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THE CARBON-20 STEREOCHEMISTRY OF PANDOLINE AND EPIPANDOLINE[1]

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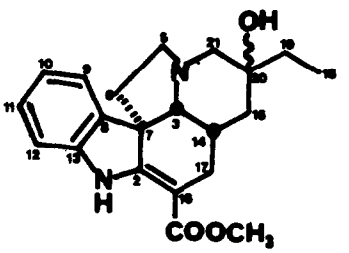
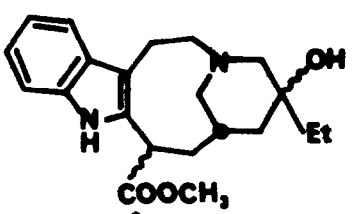
Recently there was reported the isolation of two new indole alkaloids, pandoline and epipandoline from several plants : Pandaca calcarea (Pichon) Mgf.[3], Pandaca debrayi Mgf.[3], Pandaca caducifolia Mgf.[4], Melodinus polyadenus (Baillon) Boiteau[5] and Ervatamia obtusiuscula Mgf.[6]. While the absolute configuration of the alkaloids was shown to be that in 1a and 1b, respectively,[7,8] the relative stereochemistry of C(20) was left undetermined. In order to resolve this problem, a ^{13}C NMR analysis of pandoline (1),[7,9] epipandoline (1) and their 3,7-seco derivatives (2) was undertaken.



1 a, 20α-OH
b, 20β-OH



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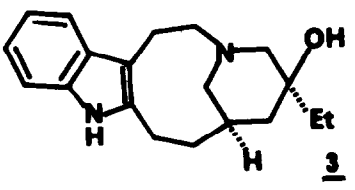
The new reduction products (2) of pandoline were prepared in the following manner. Sodium borohydride, 400 mg, was added in small portions over a 1.5 hr period to a stirring solution of 100 mg of pandoline in 5 ml of glacial acetic acid at 90° and the heating continued for 0.5 hr. The mixture was cooled, diluted with water, made alkaline with ammonia and extracted with methylene chloride. The extract was evaporated and the residue separated on

preparative tlc (Merck silica gel HF_{254}, 24:1 benzene-methanol), leading to 52 mg of 3,7-secopandoline A and 19 mg of isomer B ; amorphous 3,7-secopandoline A : $[\alpha]_D$ -21° (c = 0.9, $CHCl_3$) ; IR (film) OH, NH 2.81 (m), 3.00 (m), C=O 5.79 (s) μ ; UV (EtOH) λ_{max} 226 nm (log ε 4.35), 286 (3.77), 292 (3.74) ; ^{1}H-NMR ($CDCl_3$) δ 0.74 (t, 3, J = 7 Hz, Me), 3.54 (dm, 1, J = 14 Hz, equatorial H-3), 3.72 (s, 3, OMe), 3.98 (d, 1, J = 9 Hz, H-16) ; m/e found : 356.2098 (calcd for $C_{21}H_{28}O_3N_2$: 356.2100) ; crystalline 3,7-secopandoline B : mp 174-178° ; IR ($CHCl_3$) OH, NH 2.89 (m), C=O 5.81 (s) μ ; UV (EtOH) λ_{max} 228 nm (log ε 4.42), 286 (3.85), 294 (3.83) ; m/e found : 356.2100 (calcd for $C_{21}H_{28}O_3N_2$: 356.2100). Reduction of epipandoline under the same conditions yielded a 3,7-seco product (32%) and an uncharacterized isomer (6%) both of which were unstable on silica gel ; amorphous 3,7-secoepipandoline : IR (film) OH, NH 2.84 (m), 2.95 (m), C=O 5.79 (s) μ ; UV (EtOH) λ_{max} 227 nm (log ε 4.36), 288 (3.79), 294 (3.79) ; ^{1}H-NMR ($CDCl_3$) δ 0.96 (t, 3, J = 7 Hz, Me), 3.71 (s, 3, OMe), 5.06 (d, 1, J = 10 Hz, H-16) ; m/e found : 356.2103 (calcd for $C_{21}H_{28}O_3N_2$: 356.2100). Formic acid reductions in formamide[10] gave poorer yields of 3,7-seco products.

The carbon shifts of pandoline and epipandoline are given in the Table and based on ^{13}C-NMR data for Aspidosperma alkaloids and model compounds. The shifts of all carbons, except those of C(17), the piperidine ring and the ethyl group, correspond to those of like centers in vincadifformine[11], while those of the sidechain duplicate the C-ethyl shifts of 1,3-diethyl-3-piperidinol[12]. The allylic nature of H(17), reflected by the magnitude of the residual, one-bond, carbon-hydrogen coupling in the single-frequency, off-resonance decoupled spectra[13], leads to the C(17) shift assignment. The piperidine carbon centers are unique by virtue of the field positions and multiplicities of their signals. In view of the strong shift similarity of pandoline and epipandoline, only the C(3), C(16) and C(19) shifts differring by more than 1 ppm in the two bases, the ^{13}C-NMR data are insufficient to differentiate the C(20) configuration of the alkaloids.

