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Nitrogen Inversion in 9-*O*-Demethylhomolycorine

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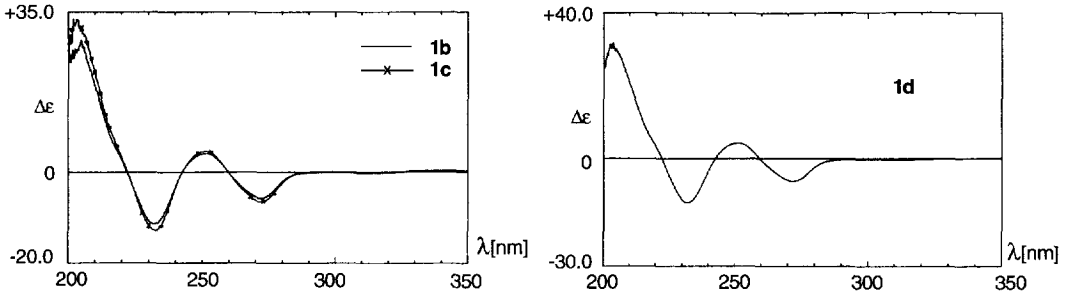
Abstract: (+)-9-*O*-Demethylhomolycorine, which has been isolated from *Galanthus elwesii*, belongs to Amaryllidaceae alkaloids. From five different subfractions five different crystalline samples were observed, all their spectra are superimposible with each other. Two of them, **1b** and **1c**, differ in the configuration at the N-atom. The other samples differ by changing solvent content in crystals.

Recently we isolated several Amaryllidaceae alkaloids from *Galanthus elwesii* Hook. f. of Turkish origin. Their structures were determined by spectroscopic methods[1,2]. In this paper we would like to report nitrogen inversion conformers observed for the well known alkaloid (+)-9-*O*-demethylhomolycorine[3-15].

Initially five seemingly different colorless crystalline samples obtained from five different subfractions of the alkaloidal extract were shown to be (+)-9-*O*-demethylhomolycorine (**1**) on the basis of the information deduced from spectral analyses[16]. The CD (*Fig. 1*), UV, ^{1}H and ^{13}C NMR and mass spectra of all five samples were superimposible with each other. They were also chromatographically identical. However, interestingly, their melting points and, to some extent, their optical rotations were different, a fact also observed in relevant reports on the same alkaloid (*Table 1*). In an attempt to clarify the phenomenon, recrystallization of these five samples of **1** were undertaken, which again furnished five different crystals designated as **1a**, **1b**, **1c**, **1d**, and **1e**. Of these, only the crystals of **1c**, **1d**, and **1e** obtained from EtOAc solutions were suitable for single crystal X-ray analyses. Since **1b** yielded only twinned crystals from EtOAc solutions, crystallization was repeated where fine single crystals could be obtained from MeOH-$CHCl_3$ solutions. Single crystal X-ray analyses[17] conducted on **1b**, **1c**, **1d**, and **1e** (*Fig. 2*) revealed that the latter two (**1d** and **1e**) are identical. ORTEP plots showed that the configurations **1b**, **1c**, and **1d** are identical only with the exception of the configuration at the N-atom, where **1c** differs from **1b** and **1d** by inversion of the configuration at this center, that is, the lone pair of electrons and the methyl group having changed places. It was also observed that one molecule of **1b** binds two molecules of water, and two molecules of **1d** contain one

Figure 1. *CD Spectra of* ***1b*** *(2.39 · 10^{-5} M),* ***1c*** *(2.39 · 10^{-5} M), and* ***1d*** *(2.56 · 10^{-5} M) in MeOH.*



disordered EtOAc molecule in the asymmetric unit, whereas **1c** contain no solvent. Apparently the geometry of the molecule in **1b** and **1d**, is such that it cannot pack efficiently in a crystal lattice without leaving significant "holes" between the molecules. The "holes" are readily filled with small molecules from the solvent used for the crystallization. On the other hand, compound **1c** has a geometry which enables it to pack neatly without "holes" and thus does not include solvent in the crystal lattice. The variations in melting points of **1b** - **1d** would therefore be due to the presence of different conformers as well as of different solvent molecules in the crystals. The differences in optical rotation are well explained by dependency of the true concentration of the sample and the assumed formulae weight.

