Chemistry of Natural Compounds, Vol. 39, No. 1, 2003

CRYSTAL STRUCTURE OF LAPPACONITINE HYDROBROMIDE HYDRATE

D. M. Turdybekov,[1] K. M. Turdybekov,[1] E. V. Burdel′naya,[1]
A. Zh. Turmukhambetov,[1] S. M. Adekenov,[1] and Yu. V. Gatilov[2]

UDC 548.737:547.944/945

The structure of lappacontine hydrobromide hydrate was solved by an x-ray structure analysis.

Key words: diterpenoid alkaloids, lappaconitine, lappaconine, XSA, molecular mechanics.

The structure of the alkaloid lappaconitine (**1**) was solved using chemical transformations and spectral data [1]. However, its three-dimensional structure has not yet been investigated. The hydrobromide salt (**2**) was prepared in order to establish the molecular structure. Compound **2** was synthesized by reaction of lappaconitine with aqueous-alcoholic HBr (5%) by the literature method [2]. An x-ray structure analysis was performed on a crystal of lappaconitine hydrobromide hydrate (**3**).

The structure of the cation of **2** (Fig. 1) indicates that the bond lengths and angles are close to the normal values [3] with the exception of the O8–C32A [1.349(18) Å] and O8–C32B [1.289(17) Å] bonds owing to disordering of C32 over two positions with occupancies 0.51 (C32A) and 0.49 (C32B). The cyclohexane ring C1C2C3C4C5C11 (A) adopts a significantly distorted boat conformation (ΔC_S^2 = 11.6°) owing to the formation of the intramolecular H-bond N1–H...O1 (distance N1...O1 2.63 Å, O1...H 1.72 Å, angle N1–H...O1 155.6°). Atoms C2 and C5 deviate from the plane of the remaining atoms (±0.07 Å) by 0.62 and 0.68 Å, respectively. Atoms O1 and O2 have the pseudoaxial α- and pseudoequatorial β-orientations with deviations from the principal plane of -1.48 and 0.59 Å, respectively (here and henceforth with respect to the diagram of the cation in Fig. 1). The 7-membered ring C5-C11(B) is found in a distorted boat conformation (ΔC_S^9 = 16.9°) slightly flattened at C9 [deviations of C5, C6, and C9 from the plane of the remaining atoms (±0.03 Å) are 1.31, 1.45, and 0.5 Å, respectively]. The ring is significantly distorted because of the presence of bridging C17, which produces a substantial difference in the torsion angles of the C5–C11 and C6–C7 bonds. Hydroxyl atoms O5 and O6 have the β-pseudoequatorial (0.85 Å deviation) and β-axial (1.91 Å) orientations, respectively. The 5-membered ring C9C10C12C13C14 (C) has the 14β-envelope conformation (ΔC_S^{14} = 1.6°) with C14 deviating by 0.725 Å from the plane of the remaining atoms (±0.006 Å). The methoxy has the β-equatorial orientation (0.707 Å). Ring C8C9C14C3C16C15 (D) adopts an almost ideal boat conformation (ΔC_S = 0.5°) with C8 oriented pseudoequatorially (deviation 1.0437 Å). Such a significant deviation for this atom is explained by the flattening of the ring at C15 [C14 and C15 deviate from the plane of the remaining atoms (±0.0007 Å) by 0.2697 and 0.8450 Å, respectively]. The 6-membered hetero- (E) and carbocycle C7-C11,C17 (J) have chair conformations (ΔC_S^{18} = 7.9° and ΔC_S^9 = 7.3°). The ethyl on N1 has the β-equatorial orientation (deviation of C19 is 0.53 Å). The 5-membered ring C5-C7,C17C11 has an almost ideal 17α,11β-half-chair shape ($\Delta C_2^{11,17}$ = 0.2°) with atom C11 deviating by 0.413 Å and C17 by -0.406 Å. Rings A/B and B/C are *trans*- and *cis*-fused, respectively (torsion angles C17C11C5H5 = 161.6°, O6C9C10H10 = 35.0°).

