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11,12-Seco-12,13-didehydromultiflorine Perchlorate Hydrate

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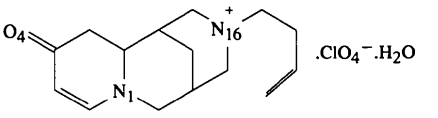
Abstract

The structure of 11,12-seco-12,13-didehydromultiflorine perchlorate hydrate [IUPAC name: 3-(but-3-enyl)-10-oxo-1,2,3,4,5,6,11,11a-octahydro-10*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocinium perchlorate hydrate], $C_{15}H_{23}N_2O^+.ClO_4^-.H_2O$, a new alkaloid found in lupin plants, has been confirmed by X-ray analysis. The cation is formed by protonation of the butenyl-bonded N atom, N16. There is significant conjugation in the N1—C2=C3—C4=O4 fragment of the cation. The structure is partially disordered and the molecular packing is governed by a network of intermolecular hydrogen bonds.

Comment

An alkaloid extracted from the seeds of *Lupinus albus* (cultivar BAC) was found to have physical properties, including an IR spectrum, almost identical to those of the alkaloid known as *N*-methylalbine (Wiewiórowski & Wolińska-Mocydlarz, 1961, 1964). Investigation by means of ^{13}C NMR and mass spectroscopy suggested, however, that this compound has the same structure as 11,12-seco-12,13-didehydromultiflorine rather than that of *N*-methylalbine (Wysocka & Brukwicki, 1988). In order to corroborate this assignment, we have performed an X-ray structural analysis of the perchlorate salt of the alkaloid, (I). The results of these studies show the structure to be correct.



(I)

Ring *A* (Fig. 1) has a distorted half-chair conformation, with atoms C5 and C6 deviating significantly and in opposite directions from the least-squares plane through the remaining four atoms [the deviations are −0.181 (9) and 0.441 (8) Å for C5 and C6, respectively]. The planarity of the N1—C2=C3—C4=O4 system, as well as the pattern of bond lengths, indicates a noticeable conjugation within the system. The *A*/*B* ring junction has a *trans* configuration [torsion angles C2—N1—C6—C5 −41.5 (5) and C7—C6—N1—C10 46.8 (5)°]. Ring *B* adopts a distorted chair conformation. A similar configurational/conformational pattern for the *A*/*B* ring system was observed in the structures of both multiflorine (Kubicki & Borowiak, 1989) and the multiflorine cation (Pyżalska, Gdaniec, Borowiak & Wolińska-Mocydlarz, 1980). Ring *C* of the title compound has a distorted chair conformation, as in the multiflorine cation, while in the multiflorine free base it has a boat conformation. This conformational change, also observed in sparteine derivatives (Kubicki, Borowiak & Boczoń, 1991, and references therein), accompanied by the inversion of configuration about the N16 atom, is a result of protonation at atom N16 and subsequent formation of the intramolecular (sparteine) or intermolecular (multiflorine) hydrogen bonds. Therefore, it would be possible for the same type of inversion to take place in

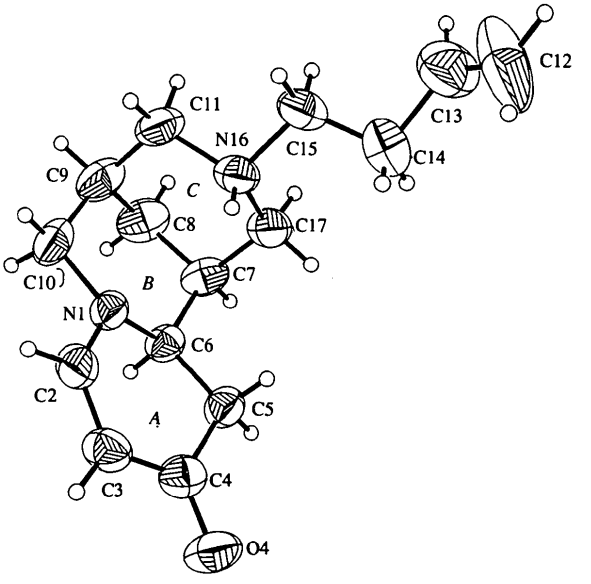


Fig. 1. Displacement ellipsoid representation of the title cation with the labelling scheme. The ellipsoids are drawn at the 50% probability level and H atoms are drawn as spheres of arbitrary radii.

the present compound in which the N16 atom is again protonated. However, the ^{13}C NMR results (Brukwicki & Wysocka, 1989) suggest that in this case both cation and free base have the same conformation, probably due to a lack of H···H repulsive interactions (8β–12β, 12β–17β and 14β–17β) as compared with sparteine.

