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Pseudaconitine

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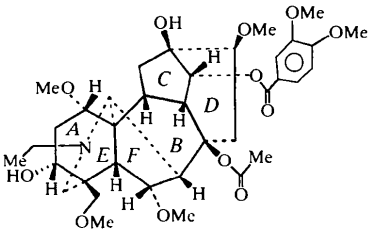
(*Received 15 May 1998; accepted 24 July 1998*)

Abstract

The crystal structure of pseudaconitine, [1α,6α,14α(*E*),-16β]-20-ethyl-1,6,16-trimethoxy-4-methoxymethyl-3,13-dihydroxyaconitane-8,14-diyl 8-acetate 14-(3,4-dimethoxybenzoate), $C_{36}H_{51}NO_{12}$, a C_{19} norditerpenoid alkaloid, contains discrete molecules separated by normal van der Waals distances. The molecular dimensions are as expected. The fused ring system contains two chair, one half-chair, one boat and two envelope conformations. There are inter- and intramolecular hydrogen bonds, with O···O separations in the range 2.671 (4)–2.865 (3) Å.

Comment

Continuing our crystallographic studies of C_{19} norditerpenoid alkaloids (Parvez *et al.*, 1998, 1998*a*,*b*,*c*), we now report the crystal structure of pseudaconitine, (1), a diterpenoid base. This has been isolated from the roots of *Aconitum falconeri*, which is found extensively in the northern areas of Pakistan.



(1)

The crystal structure contains pseudaconitine molecules (Fig. 1) separated by normal van der Waals distances. The absolute structure could not be established in this analysis; however, the absolute structure reported in this article is the same as that known for chasmanine 14-α-benzoate hydrochloride (De Camp & Pelletier, 1977). The molecular dimensions in (1) are normal and lie within expected values for the corresponding bond distances and angles, with mean bond distances as follows: Csp^3—N 1.449 (13), Csp^3—Csp^3 1.53 (3), Csp^3—O 1.41 (3), C—$C_{aromatic}$ 1.385 (17), Csp^2—O 1.350 (13) and C=O 1.19 (3) Å.

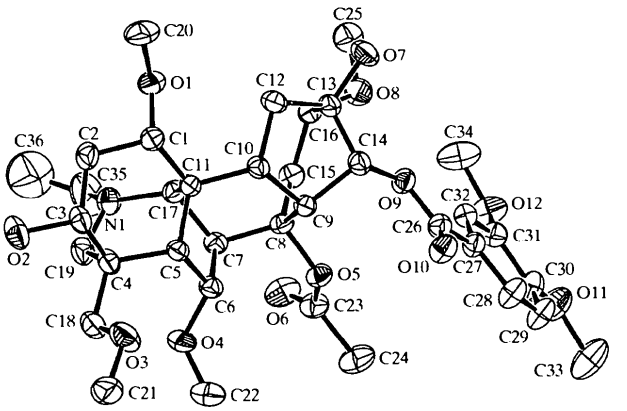


Fig. 1. *ORTEP*II (Johnson, 1976) drawing of (1), with the atomic numbering scheme. Displacement ellipsoids are plotted at the 30% probability level. The minor fractions of C25 and C36 have been excluded.

The six-membered rings *A* (C1–C5 and C11) and *E* (C4, C5, C11, C17, N1 and C19) adopt chair conformations. These rings are slightly flattened, as observed in