A recent conformational analysis of cleavamine-like compounds by ^{13}C-NMR spectroscopy showed that 3,7-secopandoline A possesses the same conformation as velbanamine (3) and permitted a complete shift allocation to this secopandoline[14]. This forms the basis of the shift assignment of 3,7-secopandoline B and 3,7-secoepipandoline (cf. the Table). Isomer B assumes a different azacyclononane conformation from that of isomer A, perturbing only minimally the piperidine unit. Finally, the extensive broadening of the C(3) (or C-5), C(6) signals of the room-temperature spectra of 3,7-secoepipandoline causes ambiguity for the assignment of the C(3)-C(5) and C(15)-C(17) pairs of resonances and indicates incomplete averaging of two or more conformers of the compound. While this precludes also the designation of the C(16) configuration, the strong deshielding of H(16), presumably by N_b, favors a H(14)-H(16) trans orientation.



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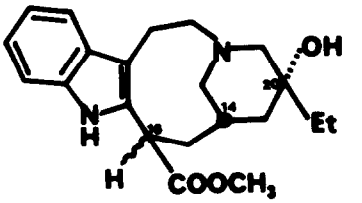

4a, 16β-H
b, 16α-H

The excellent shift correlation of 3,7-secopandoline A with velbanamine (3) shows the two substances to possess the same relative C(14), C(20) configuration and their identity of conformation reveals a H(14)-H(16) cis relationship in 3,7-secopandoline A[14]. This leads to structure 4a for the latter, 4b for 3,7-secopandoline B and 5 for 3,7-secoepipandoline (the C-16 stereochemistry advanced only tenuously). As a consequence of these considerations structures 1a (20α-OH) and 1b (20β-OH) represent pandoline and epipandoline, respectively[15].

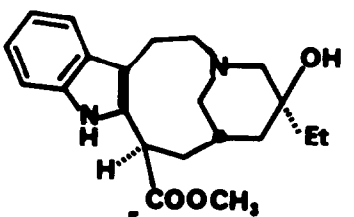

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Table. Carbon Chemical Shifts[a]

	1a	1b	3[b]	4a[b]	4b	5
C(2)	165.4	165.5		c	133.8	133.4
C(3)	68.3	66.7	50.6	50.9	55.7	50.4[d]
C(5)	50.7	50.7	52.3	52.0	53.8	51.6[d]
C(6)	44.9	44.5	22.7	22.4	26.5	25.4
C(7)	55.3	55.3		109.2	111.2	111.2
C(8)	136.8	137.2		127.7	127.2	127.2
C(9)	120.9	121.4		117.5	117.9	117.9
C(10)	120.1	120.3		119.0	118.8	119.0
C(11)	127.5	127.5		121.4	121.3	121.6
C(12)	109.1	109.0		111.1	110.5	110.6
C(13)	143.3	143.3		134.0	135.6	135.7
C(14)	35.8	35.7	30.1	30.5	30.4	29.2
C(15)	39.0	39.4	40.4	39.5	38.3	37.7[e]
C(16)	97.1	96.0	22.7	39.3	40.3	37.9
C(17)	25.5	25.0	31.5	36.1	43.3	36.2[e]
C(18)	7.2	7.8	6.9	6.9	7.1	7.4
C(19)	32.4	34.0	32.3	32.6	33.8	35.4
C(20)	70.7	71.4	71.6	71.2	71.3	72.6
C(21)	61.0	61.2	65.8	66.1	65.6	64.4
C=O	168.1	168.2		175.2	175.4	174.7
OMe	50.7	50.7		52.2	52.0	52.1

[a] In parts per million downfield from TMS ; δ (TMS) = δ ($CDCl_3$) + 76.9 ppm.
[b] From reference 14. [c] Undetected signal. [d,e] Signals may be interchanged.

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(15) The normalcy of the shift patterns of velbanamine (3) and the 3,7-secopandolines, enantio-16β-carbomethoxyvelbanamine (4a) and enantio-16α-carbomethoxyvelbanamine (4b), compared with like 16-epimer pairs of C(20) equatorially substituted 15,20-dihydrocleavamines[14], and the lack of shift correlation of either 4a or 4b with 3,7-secoepipandoline, an enantio-vinrosamine derivative (5), reminiscent of the shift abnormality and conformational anomaly of C(20) axially substituted 15,20-dihydrocleavamines[14], indicate a striking difference of the conformational effect of the syn-diaxial interaction of C(17) with the axial hydroxy group in 3, 4a and 4b vs. that with the axial ethyl group in 5. This contrast may be a consequence of a diminution of the unfavorable non-bonded interaction in the axial hydroxy cases due to hydrogen bonding of the hydroxyl function with the axial N_b lone electron pair.