The intermolecular hydrogen-bond network involves cations, anions and solvent water molecules resulting in a three-dimensional structure. The water molecule acts as an acceptor for the N—H···O hydrogen bond and as a donor for two kinds of O—H···O hydrogen bonds; one with the O4 atom of the cation and one with an O atom of the perchlorate anion. There is also a relatively short intramolecular N16···N1 contact of 2.963 (5) Å. Both the geometry of the N—H···N contact [N—H···N 106 (4)°] and the participation of atom N1 in the conjugated bond system suggest, however, that the possibility of intramolecular hydrogen bonding is very unlikely. The same geometry was observed in multiflorine perchlorate, contrary to the sparteine derivatives, where atom N1 can, and in fact does, accept an intramolecular hydrogen bond. The hydrogen-bond data are listed in Table 2.

There is partial disorder of the crystal structure involving the O atoms of the perchlorate anion and the terminal C12=C13 group of the cation. The occupancies of the alternative positions were refined at 0.63 (3) and 0.37 (3) for the C12=C13 group, and at 0.58 (2) and 0.42 (2) for the O atoms of the perchlorate. Weak constraints of the displacement parameters of the disordered fragments were applied. Both positions of the anion were refined as a rigid body.

The substituent at atom N16 occupies an equatorial position. All bond lengths and angles in the cation are typical. In the crystal structure, there are infinite chains of cations and water molecules connected by the 2_1 axis along the [010] direction.

Experimental

The extraction procedure used to obtain the alkaloid from the seeds of *Lupinus albus* has been described by Wysocka & Brukwicki (1988). Crystals were grown by vapour diffusion in an ethanol–diisopropyl ether system.

Crystal data

$C_{15}H_{23}N_2O^+.ClO_4^-.H_2O$
M_r = 364.82
Monoclinic
$P2_1$
a = 8.014 (2) Å
b = 8.633 (2) Å
c = 12.600 (3) Å
β = 90.53 (3)°
V = 871.7 (4) Å^3
Z = 2
D_x = 1.390 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 25 reflections
θ = 11.0–33.1°
μ = 2.243 mm^{-1}
T = 293 (2) K
Needle
0.30 × 0.20 × 0.20 mm
Colourless

Data collection

Kuma KM-4 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: refined from ΔF (*DIFABS*; Walker & Stuart, 1983)
T_{min} = 0.61, T_{max} = 0.66
1481 measured reflections
1380 independent reflections
1079 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0275
θ_{max} = 60.01°
$h = 0 \rightarrow 9$
$k = 0 \rightarrow 9$
$l = -14 \rightarrow 14$
2 standard reflections monitored every 200 reflections
intensity decay: 2.3%

