55. The Structure of Melinonine-E, a Quaternary Indole Alkaloid from *Strychnos melinoniana* Baillon

Part 190: Studies on Organic Natural Products[1])

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Summary

The structure of melinonine-E (**2**) with relative configuration was established on the basis of spectral data for **2** and its acetate **3.**

The isolation of the quaternary alkaloid melinonine-E from an extract of the bark of *Strychnos melinoniana* Baillon (Loganiaceae) was first reported in 1957 [2]. On the basis of microanalyses of the crystalline picrate, perchlorate and iodide salts, the molecular formula for the cation was determined to be either $C_{20}H_{23}N_2O^+$ or $C_{20}H_{25}N_2O^+$. Further, the compound was shown to be devoid of vinyl groups and methyl groups of any kind. That the oxygen was present as an alcohol was substantiated by the formation of an O-acetyl derivative on treatment with Ac_2O/pyridine. UV and IR spectra suggested the presence of a beta-carbolinium chromophore in the molecule. On the basis of these data and biogenetic reasoning, structure **1** was proposed for melinonine-E, but limited quantities of the compound precluded degradation studies. The results of a re-investigation of this compound are presented in the following.

Electron impact mass spectrometry (EI-MS) revealed for the cation a peak at *m/z* 293 which loses one H-atom to yield the base peak, *m/z* 292. This molecular formula is in agreement with ^{13}C-NMR spectral data which indicate the presence of 19 C-atoms and 19 protons bonded to C-atoms, and is still in fair agreement with the results of microanalysis. Significant fragments at $[M\text{-}18]^+$ and $[M\text{-}32]^+$ suggest the presence of a primary alcohol. This contention was confirmed by comparison of the ^{1}H-NMR spectrum of **2** with that of its acetate **3,** in which two one-proton *dd*'s at 3.75 and 3.83 ppm ($H_2C(21)$) in **2** are shifted downfield to 4.31 and 4.38 ppm in **3.** That these signals appear as the *AB*-portion of an *ABX*-subspectrum indicates further that the hydroxymethyl group is attached to a C-atom bearing a single proton, a branch point in the skeleton.

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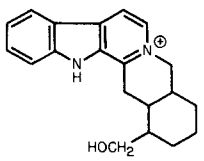

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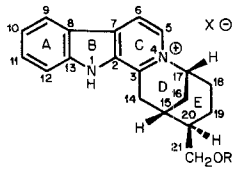
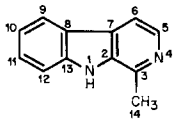
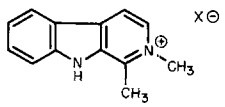


2 R = H, melinonine-E

3 R = $COCH_3$



4, harmane



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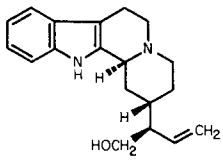

6, ontirhine

Table 1. *^{13}C-NMR Data for Melinonine-E* (**2**) *as Chloride, its* O-*Acetate* **3**, *Harmane* (**4**), *and Melinonine-F* (**5**)

C-Atom	**2**[a])	**3**[a])	**4**[b])	**5**[b])
2	142.5	142.2	141.9	141.0
3	145.3	145.2	140.3	144.6
5	133.6	133.7	137.4	135.0
6	132.7	132.7	127.5	132.6
7	132.3	132.2	126.8	132.3
8	121.4	121.3	121.1	120.6
9	123.1	123.1	119.0	122.7
10	117.1	117.2	112.3	116.1
11	124.0	124.0	121.4	123.5
12	113.9	113.9	111.8	113.5
13	135.2	135.0	134.4	135.7
14	33.4	33.2	20.4	15.9
15	25.8, 25.9	26.3	–	
16	25.7	25.7	–	–
17	62.8	62.5	–	–
18	29.4	29.2	–	–
19	18.5	18.6	–	–
20	43.2, 43.3	40.0	–	–
21	63.3	65.6	–	–
N–CH_3	–	–	–	45.6
$COCH_3$	–	172.7	–	–
$COCH_3$	–	20.8	–	–

[a]) 100.6 MHz.
[b]) 25.2 MHz.

Assignment of the eleven ^{13}C-resonances in the aromatic region of the ^{13}C-NMR spectrum of melinonine-E and its acetate **3** could be made in a straightforward manner [3] by comparison with harmane (**4**) and melinonine-F (**5**) [2], see *Table 1*.

