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MASS SPECTROMETRY IN STRUCTURAL AND STEREOCHEMICAL PROBLEMS[1a]

TABERSONINE (ALKALOIDS OF AMSONIA TABERNAEMONTANA WALT.[1b]

Monique Plat, Jean Le Men and Maurice-Marie Janot

Faculté de Pharmacie, Université de Paris

4, Avenue de l'Observatoire, Paris 6, France

and

J.M. Wilson, H. Budzikiewicz, Lois J. Durham, Y. Nakagawa and Carl Djerassi

Department of Chemistry, Stanford University, Stanford, California

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SOMETIME ago,[2] there was isolated from Amsonia Tabernaemontana Walt. (fam. Apocynaceae) a new alkaloid, named tabersonine. The analytical data ($C_{20}H_{24-26}N_2O_2$), the high rotation of the hydrochloride ($[\alpha]_D$-310°), and especially the characteristic ultraviolet and infrared spectral properties[3] indicated the presence of the grouping I and it was assumed[3,4] that tabersonine was a member of the akuammicine (II)[4,5] class. We should now like to report - largely on the basis of mass spectrometric measurements and new chemical evidence- that (-)-tabersonine possesses structure IVa,[6] thus

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[1a] Part IX. For paper VIII see C. Djerassi, H. Budzikiewicz and J.M. Wilson, Tetrahedron Letters 263 (1962), preceding paper.

[1b] Part III. For papers I and II see ref. 2 and 3.

[2] M.-M. Janot, H. Pourrat and J. Le Men, Bull. Soc. Chim. Fr. 705 (1954).

[3] M.-M. Janot, J. Le Men and C. Fan, C.R. Acad. Sci., Paris 248, 3005 (1959).

[4] R. Robinson and A.F. Thomas, J. Chem. Soc. 2049 (1955); K. Aghoramurthy and R. Robinson, Tetrahedron 1, 172 (1957).

[5a] G.F. Smith and J.T. Wrobel, J. Chem. Soc. 793 (1960); [b] K. Bernauer, W. Arnold, C. Weissmann, H. Schmid and P. Karrer, Helv. Chim. Acta 43, 717 (1960); [c] J. Levy, J. Le Men and M.-M. Janot, Bull. Soc. Chim. Fr. 979 (1960).

[6] Relative but not absolute configurations are implied by the stereoformulae.

becoming a key link in the biosynthesis of alkaloids related structurally to (-)-aspidospermine (III).[7]

The mass spectrum of tabersonine exhibited a molecular ion at m/e 336, consistent only with a $C_{21}H_{24}N_2O_2$ formulation, which immediately excludes an akuammicine skeleton (II). The strong peaks in the m/e 90-140 region (e.g. m/e 92, 107, 135) were very suggestive of an aspidospermine-like frame work with a 6-7 double bond as has been encountered recently in vindolinine (X).[8] The NMR spectrum showed the presence of two olefinic protons, a C-ethyl group as well as the expected signals for the three carbomethoxy protons, the four aromatic hydrogens and the single hydrogen attached to nitrogen (δ = 8.98 p.p.m.). Catalytic hydrogenation yielded the amorphous 6,7-dihydrotabersonine (VI) ($[\alpha]_D^{EtOH}$ -540°), the mass spectrum of which confirmed the empirical formula $C_{21}H_{26}N_2O_2$ (338) and which had its most intense peak at m/e 124 (ion XI) typical[9] of aspidospermine (III) and its relatives.[10,11] When IVb was heated at 110° with 4 N hydrochloric acid there was obtained amorphous decarbonmethoxy-6,7-dihydrotabersonine (Vb) (mass spec. mol. wt., 280($C_{19}H_{24}N_2$), $[\alpha]_D^{EtOH}$ -225°, λ_{max}^{EtOH} 220 and 265 mμ), which was reduced with potassium borohydride in an alkaline medium[5a] to furnish (+)-quebrachamine (VIb)[12] (m.p. 147°, $[\alpha]_D^{Me_2CO}$ +110°), identified by infrared and mass spectrometry[13] with an authentic specimen. Alterna-

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[7] For structure and stereochemistry see J.F.D. Mills and S.C. Nyburg, J. Chem. Soc. 1458 (1960); G.F. Smith and J.T. Wrobel, Ibid. 1463 (1960).

