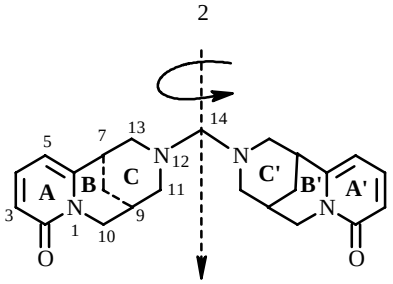
STRUCTURE OF METHYLENE-*bis*-CYTISINE

K. K. Turgunov, B. Tashkhodzhaev, T. F. Ibragimov, and Sh. B. Rakhimov

UDC 547.945+547.79+548.737

In an attempt to synthesize *N*-hydroxymethylcytisine from cytisine and formaldehyde solution (35%) in ether solution by the literature method [1], a compound with mp 131-132°C was produced. The PMR spectrum was consistent with *N*,*N*′-methylene-*bis*-cytisine with mp 220-221°C. The reason for the melting point depression could have been solvate differences or polymorphism of the crystals because the conformational mobility of the *bis*-alkaloid favors the appearance of these phenomena.

An x-ray crystal structure (XCS) of crystals of the product was carried out in order to elucidate the reason and to determine the molcular structure. The XCS results confirmed the structure *N*,*N*′-methylene-*bis*-cytisine (**1**), in which the cytisine molecules are bound through a C14 methylene bridge. Crystals of **1** were the monohydrate, which may be the reason for the low melting point compared with the reported one [1]. Figure 1 shows the molecular structure of *N*,*N*′-methylene-*bis*-cytisine monohydrate.



The dimeric molecule is situated in the crystal on a special position, a two-fold symmetry axis (0, y, 0.5), because the molecule has intrinsic symmetry that passes through C14 that binds the monomers. The water of crystallization is located on a two-fold symmetry axis along *b* (0.5, y, 0).

The relative placement of the two monomers is characterized by the torsion angles C11–N12–C14–N12′ and C11′–N12′–C14–N12, which have the values 179.0°, i.e., the C9–C11–N12–C14–N12′–C11′–C9′ moiety has a planar zig-zag shape, from the center of which the two-fold symmetry axis runs (Fig. 2).

The aromatic rings and adjacent atoms are planar within ±0.036 Å. The neighboring six-membered rings have the half-chair conformation with C8 and C9 deviating from the plane of the remaining four atoms by 0.57 and -0.27 Å, respectively. However, this ring in starting cytisine and its N12 derivatives adopts the C8-sofa conformation [2-5]. The third six-membered ring has the chair conformation.

Figure 2 shows the crystal structure of *N*,*N*′-methylene-*bis*-cytisine projected on the x0z plane. Molecules bound through water molecules by H-bonds (–C2=O1...H–Ow–H′...O1′=C2′–) form an infinite chain along the diagonal of the *a* and *c* axes. The parameters of the H-bonds are O1...O, 2.96; O1...H, 2.06 Å; and angle O1...H–O, 161.3°.

X-ray Crystal Structure. Crystals of **1** ($C_{23}H_{28}N_4O_2 \cdot H_2O$) were grown as transparent elongated prisms. A crystal of dimensions 0.85×0.35×0.55 mm was selected for the structure analysis. Unit-cell constants were determined and refined on a STOE Stadi-4 diffractometer at 295 K. Crystals of **1** were monoclinic, a = 15.107(3), b = 8.604(2), c = 8.660(2) Å, β = 110.00(3)°, V = 1057.7(4) Å^3, d_{calc} = 1.289 g/cm^3, absorption coefficient μ = 0.087 mm^{-1}, space group $C2$, Z = 4. A three-dimensional set of intensities was collected on the same diffractometer using $\omega/2\theta$-scanning, Mo Kα-radiation (graphite monochromator), and $2\theta \leq 50°$.

S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (99871) 120 64 75, e-mail: rentgen@uzsci.net. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 402-403, July-August, 2006. Original article submitted May 1, 2006.