It is noteworthy that the π-electron systems of the carbonyl and aromatic ring should be conjugated in the $OCOC_6H_4NHCOCH_3$ ester. On the other hand, the acetamido group also strives to be positioned in the plane of the benzene so that a H-bond arises between the CO and the H of the *ortho*-substituent [4]. As a result, carbonyl C22=O3 in **2** is more planar relative to the benzene ring (torsion angle O3C22C23C24 = 11.0°) because the dihedral angle between the average planes of the aromatic ring (±0.0005 Å) and the acetamido group (± 0.0045 Å) is 22.0°. A rather stable intramolecular H-bond N2–H...O3 (distance N2...O3 2.644 Å, N2–H 0.63 Å, O3...H 2.314 Å, angle N–H...O 139.6°) is formed.

---

1) Institute of Phytochemistry, Ministry of Education and Science of the Republic of Kazakhstan, Karaganda, ul. M. Gazalieva, 4, e-mail: arglabin@phyto.kz; 2) Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences, Novosibirsk, ul. Lavrent′eva, 9. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 17-18, January-February, 2003. Original article submitted December 23, 2002.

TABLE 1. Fractional Atomic Coordinates (×10^4 Å; for H, ×10^3) for **3**

Atom	x	y	z	Atom	x	y	z
O1	5660(3)	2653(3)	8093(3)	C15	8214(4)	5534(5)	5804(4)
O2	2616(3)	5668(3)	8101(3)	C16	8672(4)	4379(5)	5523(4)
O3	2277(4)	5258(4)	9856(3)	C17	6244(4)	4707(4)	7402(3)
O4	-94(6)	7737(6)	12108(5)	C18	4666(4)	5220(4)	8880(4)
O5	6662(4)	6891(3)	5312(3)	C19	6935(4)	5248(5)	9316(4)
O6	5037(3)	5548(3)	4436(3)	C20	8135(6)	4581(8)	9337(6)
O7	7511(3)	5318(3)	3494(3)	C21	5575(7)	1549(5)	8427(6)
O8	9836(4)	4495(5)	4953(5)	C22	2002(4)	5779(5)	9043(4)
N1	5928(3)	4728(3)	8610(3)	C23	941(5)	6574(4)	8957(5)
N2	665(6)	6486(6)	10928(5)	C24	309(5)	6906(5)	9921(5)
C1	4848(4)	2915(4)	7167(4)	C25	-699(6)	7631(7)	9778(7)
C2	3465(5)	2863(5)	7441(4)	C26	-1086(6)	7994(6)	8779(7)
C3	3104(5)	3696(4)	8299(4)	C27	-471(6)	7682(6)	7834(7)
C4	3632(4)	4842(4)	8063(4)	C28	554(5)	6962(5)	7951(5)
C5	4117(4)	4944(4)	6895(4)	C29	477(6)	6895(7)	11949(6)
C6	4737(4)	6064(4)	6734(4)	C30	1041(8)	6201(9)	12859(7)
C7	6168(4)	5847(4)	6859(4)	C31	7963(7)	4926(7)	2485(5)
C8	6784(4)	5796(4)	5724(4)	C32A	10719(18)	3750(30)	5237(18)
C9	6047(4)	4980(4)	4950(4)	C32B′	10877(12)	4560(30)	5508(17)
C10	5633(4)	3948(4)	5575(3)	Brl	5141(1)	3294(1)	1046(1)
C11	5195(4)	4089(4)	6768(3)	O1W	3634(5)	3945(5)	3228(5)
C12	6751(4)	3145(4)	5489(4)	H1N	577(5)	395(6)	863(5)
C13	7763(4)	3737(4)	4792(4)	H2N	109(6)	612(6)	1094(5)
C14	6918(4)	4485(4)	4096(4)				