Examination of the ^{13}C-NMR spectrum of **2** obtained in the off-resonance decoupled (SFORD) mode indicated the presence of five methylenes (one as the hydroxymethyl group) and three methines (one as the point of attachment of the hydroxymethyl group) in the aliphatic region. Two ^{13}C-resonances were found in the region of 50–70 ppm, thus representing aliphatic C-atoms directly bonded to heteroatoms. Of these, the *t* at 63.3 ppm was assigned to the hydroxymethyl group, and this assignment was confirmed by a proton-carbon shift correlation experiment [4]. The remaining *d* must then be due to a methine C-atom (C(17)) attached to the quaternary N-atom. The proton-carbon shift correlation experiment indicated that this C-atom was attached to a proton giving rise to a broadened *s* at 5.10 ppm in the ^{1}H-NMR spectrum *(Table 2)*. Such a chemical shift is consistent with a position adjacent to a positively charged N-atom. That this C-atom is a methine C-carbon indicates that it must be at the junction of the two remaining rings in this molecule.

The proton-carbon shift correlation experiment indicated that the methine C-atom at 43.2 ppm is attached to a *m* at 2.03 ppm while the methine C-atom at 25.8 ppm is attached to the proton showing a *m* at 2.71 ppm in the ^{1}H-NMR spectrum. Proton-

Table 2. *^{1}H-NMR Data for Melinonine-E* (**2**) *as Chloride, and its* O*-Acetate* **3**

Proton	Multiplicity	Chemical Shift[b]) δ in ppm		Measured Coupling Constants[a]) in Hz
		2	**3**	
H–C(5)	*d*	8.51	8.49	6.5
H–C(6)	*d*	8.40	8.39	6.5
H–C(9)	*m*	8.38	8.34	–
H–C(10)	*m*	7.46	7.43	–
H–C(11)	*m*	7.79	7.75	$w_{1/2} \approx 4$
H–C(12)			7.78	
H_{exo}–C(14)	*dd*	3.97	4.00	19.9, 7.3
H_{endo}–C(14)	br. *d* (*dd*)	3.50	3.55	19.9, 1.9
H–C(15)	br. *s* (*ddm*)	2.71	2.66	($w_{1/2}$ = 14.5[c]), 7.3[c]), 3.6
H_b–C(16)	*dm*	2.25	2.12–2.35	14.2
H_a–C(16)	*dddd*	2.43	2.46	14.2, 3.6, 2.0, 1.9
H–C(17)	br. *s* (*dddm*)	5.10	5.16	($w_{1/2}$ = 9), 2.6, 2.0, 1.0
H_{exo}–C(18)	*dddd*	2.19	2.12–2.35	16.0, 15.0, 4.9, 2.6
H_{endo}–C(18)	*dddd*	1.92	1.94	16.0, 5.5, 2.5, 1.0
H_{endo}–C(19)	*dddd*	1.21	1.29	14.5, 15.0, 5.5, 5.0
H_{exo}–C(19)	*dddm*	1.64	1.60	14.5, 4.9, 2.5
H–C(20)	*dddm*	2.03	2.12–2.35	7.5, 7.5, 5.0
H–C(21)	*dd*	3.75	4.31	11.5, 7.5
H–C(21)	*dd*	3.83	4.38	11.5, 7.5
$COCH_3$	*s*	–	2.10	–

[a]) All coupling reported here were confirmed by double-resonance experiments in melinonine-E chloride at 200 MHz unless otherwise indicated.

[b]) In the case of the *m* only the center positions is given.

[c]) Measured: melinonine-E *O*-acetate chloride.

proton shift correlation experiments [5] reveal that the one proton *m* at 2.03 ppm is coupled to the two protons of the hydroxymethyl group, as well as protons with the signals at 2.71 and 1.21 ppm, indicating that the C-atom at 43.2 ppm is the point of attachment of the hydroxymethyl group (C(20)), and, therefore, the methine at 25.8 ppm must be the remaining ring junction C-atom C(15). As the protons coupled to these two C-atoms are coupled to each other, it is evident that the hydroxymethyl group is attached to a C-atom adjacent to the ring junction.