[8] C. Djerassi, S.E. Flores, H. Budzikiewicz, J.M. Wilson, L.J. Durham, J. Le Men, M.-M. Janot, M. Plat, M. Gorman and N. Neuss, Proc. Nat. Acad. Sci. Wash. 48, 113 (1962).

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

[10] C. Djerassi, H.W. Brewer, H. Budzikiewicz, O.O. Orazi and R.A. Corral, Experientia 18, 113 (1962).

[11] C. Djerassi, H. Budzikiewicz, J.M. Wilson, J. Gosset, J. Le Men and M.-M. Janot, Tetrahedron Letters 235 (1962).

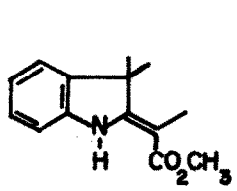
[12] F. Walls, O. Collera and A. Sandoval, Tetrahedron 2, 173 (1958).

[13] K. Biemann and G. Spiteller, Tetrahedron Letters 299 (1961).

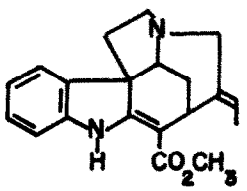
tively, (+)-quebrachamine could also be obtained by conversion of (-)-tabersonine (IVa) to decarbomethoxytabersonine (Va) (mass spec. mol. wt., 278 ($C_{19}H_{22}N_2$), m.p. 87°, $[\alpha]_D^{EtOH}$ -34°) followed by potassium borohydride reduction and catalytic hydrogenation of the intermediate 6,7-dehydroquebrachamine (VIa).

These two reaction sequences establish all of the structural features of tabersonine except for the location of the double bond. It follows that 6,7-dihydrotabersonine (IVb) should be an enantiomer of vincadifformine, the structure (racemic IVb) of which was elucidated recently in our laboratories.[11] Indeed, the infrared, nuclear magnetic resonance and mass spectra of vincadifformine and 6,7-dihydrotabersonine were superimposable and a similar structural identity (infrared and mass spectrometric comparison) could also be established for decarbomethoxyvincadifformine (racemic Vb)[11] and decarbomethoxy-6,7-dihydrotabersonine.

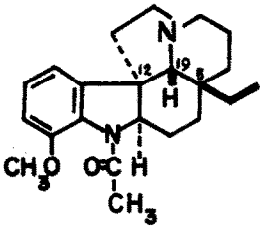
The isolated double bond of tabersonine (IVa) is stable towards potassium borohydride and is not affected by zinc-sulfuric acid treatment, which provided amorphous 2,3-dihydrotabersonine (VIIa) (mass spec. mol. wt., 338 ($C_{21}H_{26}N_2O_2$), typical indolinine U.V. spectrum with λ_{max}^{EtOH} 245 mμ (log ε 3,86) and 298 mμ (log ε 3.48), $\lambda_{max}^{CHCl_3}$ 5.78 μ), the mass spectrum of which n exhibited a strong M-86 peak (m/e 252) due to the loss of methyl acrylate (arrows in VII) as well as the expected[8] strong peaks at m/e 121 and 122. Consequently, the double bond cannot be located adjacent to nitrogen, thus leaving only the 6,7-position as its possible locus. A double bond in such a position has so far been encountered only in vindolinine (X)[8] where it gives rise to a very characteristic 12-line NMR pattern between 5.6-6.3 p.p.m. This is <u>not</u> the case in the NMR spectrum of tabersonine, where the two olefinic protons produce a fairly sharp signal at δ = 5.75 p.p.m. That this is due to a peculiar spatial relationship (also indicated by the remarkably large rotational shifts associated with reduction of this double