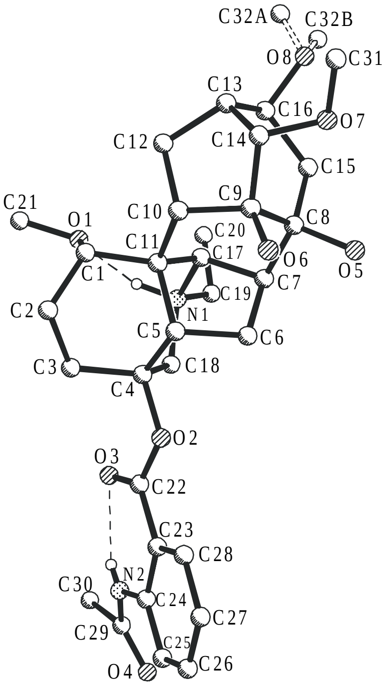

Fig. 1. Molecular structure of lappaconitine hydrobromide hydrate.

In general, the conformations of the rings in the polycyclic framework agree with those in lappaconine (**4**) [5]. Aconitine [6] and acoforestine [7], which also have the lycoctonine skeleton for ring A, have the chair conformation, which, at first glance, is more favorable than the boat conformation. However, molecular-mechanics calculations for the cation of **4** protonated on the N atom showed that the boat conformation of ring A for this skeleton is more favored by 1.4 kcal/mol mainly due to lower strain for this part from nonbonded repulsion of the atoms.

EXPERIMENTAL

X-ray Structure Analysis. Cell constants and intensities of 3138 independent reflections were measured on a Syntex $P2_1$ diffractometer (Cu Kα, graphite monochromator, $\theta/2\theta$-scanning, $2\theta \leq 140°$). Crystals are monoclinic, $a = 10.636(2)$, $b = 12.208(2)$, $c = 12.233(2)$ Å, $\beta = 91.06(3)°$, $V = 1588.2(5)$ Å^3, $d_{calc} = 1.430$ g/cm^3, $Z = 4$ $(C_{32}H_{44}N_2O_8)\cdot HBr\cdot H_2O$, space group $P2_1$. Absorption corrections were made using a semi-empirical method and the crystal habit. The structure was solved by direct methods using the program SHELXS-97 and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms using the program SHELXL-97. H atoms of hydroxyls and water could not be found in a difference electron synthesis. Therefore, H atoms were fixed geometrically as riders except for those on N1 and N2, which were found and refined isotropically. A total of 3081 reflections with $I > 2\sigma(I)$ was used. The final agreement factors were $R = 0.054$ and $R_w = 0.175$. The Flack parameter is 0.01(3), which corresponds to the expected value 0.0 for the correct absolute configuration [8]. Atomic coordinates are listed in Table 1.

Conformational calculations for the lappaconine cation were performed using MM3 with full optimization of the molecular geometry.

REFERENCES

1. V. A. Tel′nov, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 583 (1970).
2. A. Z. Sadikov and T. T. Shakirov, *Khim. Prir. Soedin.*, 91 (1988).
3. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc. Perkin Trans. II*, S1 (1987).
4. V. M. Potapov, *Stereochemistry* [in Russian], Khimiya, Moscow (1989).
5. G. I. Birnbaum, *Tetrahedron Lett.*, **26**, 2193 (1969).
6. P. W. Codding, *Acta Crystallogr. Sect B: Struct. Crystallogr. Cryst. Chem.*, **38**, 2519 (1982).
7. S. W. Pelletier, B. S. Joshi, J. A. Glinski, H. P. Chokshi, S. Y. Chen, K. Bhandary, and K. Go, *Heterocycles*, **25**, 365 (1987).
8. H. D. Fleck, *Acta Crystallogr. Sect. A: Found. Crystallogr.*, **39**, 876 (1983).