The proton giving rise to the br. *s* at 5.10 ppm in the ^{1}H-NMR spectrum is not coupled to the second ring junction proton at 2.71 ppm, indicating that the ring system must be bridged rather than fused. Both of these protons are further coupled to two protons (signals at 2.25 and 2.43 ppm). The proton-carbon shift correlation experiment confirmed that these latter two protons are attached to the same C-atom (C(16)), which resonates at 25.7 ppm in the ^{13}C-NMR spectrum. These data indicate that a single C-atom bridges the two ring-junction C-atoms. The proton at 2.71 ppm is further coupled to a proton giving rise to a *dd* at 3.97 ppm. This signal is, in turn, coupled to a signal at 3.50 ppm. Proton-carbon shift correlation again ascertained that these latter two protons are a geminal pair. These signals are noteworthy in that they each integrate for less than one proton. Further, the resonance at 33.4 ppm (C(14)) in the ^{13}C-NMR spectrum appears as a 'triplet' in the proton-noise-decoupled mode. These data are consistent with the presence of a CHD-group formed by partial deuteration of a methylene[3]). One can rationalize these phenomena as occurring at C(14), a benzylic position adjacent to the equivalent of a C-heteroatom multiple bond. The inductive effects of the positively charged N-atom would be expected to increase the lability of these protons, perhaps to the extent that significant exchange cold occur in alcoholic solution. It should be further noted that the overall basicity of the compound would also faciliate exchange. The signal at 3.97 ppm is assigned to the pseudo-axial proton at C(14) as this proton shows a measurable (7 Hz) coupling to the ring junction proton, H–C(15), at 2.71 ppm. Its geminal, pseudoequatorial partner at 3.50 ppm shows no measurable coupling to H–C(15), but does exhibit a long-range (zigzag path) coupling to the equatorial proton at C(16), the bridge C-atom, at 2.43 ppm. These data are consistent with the gross structure **2** for melinonine-E.

The relative configuration of melinonine-E was deduced in the following manner. To form the bridged ring system present in the molecule, the bonds connecting N(4) and C(14) to the cyclohexane ring must both be axial, and the ring junction protons equatorial. If the cyclohexane ring were in a boat conformation, the equatorial protons of C(18) and C(20) would eclipse or nearly eclipse (dihedral angle from *Dreiding* models approximately 10–15°) the protons of the relative adjacent ring junction C-atoms. This relationship would be expected to result in large values of $^3J_{(H,H)}$, a situation clearly not consistent with the observed multiplicities of either ring junction proton. A chair conformation is therefore indicated for the cyclohexane ring. The stereochemistry of the hydroxymethyl group was deduced from the observed multiplicities of several of the ring protons. Thus, H–C(15) appears as a broad 'singlet' ($W_{1/2}$ = 14 Hz in

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[3]) Indeed, upon prolonged standing in CD_3OD at 0°, the apparent 'triplet' at 33.4 ppm gradually evolves to an apparent 'quintuplet' indicating almost complete deuteration and formation of a CD_2-group.

the acetate[4]). A 7.3-Hz coupling to the pseudo-axial H–C(14) was confirmed in double-resonance experiments, but no similar axial-equatorial coupling was observed between H–C(15) and H–C(20). Further, in melinonine-E H_{endo}–C(19) is observed as an apparent *tt (dddd)* at 1.21 ppm with two large couplings (14–15 Hz) and two smaller couplings (5–6 Hz). One of the large couplings is to H_{exo}–C(19), the geminal partner, at 1.64 ppm, and the other is to H_{exo}–C(18) at 2.19 ppm. One of the smaller couplings is to H_{endo}–C(18) at 1.92 ppm, and the remaining coupling is to H–C(20). If H–C(20) were axial, then one would expect H_{endo}–C(19) to exhibit three large couplings and only one small coupling. This is clearly not the case. If, however, H–C(20) were equatorial, then it and H_{endo}–C(18) could be expected to exhibit coupling constants of similar magnitude due to their interactions with H_{endo}–C(19). This is indeed consistent with the observed results.

It should be noted that in the proton-noise-decoupled ^{13}C-NMR spectrum of melinonine-E chloride, the resonances for C(15) and C(20) each appear as two lines, (25.8 and 25.9 ppm, and 43.2 and 43.3 ppm, respectively). Each of these pairs of lines integrates for one C-atom in an NOE-suppressed spectrum, indicating the presence of two conformers or rotamers. It is believed that the observed duplicity of these signals is due to rotation about the C(20)–C(21) bond. As the hydroxymethyl group is axially oriented, it is sterically proximate to the axial protons at C(16) and C(18). In a rotamer in which the OH-group is directed back over the ring, the degree of ring strain due to these, 1,3-diaxial interactions would be expected to be substantially greater than in a rotamer in which the OH-group is directed away from the ring. Such interactions could result in a doubling of some of the ring resonances. Additionally, this phenomenon is not observed in the acetate **3**. Examination of *Dreiding* models suggests that the bulkier acetate group should prevent rotation over the ring, thus a single rotamer could be expected.