Refinement

Refinement on F^2
$R(F)$ = 0.0360
$wR(F^2)$ = 0.0976
S = 1.076
1313 reflections
262 parameters
H-atom parameters not refined, except for H16, H1*W*1, H1*W*2, which were refined isotropically
$w = 1/[\sigma^2(F_o^2) + (0.0735P)^2 + 0.1331P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.271 e Å^{-3}
$\Delta\rho_{min}$ = −0.202 e Å^{-3}
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983); χ = 0.01 (3)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	Occupancy	x	y	z	U_{eq}
N1	1.0	0.2605 (5)	0.6738 (5)	0.9186 (3)	0.0433 (9)
C2	1.0	0.1943 (6)	0.7354 (6)	1.0052 (4)	0.0531 (12)
C3	1.0	0.1841 (6)	0.8897 (7)	1.0259 (4)	0.0557 (13)
C4	1.0	0.2321 (6)	1.0008 (6)	0.9492 (5)	0.0517 (13)
O4	1.0	0.2260 (5)	1.1433 (4)	0.9635 (3)	0.0694 (12)
C5	1.0	0.2833 (6)	0.9350 (6)	0.8438 (4)	0.0473 (11)
C6	1.0	0.3645 (6)	0.7766 (5)	0.8525 (4)	0.0416 (11)
C7	1.0	0.4044 (5)	0.7014 (6)	0.7469 (4)	0.0500 (12)
C8	1.0	0.4825 (7)	0.5428 (6)	0.7643 (5)	0.066 (2)
C9	1.0	0.3523 (7)	0.4448 (6)	0.8194 (5)	0.0622 (15)
C10	1.0	0.3146 (7)	0.5104 (6)	0.9268 (5)	0.0571 (14)
C11	1.0	0.2003 (7)	0.4224 (6)	0.7492 (4)	0.0595 (13)
C12	0.63 (3)	−0.3445 (19)	0.656 (3)	0.4759 (13)	0.138 (8)
C13	0.63 (3)	−0.1959 (20)	0.608 (3)	0.4888 (18)	0.090 (5)
C12′	0.37 (3)	−0.320 (3)	0.517 (4)	0.4995 (21)	0.119 (9)
C13′	0.37 (3)	−0.253 (4)	0.647 (3)	0.5166 (22)	0.081 (8)
C14	1.0	−0.0864 (9)	0.6713 (9)	0.5776 (5)	0.090 (2)
C15	1.0	−0.0044 (8)	0.5349 (7)	0.6257 (4)	0.066 (2)
N16	1.0	0.1259 (5)	0.5734 (5)	0.7098 (3)	0.0496 (10)
C17	1.0	0.2560 (6)	0.6836 (6)	0.6709 (3)	0.0530 (12)
Cl1	1.0	0.23333 (14)	1.59668 (14)	1.30142 (9)	0.0586 (4)
O1*A*	0.58 (2)	0.3259 (12)	1.7262 (8)	1.2921 (6)	0.190 (8)
O2*A*	0.58 (2)	0.2965 (12)	1.4866 (7)	1.2317 (5)	0.097 (4)
O3*A*	0.58 (2)	0.0716 (4)	1.6279 (14)	1.2687 (5)	0.158 (7)
O4*A*	0.58 (2)	0.2570 (9)	1.5209 (9)	1.3943 (3)	0.166 (7)
O1*B*	0.42 (2)	0.2336 (15)	1.7536 (2)	1.2840 (6)	0.173 (10)
O2*B*	0.42 (2)	0.3575 (7)	1.5402 (10)	1.2481 (4)	0.176 (11)
O3*B*	0.42 (2)	0.0848 (7)	1.5412 (14)	1.2570 (5)	0.160 (10)
O4*B*	0.42 (2)	0.2450 (8)	1.5813 (10)	1.40761 (11)	0.168 (10)
O1*W*	1.0	0.1159 (5)	1.2206 (6)	1.1636 (3)	0.0669 (10)

Table 2. *Selected geometric parameters* (Å, °)

N1—C2	1.330 (6)	C12—C13	1.27 (2)
N1—C6	1.478 (6)	C13—C14	1.52 (2)
N1—C10	1.479 (6)	C12′—C13′	1.26 (2)