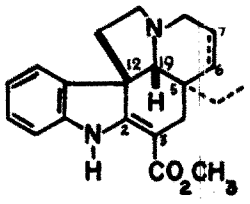
I



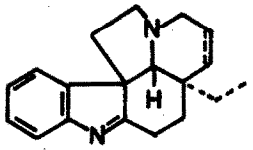
II



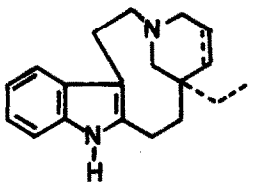
III



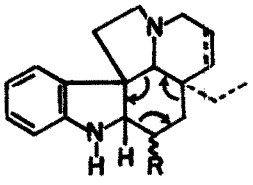
IV



V



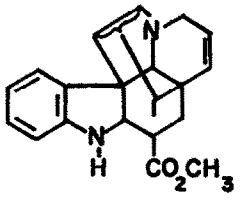
VI



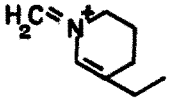
VII R = CO_2CH_3

VIII R = CH_2OH

IX R = CH_3



X



XI

a with 6-7 double bond b with saturated 6-7 bond

bond) of the 6,7-double bond with respect to the 2-3 chromophoric system is shown by the course of the lithium aluminum hydride reduction of tabersonine (IVa). This reaction proceeded in much more complicated fashion than that[5c,14] of akuammicine (II) and led to a mixture of products, two of

[14] M.-M. Janot, J. Le Men, A. Le Hir, J. Levy and F. Puisieux, C.R. Acad. Sci., Paris 250, 4383 (1960).

which were identified unambiguously.

The more polar one is the earlier described[3] (2,3-dihydro)-tabersonol (VIIIa) (mass spec. mol. wt., 310 ($C_{20}H_{26}N_2O$), m.p. 186°, $[\alpha]_D^{EtOH}$ +81.5°) which showed a strong M-58 peak in its mass spectrum at m/e 252 due to the loss of allyl alcohol (arrows in VIII) and which was catalytically hydrogenated to tetrahydrotabersonol (VIIIb) (mass spec. mol. wt., 312($C_{20}H_{28}N_2O$); its mass spectrum exhibited the same M-58 peak as well as an enormous peak at m/e 124 (XI) typical of the aspidospermine (III) class.[9-11] The infrared and mass spectra of tetrahydrotabersonol (VIIIb) proved to be identical with those of dihydrovincadifforminol (racemic VIIIb).[11]

The less polar product in the tabersonine lithium aluminum hydride reduction was the oxygen-free product IXa [mass spec. mol. wt., 294 ($C_{20}H_{26}N_2$)], whose mass spectrum was very similar to that of 2,3-dihydrotabersonol (VIIIa) in the m/e 90-160 region, but which showed a M-42 peak at m/e 252 due to the expulsion of propene (arrows in IX). The NMR spectra of both VIIIa and IXa now showed olefinic proton signals which were very similar to those reported earlier[8] for vindolinine (X); furthermore, the spectrum of IXa also exhibited a new doublet at 0.92 p.p.m. (J = 7 cps) associated with the newly formed $-CHCH_3$ grouping.

The above results rigorously establish structure IVa for (-)-tabersonine, which thus represents one of the strongest supports for Wenkert's[15] biogenetic scheme of the Aspidosperma alkaloids and also accounts for the biosynthesis of vindolinine (X)[8] as well as the existence of C-6 oxygenated aspidospermine-like alkaloids such as refractidine and pyrifoline.[16] Of interest is the observation that the C-5 asymmetric center of (-)-tabersonine (IVa) - by virtue of its relation to (+)-quebrachamine (VIb)[12] -

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[15] E. Wenkert, J. Amer. Chem. Soc. 84, 98 (1962).

[16] B. Gilbert, J.M. Ferreira, R.J. Owellen, C.E. Swanholm, H. Budzikiewicz, L.J. Durham and C. Djerassi, Tetrahedron Letters 59 (1962).

is antipodal to that of (-)-aspidospermine (III), which is related to (-)-quebrachamine,[13] and that both (+)-quebrachamine and (-)-tabersonine have been encountered in the same plant (Stemmadenia species[17]). The biosynthetic implication of the existence of such antipodal types has already been commented upon.[11,18]

The NMR spectra of a number of tabersonine derivatives, notably VIIIa, VIIIb and IXa, show a remarkable shift to higher field of the various signals associated with methylene protons (including the C-ethyl signals). These shifts will be discussed in detail in the full paper; when contrasted with the NMR spectrum[19] of aspidospermine, this observation suggests a stereochemistry permitting increased shielding by the aromatic nucleus and this appears to be best accomodated by a 12-19 cis stereochemistry (IV) in contrast to the trans situation existing[7] in (-)-aspidospermine (III) itself.

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17 Private communication from Dr. A. Sandoval (Instituto de Quimica, Mexico, D.F.).

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

19 C. Djerassi, A.A.P.G. Archer, T. George, B. Gilbert, J.N. Shoolery and L.F. Johnson, Experientia 16, 532 (1960).