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(5*R*,6*R*,7*R*,9*R*,13*R*,14*S*)-21-Cyclopropylmethyl-6,14-*endo*-ethano-2′,3′,4′,5′,7,8-hexahydro-4′,4′,5′,5′-tetramethylfurano[2′,3′6,7]normorphide hydrochloride methanol solvate

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Key indicators

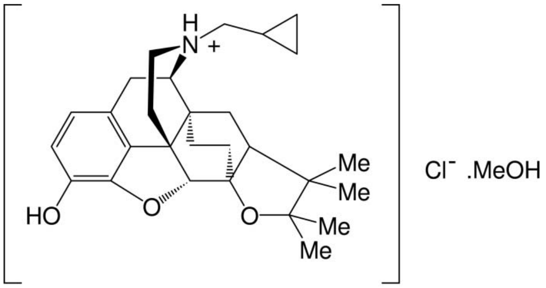
Single-crystal X-ray study
T = 295 K
Mean σ(C–C) = 0.002 Å
R factor = 0.041
wR factor = 0.049
Data-to-parameter ratio = 10.0

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The title compound, $C_{28}H_{38}NO_3^+\cdot Cl^-\cdot CH_4O$, is demethoxy-buprenorphine hydrochloride (buprenorphine degradation product). Crystal structure determination has confirmed that the elimination of methanol and rearrangement with the formation of a new ring proceeds with the retention of chirality of all chiral centres of the molecule.

Comment

Buprenorphine, an opioid mixed agonist–antagonist, is a potent analgesic that also appears to be effective for the treatment of opiate abuse. It is usually used in the form of the hydrochloride salt (Kratochvíl *et al.*, 1994). Buprenorphine differs from the majority of morphinane alkaloids by the presence of an additional 4,6-ethano junction. Acid and heat catalyse an interesting rearrangement of buprenorphine with the loss of methanol (Cone *et al.*, 1984; Everhart *et al.*, 1997) and formation of demethoxy-buprenorphine. We report here the structure of demethoxy-buprenorphine hydrochloride in the form of its methanol solvate, (I).



(I)

Demethoxy-buprenorphine possesses a typical opiate T shape (Fig. 1), similar to that of buprenorphine (Kratochvíl *et al.*, 1994) and related morphinanes with a 6,14-etheno bridge (Van den Hende & Nelson, 1967; Van Koningsveld *et al.*, 1984; Michel *et al.*, 1988; Michel & Michel-Dewez, 1990; Hušák *et al.*, 1993; Bulej *et al.*, 1993). Benzene ring *A* (atoms C1–C4/C12/C11) and atom O1 are almost planar. Ring *B* (C9–C14) possesses a conformation near to a ^6E envelope [puckering parameters (Cremer & Pople, 1975) Q = 0.579 (2) Å, φ = 109.2 (2)° and θ = 124.4 (2)°], with atom C14 displaced by 0.780 (2) Å from the mean plane. Ring *C* (C5–C8/C14/C13) has a boat $^{2,5}B$ form [Q = 0.859 (2) Å, φ = −113.6 (1)° and θ = 95.8 (1)°], with displacements of atoms C14 [0.648 (2) Å] and C6 [0.826 (2) Å]. The piperidine ring, *D* (N17/C9/C14/C13/C15/C16), adopts a chair $^4C_1$ shape [Q = 0.614 (2) Å, φ = 68 (1)° and θ = 8.5 (1)°], with atoms C13 above [0.688 (2) Å] and N17 below [0.723 (1) Å] the plane of the remaining four atoms. The 4,5-epoxy ring *E* (O2/C4/C12/C13/C5) is almost