the structures of a chasmanine intermediate (Przybylska & Ahmed, 1980), aconitine (Codding, 1982), chasmanthinine (Parvez *et al.*, 1998*a*), chasmaconitine methanol solvate (Parvez *et al.*, 1998), 14-*o*-benzoyl-8-ethoxy- and 14-*o*-benzoyl-8-methoxy-bikhaconines (Parvez *et al.*, 1998*b*) and 3α-bikhaconine acetone solvate (Parvez *et al.*, 1998*c*). The six-membered ring *D* (C8, C9 and C13–C16) has a half-chair conformation, with C14 0.895 (4) Å out of the plane of the remaining ring atoms [maximum deviation 0.070 (2) Å]. The seven-membered ring *B* (C5–C11) adopts a boat conformation. The five-membered rings *C* (C9, C10, C12, C13 and C14) and *F* (C5–C7, C11 and C17) display C14- and C17-envelope conformations, respectively. Atom C14 is 0.701 (5) Å out of the plane of the remaining four atoms of ring *C*, which are essentially planar [maximum deviation 0.021 (2) Å]. Atom C17 is 0.739 (5) Å out of the plane formed by the rest of the atoms of ring *F*. The aromatic ring is essentially planar, with a maximum deviation of 0.026 (3) Å and with the methoxy C33 atom lying 0.216 (10) Å above and atom C34 0.220 (9) Å below this plane.

The crystal structure is stabilized by a network of hydrogen bonds, consisting of an intramolecular interaction between O7 and O8, and two intermolecular contacts, O7···O2 and O2···O10; details of the hydrogen-bonding geometry are given in Table 1.

Experimental

The title compound was isolated from *Aconitum falconeri* and characterized by ^{1}H and ^{13}C NMR spectroscopy. Crystals suitable for X-ray crystallographic studies were grown from acetone in a cold-room at 263 (1) K.

Crystal data

$C_{36}H_{51}NO_{12}$
M_r = 689.78
Monoclinic
$P2_1$
a = 11.9156 (12) Å
b = 12.7033 (19) Å
c = 11.9651 (17) Å
β = 100.415 (10)°
V = 1781.3 (4) Å^3
Z = 2
D_x = 1.286 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 20–30°
μ = 0.796 mm^{-1}
T = 293 (1) K
Prism
0.40 × 0.38 × 0.30 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
6921 measured reflections
6131 independent reflections
5242 reflections with $I > 2\sigma(I)$
R_{int} = 0.032
θ_{max} = 68°
h = 0 → 14
k = −15 → 15
l = −14 → 14
3 standard reflections
every 200 reflections
intensity decay: 1.06%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.161
S = 1.044
6131 reflections
453 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.10P)^2 + 0.38P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.012
$\Delta\rho_{max}$ = 0.357 e Å^{-3}
$\Delta\rho_{min}$ = −0.263 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = −0.2 (2) (3385 Friedel pairs)

Table 1. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
O2—H02···O10^i	0.82	2.04	2.831 (4)	160.8
O7—H07···O8	0.82	2.18	2.671 (4)	118.5
O7—H07···O2^{ii}	0.82	2.38	2.865 (3)	118.7

Symmetry codes: (i) $2-x, y-\frac{1}{2}, 1-z$; (ii) $x-1, y, z$.

Two of the methyl atoms, C25 and C36, were disordered and so were refined on two sites with variable site occupancy factors and isotropic displacement parameters, using the *EADP* command. The methylene-H atoms on C35 were placed appropriately, to allow for the disordered C36 atom. The remaining H atoms were included at geometrically idealized positions, with C—H 0.95 and O—H 0.82 Å.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1994). Program(s) used to solve structure: *SAPI91* (Fan, 1991). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *TEXSAN*. Software used to prepare material for publication: *SHELXL97*.

The authors thank Professor M. H. Benn for laboratory space, spectroscopic characterization of the title compound and financial assistance (to WG), and The University of Calgary for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1489). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1999). C**55**, 74–75

Gliclazide

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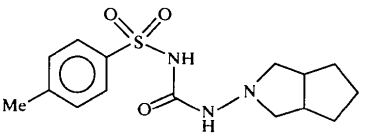
(*Received 27 May 1998; accepted 21 July 1998*)

Abstract

The crystal structure of gliclazide, *N*-[(perhydrocyclopenta[*c*]pyrrol-2-yl)aminocarbonyl]-*p*-toluenesulfonamide, $C_{15}H_{21}N_3O_3S$, a second-generation oral hypoglycemic agent, contains discrete molecules with normal molecular dimensions. Both of the five-membered fused rings adopt envelope conformations. The molecules are linked into chains by intermolecular hydrogen bonds involving amino-H atoms, with N···O separations of 2.967 (3) and 2.949 (3) Å.