C2—C3	1.360 (8)	C13′—C14	1.55 (3)
C3—C4	1.416 (8)	C14—C15	1.476 (9)
C4—O4	1.244 (7)	C15—N16	1.518 (7)
C4—C5	1.506 (7)	N16—C17	1.497 (6)
C5—C6	1.518 (7)	Cl1—O2*B*	1.30 (2)
C6—C7	1.518 (7)	Cl1—O4*B*	1.35 (2)
C7—C8	1.521 (8)	Cl1—O1*A*	1.35 (2)
C7—C17	1.527 (7)	Cl1—O4*A*	1.35 (2)
C8—C9	1.517 (8)	Cl1—O1*B*	1.37 (2)
C9—C10	1.500 (9)	Cl1—O3*A*	1.38 (2)
C9—C11	1.512 (8)	Cl1—O2*A*	1.39 (2)
C11—N16	1.515 (7)	Cl1—O3*B*	1.40 (2)
C2—N1—C6	116.9 (4)	C12—C13—C14	121.0 (20)
C2—N1—C10	116.3 (5)	C12′—C13′—C14	124.7 (25)
C6—N1—C10	116.5 (4)	C15—C14—C13	105.7 (11)
N1—C2—C3	125.0 (4)	C15—C14—C13′	118.3 (12)
C2—C3—C4	121.0 (5)	C14—C15—N16	114.4 (5)
O4—C4—C3	124.0 (5)	C17—N16—C11	112.4 (4)
O4—C4—C5	120.8 (5)	C17—N16—C15	112.8 (4)
C3—C4—C5	115.1 (5)	C11—N16—C15	107.8 (4)
C4—C5—C6	113.3 (4)	N16—C17—C7	113.5 (4)
N1—C6—C5	109.8 (4)	O2*B*—Cl1—O4*B*	115 (1)
N1—C6—C7	111.2 (4)	O1*A*—Cl1—O4*A*	114 (1)
C5—C6—C7	114.5 (4)	O2*B*—Cl1—O1*B*	107 (1)
C6—C7—C8	110.4 (5)	O4*B*—Cl1—O1*B*	105 (1)
C6—C7—C17	115.0 (4)	O1*A*—Cl1—O3*A*	109 (1)
C8—C7—C17	108.5 (5)	O4*A*—Cl1—O3*A*	118 (1)
C9—C8—C7	106.5 (4)	O1*A*—Cl1—O2*A*	108 (1)
C10—C9—C11	114.1 (5)	O4*A*—Cl1—O2*A*	100 (1)
C10—C9—C8	110.3 (5)	O3*A*—Cl1—O2*A*	107 (1)
C11—C9—C8	111.0 (5)	O2*B*—Cl1—O3*B*	109 (1)
N1—C10—C9	111.0 (5)	O4*B*—Cl1—O3*B*	115 (1)
C9—C11—N16	113.2 (4)	O1*B*—Cl1—O3*B*	106 (1)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N16—H16···O1*W*^{i}	0.86 (6)	1.99 (6)	2.823 (6)	165 (5)
O1*W*—H1*W*1···O4	0.83 (8)	1.94 (8)	2.761 (5)	171 (8)
O1*W*—H1*W*2···O2*A*	1.00 (10)	1.84 (10)	2.843 (10)	171 (7)

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

Data collection: Kuma KM-4 software (Kuma, 1991). Cell refinement: Kuma KM-4 software. Data reduction: Kuma KM-4 software. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *Stereochemical Workstation Operation Manual* (Siemens, 1989). Software used to prepare material for publication: *SHELXL*93.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AB1207). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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A Morphine Metabolite: (–)-Morphine-3-*O*-*β*-D-glucuronide Trihydrate (M3G.3H_2O)

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Abstract

The title compound, $C_{23}H_{27}NO_9.3H_2O$, occurs in the solid state as a zwitterion solvated by three water molecules. The conformation of this morphine conjugate is extended with the strongest proton donor (hydroxyl group at C6) and acceptors (two O atoms of the carboxyl group) located on one side of the molecule. The three-dimensional hydrogen-bonding pattern shows many competing possibilities of bonding and resembles one of the probable dynamic structures in solution.

Comment

The important role of morphine in modern pain therapy, even with its numerous side effects, is unquestionable. However, the role of metabolites in neuropharmacological mechanisms is not yet fully understood. Recently, the two main metabolites of morphine, 3-*O*-*β*-D-glucuronide (M3G) and 6-*O*-*β*-D-glucuronide (M6G), have been studied at many laboratories. These conjugates of morphine and glucuronic acid, produced in the liver, have been found in blood plasma and the brain, suggesting that, in contrast to morphine itself, they can penetrate the blood–brain barrier (Yoshimura, Ida, Oguri & Tsukamoto, 1973). Other studies have demonstrated that both metabolites of morphine could be formed enzymatically in various parts of the human brain (Wahlström, Windblad, Bixo & Rane, 1988). Morphine glucuronides have adverse effects on the nervous system (Smith, Watt & Cramond, 1990). M6G is a very potent μ-receptor agonist and is much more active *in vivo* than morphine (Shimomura *et al.*, 1971). M3G does not act as an analgesic but plays an important role in developing morphine tolerance (Lipkowski, Langlade, Osgood, Szyfelbein & Carr, 1992). Lipophilicity studies, along with molecular modelling of these compounds,