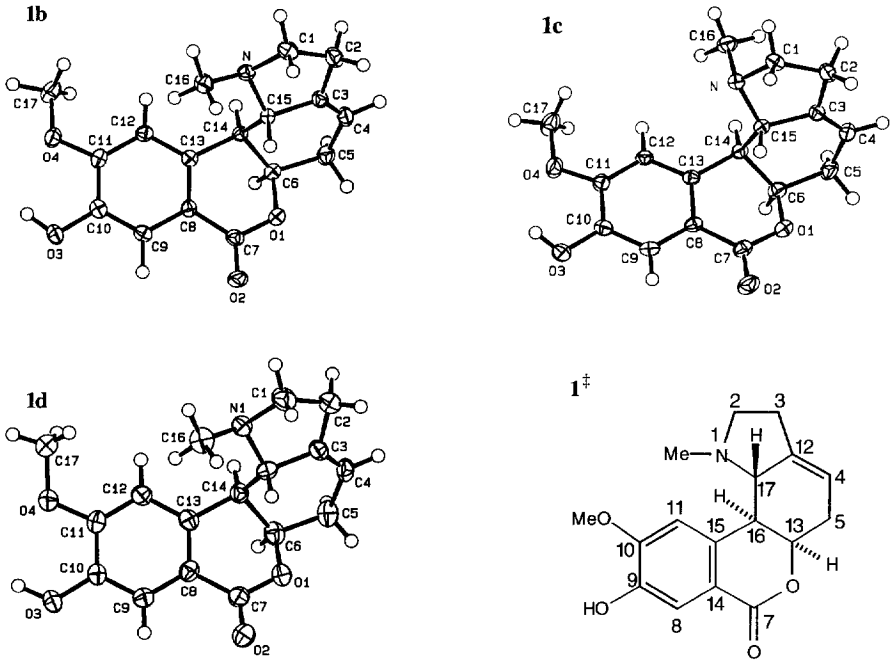
The water molecules in **1b** lie in one-dimensional channels within the crystal lattice, which run parallel to the **a**-axis, and combine with molecules of **1** in a complex three-dimensional hydrogen bonding network. The base **1c** is involved in one weak intramolecular and one stronger intermolecular hydrogen bond, both involving the hydrogen atom of the hydroxy group, which therefore forms bifurcated hydrogen bonds. The intramolecular hydrogen bond forms a five-membered ring between the methoxy and hydroxy groups. The intermolecular interaction links the hydroxy group with the nitrogen atom of an adjacent molecule, thereby forming infinite one-dimensional chains running parallel to the **c**-axis. The molecules of **1d** have the same

Table 1. *Physical Data of* ***1a-1e.***

Compound	Crystallized from	M.p. [°]	$[\alpha]_D^{22}$ (*c*)
1a	MeOH	118-119	+99.0 (MeOH; 0.22)
1b	EtOAc (twins)	214-216	+101.8 (MeOH; 0.33)
1·2 H_2O (*Fig. 2*)	MeOH-$CHCl_3$	207-210	
1c (*Fig. 2*)	EtOAc	183-185	+115.6 (MeOH; 0.85)
1d	MeOH	181-184	+125.0 (MeOH; 1.18)
1·1/2 EtOAc (*Fig. 2*)	EtOAc	217-219	+99.4 (MeOH; 0.50)
1e	EtOAc	211-213	
References†			
3	EtOAc or H_2O	213-214	+96.4 ($CHCl_3$; 0.28)
4	EtOAc	210-212	+93.7 ($CHCl_3$; 0.26)
7	EtOAc	207-208	+98.0 ($CHCl_3$; 0.68)
8	different solvents	138-140	–
9	EtOAc	211-212	+89.6 ($CHCl_3$; 0.41)
12	Me_2CO-MeOH	128-130	+53.0 ($CHCl_3$; 0.75)
13	EtOAc	213-214	+111 (0.1)
14		127-130	+71.6 (EtOH; 0.20)
15	MeOH	272	+66.2 (MeOH; 0.2)

† Missing data are in accordance with the literature.

Figure 2. *ORTEP Plots* [18] *with 50% Probability Ellipsoids of the Molecular Structures of* **1b**, **1c**, *and* **1d**. *(solvent molecules in* **1b** *and* **1d** *have been omitted).*



pattern of inter- and intramolecular hydrogen bonds that were found in **1c**. The intermolecular interactions link the molecules into infinite, one dimensional, zig-zag chains running parallel to the **b**-axis.

To our knowledge it is the first time that it has been unequivocally demonstrated by X-ray analyses that, depending on the crystallization conditions, both nitrogen inverted isomers of the same natural alkaloid were crystallized. In solution, the interchange between axial and equatorial form are too fast to be observed.

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‡ *Chemical Abstracts* numbering used in our spectral data.