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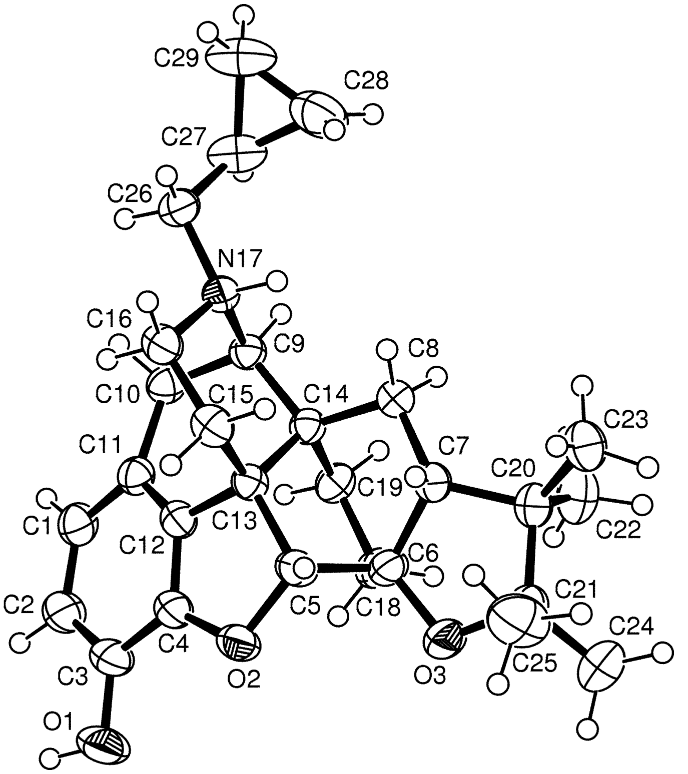

Figure 1
ORTEP-3 (Farrugia, 1997) drawing of (I) (Cl and solvent omitted for clarity), with the atom-numbering scheme and 50% probability displacement ellipsoids.

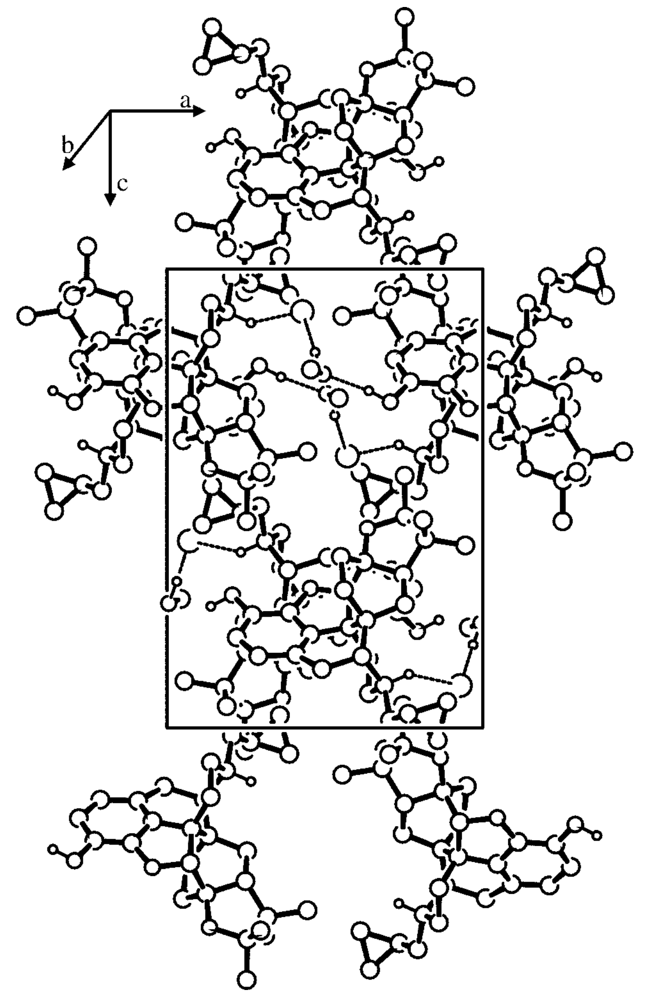

Figure 2
A packing diagram of (I) projected along the *b* axis (only those H atoms involved in hydrogen bonds are shown). Broken lines indicate hydrogen bonds.

planar, but slightly distorted to a twisted $^4T_5$ conformation [Q = 0.111 (2) Å and $\varphi = -55.2$ (8)°], with atoms C13 lying above [0.102 (1) Å] and C5 [0.087 (2) Å] below the mean plane of the other atoms. Ring *F* (C6–C8/C14/C19/C18) forms a boat $B_{4,1}$ conformation [Q = 0.829 (2) Å, φ = 174.8 (1)° and θ = 80.8 (1)°], with both atom C14 [0.845 (2) Å] and atom C6 [0.550 (2) Å] above the plane. Ring *G* (O3/C6/C7/C20/C21) forms a twisted $^3T_4$ conformation distorted to E_4 [Q = 0.385 (2) Å and φ = 98.5 (3)°], where atom C7 is above the plane [0.161 (2) Å] and C20 [0.471 (2) Å] is below the plane.

