 60 units (=2MeO) in the upper ranges; the molecular weight, 354, suggested (in combination with the above data) the formula $C_{21}H_{26}N_2O_3$.

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[10] B. Gilbert, J. Brissolese, J. M. Wilson, H. Budzikiewicz, L. J. Durham and C. Djerassi, Chem. and Ind., 1949 (1962).

[11] C. Djerassi, H. W. Brewer, H. Budzikiewicz, O. O. Orazi and R. A. Corral, J. Am. Chem. Soc., 84, 3480 (1962).

Methylation of this alkaloid, assigned structure V (1-acetyl-17-hydroxyaspidoalbidine),[12] with dimethyl sulfate gave the O-methyl derivative (VI), m.p. 237-239° (dec.), $[\alpha]_D^{CHCl_3}$ + 6°, whose U.V. and I.R. (2.0-8.0μ region) spectra were very similar to those of aspidospermine. Acid hydrolysis of VI led to VII, m.p. 145-147°, lacking the bands in the I.R. spectrum corresponding to the N-acetyl group, and having a mass spectrometric molecular weight of 326 (=$C_{20}H_{26}N_2O_2$, confirming loss of acetyl) with a base peak at m/e 138 (XVII). Lithium aluminum hydride reduction of VII gave a mixture identical to that obtained by reduction of deformyldichotamine (IV), from which could be isolated by partition chromatography pure deacylcylindrocarpol (XIb),[7] m.p. and mixture m.p. 147-148°. As the n.m.r. spectrum of the original alkaloid (V) showed no signal attributable to a methine proton on a carbon bearing an ether linkage, structure V can be considered as settled.

The second non-polar alkaloid (m.p. 173-174°, $[\alpha]_D^{CHCl_3}$ + 46°, $\lambda_{max}^{CHCl_3}$ 6.13μ (N-acetyl)) showed an ultraviolet spectrum almost identical with that of demethoxypalosine:[10] λ_{max}^{EtOH} 212 (log ε 4.43) and 253 mμ (4.17), λ_{min}^{EtOH} 234 mμ (3.89), λ_{infl}^{EtOH} 281 (3.64) and 288 mμ (3.57). The mass spectrum indicated the formula $C_{21}H_{26}N_2O_2$ (molecular ion at m/e 338) and showed strong peaks at m/e 310 (M-28), 294 (-44), 138 (XVII), and 130, 144 (unsubstituted indole peaks); the overall pattern was practically identical to that of VI, except shifted downward in the upper ranges and the 130 and 144 mass peaks by 30 mass units (=MeO). Therefore, structure VIII (1-acetylaspidoalbidine[12]) was assigned to the alkaloid. Good support for this structure came from acid hydrolysis to aspidoalbidine (IX), m.p. about 180° (poorly crystalline), lacking the N-acetyl absorptions in the infrared spectrum, and having a mass spectrum bearing the same close relationship to that of VII as those of VIII and VI respectively (molecular ion at 296, confirming loss of acetyl). Finally, reduction

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[12] Following the use, for simplicity, of aspidospermidine for the unsubstituted parent in the aspidospermine group, we are naming the parent (IX) of this class aspidoalbidine (K. Biemann, M. Spiteller-Friedmann and G. Spiteller, J. Am. Chem. Soc., 85, 631 (1963)).

of IX with lithium aluminum hydride and deuteride led to mixtures, obtained in quantities too small to permit separation, whose mass spectra were fully consistent with structures XIII (a and b) and XIV (a and b) respectively; the spectrum of XIV mixture also demonstrated a strong M-2 peak for loss of the C-19 deuterium atom (in XIVa). We therefore conclude that structure VIII properly represents the new alkaloid.

Further work is progressing on the remaining alkaloids of Vallesia dichotoma, which seems to be one of the richest plant sources of new alkaloidal material we have examined.

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