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16. Spectral data of **1**. CD see *Fig. 1. UV* (MeOH): λ_{max} 201 nm (log ε 4.38), 227 (4.43), 264 (3.94), 305 (3.74); λ_{min} 216 (4.29), 247 (3.73), 284 (3.46). *IR* (KBr) **1b**: 3570, 3420, 3150, 1695, 1616, 1508, 1350, 1312, 1282, 1028, 1010; **1c**: 3400, 1705, 1610, 1585, 1510, 1345, 1300, 1085, 1065. *^{1}H-NMR* (400 MHz, $CDCl_3$): 7.60 (1H, *s*, H-8); 6.98 (1H, *s*, H-11); 5.50 (1H, *d*, *J* = 2.4 Hz, H-4); 4.78 (1H, *m*, H-13); 3.95 (3H, *s*, OMe); 3.14 (1H, *ddd*, *J* = 10.0, 6.6, 3.4 Hz, H-2); 2.73 (1H, *dd*, *J* = 9.7, <1 Hz, H-17); 2.63 (1H, *dd*, *J* = 9.7, 2.0 Hz, H-16); 2.59 (2H, *m*, H-5); 2.50 (2H, *m*, H-3); 2.25 (1H, *dd*, *J* = 18.8, 9.4 Hz, H-2); 2.00 (3H, *s*, NMe). *^{13}C-NMR* (50 MHz, CD_3OD): 167.87 (*s*, C-7); 153.81 (*s*, C-10); 147.94 (*s*, C-9); 141.30 (*s*, C-12); 137.65 (*s*, C-15); 117.93 (*s*, C-14); 117.07, 116.93 (2*d*, C-4, C-8); 112.33 (*d*, C-11); 79.23 (*d*, C-13); 68.03 (*d*, C-17); 57.26 (*t*, C-2); 56.75 (*q*, OMe); 44.14 (*q*, NMe); 43.69 (*d*, C-16); 32.13 (*t*, C-5); 28.64 (*t*, C-3). *EI-MS*: 301 (<3, $M^{+\cdot}$), 109 (100), 108 (65). *CI-MS* (NH_3): 302 $[M+1]^+$. Anal. calc. for **1b** $C_{17}H_{19}NO_4 \cdot 2H_2O$ (337.370): C 60.52, H 6.87, N 4.15; found C 61.39, H 6.64, N 3.71. Anal. calc. for **1c** $C_{17}H_{19}NO_4$ (301.340): C 67.76, H 6.35, N 4.65; found C 67.47, H 6.29, N 4.87.
17. X-Ray Diffraction Measurements (see also *Ref. 1 and 2*). Crystal Data of **1b**: $C_{17}H_{19}NO_4 \cdot 2\ H_2O$, Mr = 337.37, orthorhombic, space group $P2_12_12_1$ (#19), a = 9.320 (2), b = 11.999 (2), c = 14.865 (2) Å, V = 1662.2 (5) Å^3, Z = 4, D_{calc} = 1.348 g cm^{-3}, F(000) = 720, $\mu(MoK_\alpha)$ = 0.955 cm^{-1}, R = 0.0363, R_w = 0.0285 for 2142 reflections with I>3σ(I). **1c**: $C_{17}H_{19}NO_4$, Mr = 301.34, orthorhombic, space group $P2_12_12_1$ (#19), a = 10.094 (2), b = 14.654 (1), c = 9.6724 (9) Å, V = 1430.8 (3) Å^3, Z = 4, D_{calc} = 1.399 g cm^{-3}, F(000) = 640, $\mu(MoK_\alpha)$ = 0.932 cm^{-1}, R = 0.0352, R_w = 0.0340 for 2397 reflections with I>3σ(I). **1d**: $C_{17}H_{19}NO_4 \cdot 1/2$ EtOAc, Mr = 345.39, monoclinic, space group $P2_1$ (#4), a = 7.288 (5), b = 12.161 (3), c = 20.210 (3) Å, β = 92.21 (3)°, V = 1790 (1) Å^3, Z = 4, D_{calc} = 1.282 g cm^{-3}, F(000) = 736, $\mu(MoK_\alpha)$ = 0.866 cm^{-1}, R = 0.0499, R_w = 0.0436 for 3290 reflections with I>3σ(I). *Rigaku AFC5R* diffractometer, T = −100 ± 1°C. The structures were refined using the *TEXSAN* program package of Molecular Structure Corporation. Atomic coordinates for each structure have been deposited at the Cambridge Crystallographic Data Centre, U.K.
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