Atom N17 is protonated and the Cl1 anion is linked through an N—H···Cl hydrogen bond (Table 1). The hydrogen-bonded chain continues *via* methanol and hydroxy groups of a neighbouring demethoxy-buprenorphine molecule translated along the *a* axis (Fig. 2).

Experimental

Buprenorphine (7.3 g) in aqueous hydrochloric acid (10%, 150 ml) was heated to 393 K for 30 min in an autoclave. After cooling to room temperature, the pH of the reaction mixture was set to 8.4 by addition of aqueous ammonia. The resulting suspension was extracted four times with a mixture of dichloromethane and acetone (4:1, 125 ml). The organic layers were evaporated to dryness, and the oily residue was crystallized from methanol. The product was collected by suction, washed with chilled methanol (10 ml) and dried at 333 K for 8 h (yield 3.5 g, 49%). This base was stirred in methanol (40 ml) and neutralized with methanolic hydrogen chloride. The solution was evaporated to *ca* 10 ml and diethyl ether (30 ml) was added dropwise. The suspension was stirred at 283 K for 2 h. The product was collected by suction, washed with diethyl ether (10 ml) and dried at 333 K for 16 h (yield 3.4 g, 90%). Single crystals of (I) were obtained by slow evaporation in air of a saturated solution in methanol (250 mg per 2.5 ml).

Crystal data

$C_{28}H_{38}NO_3^+ \cdot Cl^- \cdot CH_4O$
M_r = 504.11
Orthorhombic, $P2_12_12_1$
a = 11.5861 (5) Å
b = 13.7665 (7) Å
c = 16.8391 (8) Å
V = 2685.8 (2) Å^3
Z = 4
D_x = 1.247 Mg m^{-3}

Cu *Kα* radiation
Cell parameters from 16127 reflections
θ = 5–77°
μ = 1.53 mm^{-1}
T = 295 K
Prism, colourless
0.32 × 0.23 × 0.14 mm

Data collection

Oxford Diffraction XCALIBUR diffractometer
φ and ω scans
Absorption correction: numerical (de Meulenaer & Tompa, 1965)
$T_{\min}$ = 0.58, $T_{\max}$ = 0.81
29111 measured reflections

5505 independent reflections
4754 reflections with $I > 1.96\sigma(I)$
$R_{\rm int}$ = 0.090
$\theta_{\max}$ = 76.9°
$h = -14 \rightarrow 14$
$k = -17 \rightarrow 16$
$l = -20 \rightarrow 20$

Refinement

Refinement on F
$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.049$
$S = 1.08$
4754 reflections
474 parameters
H atoms treated by a mixture of independent and constrained refinement
Weighting scheme see below
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.40$ e Å^{-3}
$\Delta\rho_{\min} = -0.34$ e Å^{-3}
Extinction correction: Larson (1970)
Extinction coefficient: 219 (18)
Absolute structure: Flack (1983), 1563 Friedel pairs
Flack parameter: 0.016 (14)

Table 1
Hydrogen-bond geometry (Å, °).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
N17—H171$\cdots$Cl1	1.00 (2)	2.32 (2)	3.151 (1)	140 (2)
O1—H511$\cdots$O4	0.89 (3)	1.82 (3)	2.700 (3)	170 (3)
O4—H541$\cdots$Cl1$^{\rm i}$	1.02 (4)	2.04 (5)	3.052 (3)	172 (4)

Symmetry code: (i) $x + 1, y, z$.

The weighting scheme used a Chebychev polynomial (Watkin *et al.*, 1994; Prince, 1982): $w = [1 - (F_o - F_c)^2/36\sigma^2(F_o)]^2/13.3T_0(x) - 3.19T_1(x) + 10.8T_2(x)]$, where $x = F_o/F_{\max}$ and $T_n(x)$ are the Chebychev polynomials.

H atoms bonded to N and O atoms were located in difference density maps and refined isotropically. H atoms bonded to the C atoms were restrained using an automatic C—H restraint routine, restrained with C—H = 0.98 (2) Å and target angles appropriate to the hybridization, and with $U_{\rm iso}$(H) restrained to $1.2U_{\rm eq}$(C).

Data collection: *CrysAlis RED* (Oxford Diffraction, 2002); cell refinement: *CrysAlis RED*; data reduction: *CrysAlis RED*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *CRYSTALS*.

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