From the date presented above, summarized in *Tables 1* and *2*, the gross structure and relative configuration was deduced for melinonine-E (**2**), which, to the best of our knowledge, is the first of a new skeleton class. Biogenetically, this compound could be derived from an alkaloid such as antirhine (**6**) [6] by ring closure and aromatization of ring C. Derivation from antirhine would suggest an absolute configuration as shown in **2**, but no proof of this possibility is offered at this time. The isolation of antirhine from a *Strychnos* species, *S. camptoneura* [7], can be regarded as additional support for a possible biogenetic relationship between these two alkaloids.

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[4]) This coupling was more easily defined in the acetate as the rate of deuteration of H_2C(14) was apparently slower than in the parent compound. In melinonine-E chloride, H_{exo}–C(14) was rapidly exchanged, resulting in a broadened *s* for H_{endo}–C(14) and a broadened *s* ($w_{1/2}$ = 8 Hz) for H–C(15).

Experimental Part

General. Thin layer chromatography (TLC) was performed on 0.2-mm layers of silica gel *60F$_{254}$ (Merck)*, with PrOH/HCOOH 9:1 as developing solvent, and visualized with potassium iodoplatinate reagent. Optical rotation on *Perkin-Elmer* model *241* polarimeter. UV spectra were recorded with a *Perkin-Elmer* model *555* instrument, absorptions in nm (log ε). IR spectra were determined with a *Perkin-Elmer* model *297* spectrophotometer in KBr, data in wavenumber (cm^{-1}). ^{1}H-NMR spectra were determined at 200 MHz with a *Varian XL-200* superconducting spectrometer, or at 400 MHz with a *Bruker AM-400* superconducting spectrometer, ^{13}C-NMR spectra at 25.2 MHz with a *Varian LX-100* instrument, or at 100.6 MHz with a *Bruker AM-400* instrument; chemical shifts (δ) in ppm, and coupling constants (J) in Hz; all NMR spectra in CD_3OD. NOE = Nuclear *Overhauser* Effect, SFORD = Single-Frequency off-Resonance Decoupling. Electron impact mass spectra (EI-MS) were obtained with a *Varian MAT 711* instrument coupled to a *Varian SS-100* MS data system, signals ($\geq 5\%$) in *m/z* (rel. %).

Melinonine-E Chloride (**2**). The isolation of melinonine-E from extracts of the bark of *Strychnos melinoniana* Baillon has been described in [2]. The purified alkaloid, as the chloride salt, was recrystallized several times from MeOH to yield fine brown crystals of **2** (homogeneous by TLC), m.p. 283.6–283.8°. $[\alpha]_D^{22} = -13.9°$ (c = 1.02, MeOH). UV (MeOH): λ_{max} 366 (3.65), 307 (4.33), 252 (4.48), 307 (4.36); λ_{sh} 300 (4.19), 286 (3.91), 260 (4.43), 218 (4.18); λ_{min} 325 (3.29), 278 (3.83), 226 (4.10); λ_{max} (0.2N methanolic NaOH): 417 (3.49), 328 (4.05), 283 (4.70), 217 (4.22); λ_{sh} 320 (4.00), 276 (4.61), 250 (4.13); λ_{min} 348 (2.80), 298 (3.75), 237 (3.99). IR: 3460, 3220, 3100, 2930, 2900, 1638, 1572, 1520, 1455, 1338, 1325, 1277, 1150, 1057, 792, 752, 730. ^{1}H-NMR: see *Table 2.* ^{13}C-NMR: see *Table 1.* EI-MS: 293 (24), 292 (100), 291 (6), 275 (9), 262 (6), 261 (18), 259 (5), 233 (9), 220 (9), 219 (46), 218 (7), 207 (6), 206 (10), 205 (7), 199 (16), 198 (18), 197 (12), 196 (7), 193 (5), 183 (13), 182 (60), 181 (14), 154 (10), 140 (5), 129 (12), 128 (10), 127 (6), 115 (5), 110 (19), 101 (5), 95 (34), 91 (17), 81 (6), 79 (8), 77 (11), 69 (11), 68 (9), 67 (10), 65 (8), 59 (21), 55 (9), 53 (7), 51 (6), 46 (9), 45 (25), 44 (6), 43 (12), 42 (6), 41 (23). Anal. calc. for $C_{19}H_{21}ClN_2O$ (328.844): C 69.40, H 6.44, N 8.52; found: C 68.41, H 6.84, N 8.23.

Acetylation of **2**. To **2** (50 mg) in pyridine (5 ml) was added Ac_2O (3 ml). The resulting mixture was stirred at ambient temp. for 36 h. Removal of excess reagent *in vacuo* (oil pump) afforded the acetate **3** as a yellow oil (homogeneous by TCL). ^{1}H-NMR: see *Table 2.* ^{13}C-NMR. see *Table 1.*

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