0009-3130/06/4204-0503

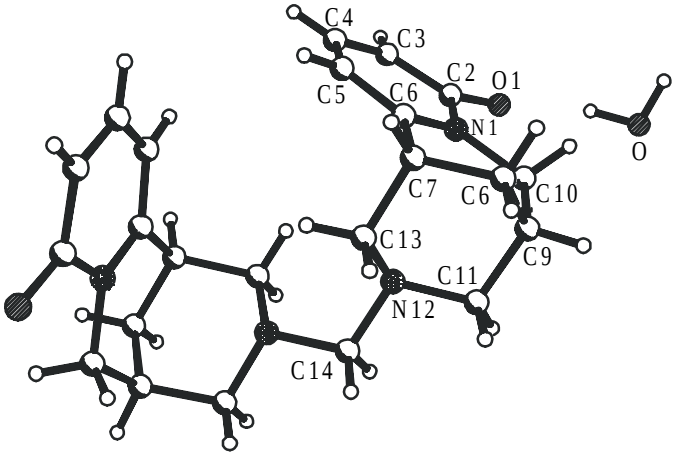


Fig. 1

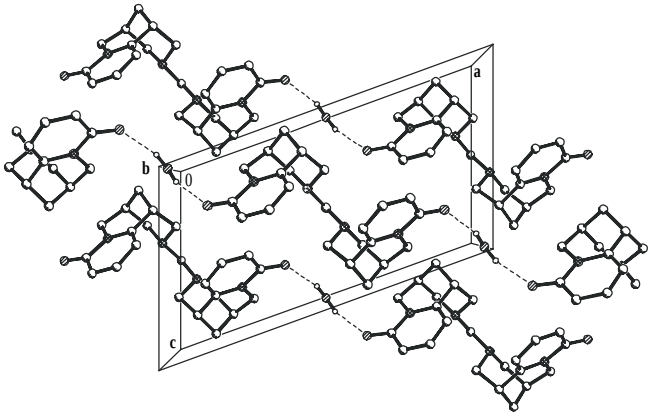


Fig. 2

Fig. 1. Molecular structure of *N*,*N*′-methylene-*bis*-cytisine hydrate.
Fig. 2. Molecular packing of *N*,*N*′-methylene-*bis*-cytisine hydrate.

The structure of **1** was solved by direct methods and refined using the program sets SHELXS-97 and SHELXL-97. Nonhydrogen atoms were refined by full-matrix anisotropic least-squares methods (on F^2). Hydrogen atoms on C14 and molecules of water were found in a difference electron-density synthesis. Remaining H atoms were fixed geometrically. The final agreement factors $R_1(F) = 0.0387$ ($wR_2 = 0.1044$) for 953 reflections with $I > 2\sigma(I)$ and 0.0424 ($wR_2 = 0.1100$) over all 1005 independent reflections included in the final refinement cycle.

Data from the XCS were deposited as CIF files in the Cambridge Crystallographic Data Centre (CCDC 606387).

REFERENCES

1. H. Auterhoff and F. Moll, *Arch. Pharm.*, 132 (1960).
2. A. A. Freer, D. J. Robins, and G. N. Sheldrake, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, **43**, 1119 (1987).
3. R. B. Barlow and O. Johnson, *Br. J. Pharmacol.*, **98**, 799 (1989).
4. O. A. Nurkenov, A. M. Gazaliev, A. B. Shalbaeva, K. M. Turdybekov, A. Abubakirova, and M. Z. Zhurinov, *Zh. Obshch. Khim.*, **69**, 675 (1999).
5. O. A. Nurkenov, A. M. Gazaliev, B. Ibragimov, B. Z. Kokzalova, A. B. Shalbaeva, K. M. Turdybekov, M. Z. Zhurinov, and A. E. Gulyaev, *Zh. Obshch. Khim.*, **68**, 328 (1998).