Comment

Gliclazide, (I), is a second-generation oral hypoglycemic agent which is approximately 100 times more potent than the first-generation hypoglycemic agents (Lebovitz & Feinglos, 1983). It is used to assist in the control of mild to moderately severe type II diabetes mellitus (adult, maturity-onset), which does not require insulin but can be adequately controlled by diet alone, and it is the drug of choice for initiating treatment in non-insulin-dependent diabetes when diet and weight control fail. It stimulates the secretion and enhances the utilization of insulin by the appropriate tissues (Long, 1990). The pharmacokinetics and adverse effects of gliclazide are the same as those of chloropropamide and other second-generation oral hypoglycemic agents (Reynolds, 1994). However, there are conflicting data on the existence of extrapancreatic effects brought about by gliclazide (Webster & Taylor, 1996). The possible drug interactions include synergism with salicylates, cimetidine, clofibrate, fenfluramine and monoamine oxidase (MAO) type A inhibitor drugs (Stockley, 1991). In this paper, we report the crystal structure of the title compound.



(I)

The structure of (I) (Fig. 1) is composed of discrete molecules, with molecular dimensions within the expected ranges. Similar corresponding bond distances and angles have been reported in the related hypoglycemic agents 1-(4-chlorophenylsulfonyl)-3-(hexahydro-1*H*-azepin-1-yl)urea (Kamenar *et al.*, 1983) and 1-(4-methylphenylsulfonyl)-3-(hexahydro-1*H*-azepin-1-yl)urea (Kamenar *et al.*, 1983; Koo *et al.*, 1988). In the perhydrocyclopenta[*c*]pyrrole moiety in (I), the mean values of the bond distances are Csp^3—Csp^3 = 1.52 (2) and Csp^3—N = 1.469 (4) Å, and the fused five-membered cyclopentane (C10–C14) and pyrrole (N3, C9, C10, C14, C15) rings adopt C12- and N3-envelope conformations, respectively, with C12 0.574 (4) and N3 0.523 (7) Å out of the planes of the remaining atoms of the corresponding rings. The mean bond distances in the *p*-toluenesulfonyl moiety are C—$C_{aromatic}$ = 1.374 (3), S—O = 1.423 (4), Csp^3—Csp^3 = 1.497 (4) and S—Csp^2 = 1.758 (3) Å, the aromatic ring being essentially planar.

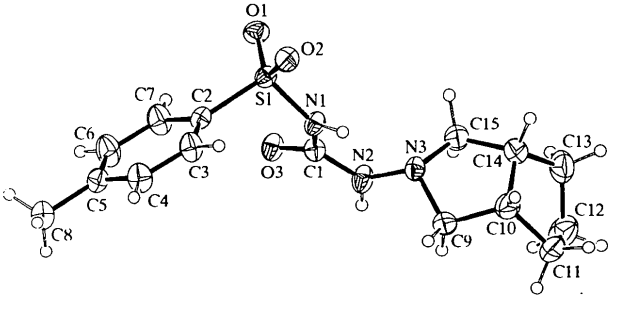


Fig. 1. *ORTEP*II (Johnson, 1976) drawing of (I), showing the atomic numbering scheme. Displacement ellipsoids are plotted at the 30% probability level. H atoms have been shown as circles of an arbitrary radius.

There are short intermolecular hydrogen bonds involving both of the amino-H atoms and the carbonyl- and one of the sulfonyl-O atoms; the other sulfonyl-O atom is not involved in such interactions. Molecules are linked by N—H···O hydrogen bonds to give chains extending in the *c* direction (Table 2); a packing diagram is deposited with the supplementary material.

Experimental

Gliclazide powder was a gift from Ali Gohar Pharmaceuticals (Pvt) Limited, Karachi, Pakistan. It was crystallized from absolute methanol by slow evaporation at room temperature.