

THE CRYSTAL AND MOLECULAR STRUCTURE OF BUTORPHANOL HYDROGEN TARTRATE

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The structure of butorphanol hydrogen tartrate {(9*R*,13*S*,14*S*)-(-)-17-(cyclobutylmethyl)morphinan-3,14-diol (2*S*,3*S*)-(-)-hydrogen tartrate} (C₂₁H₂₉NO₂ · C₄H₆O₆) was solved by direct methods and refined anisotropically to the *R* value of 0.029 for 2 069 observed reflections. The title morphine analogue crystallizes in the triclinic space group *P*1 with lattice parameters *a* = 7.620(1), *b* = 9.140(1), *c* = 9.591(1) Å, α = 105.48(1), β = 112.91(1), γ = 84.29(1)°, *Z* = 1. The butorphanol B ring possesses the ³*E* envelope conformation with small ³H₂ distortion, C and D rings have a regular chair conformation. The intramolecular N17–H17 ··· O2 hydrogen bond is observed in crystal structure of the title compound. The butorphanol and hydrogen tartrate molecules are joined together by means of O2–H(O2) ··· O7, O1–H(O1) ··· O7' and O3–H(O3) ··· O8'' hydrogen bonds to form networks.

Several models have been proposed for the interaction between the opioid analgesic and the opiate receptor¹. Since opiates are presumed to exist in the N-protonized form at physiological pH, an "anionic" site of the receptor which accommodate the tertiary amine nitrogen, as a common structural feature of all morphine analogues plays an important role in most models. Recent results, however, unexpectedly revealed the presence of some negative charge even on the N-protonated opiates². Since the majority of crystallographic studies on opiates has been carried out on free bases, this results makes a virtue of necessity of detailed structural information and comparison of their protonized forms. The aim of present work is to establish the basic structural parameters of the butorphanol (Scheme 1) in the form of its hydrogen tartrate salt.

EXPERIMENTAL

Preparation of Crystals

Butorphanol was used in the commercially available form of its (2*S*,3*S*)-(-)-hydrogen tartrate obtained from Galena Co. (The Czech Republic). Single crystals were obtained by slow cooling of the hot solution of butorphanol hydrogen tartrate (200 mg) in ethanol (6 ml)–water (1.3 ml) mixture. Crystals were separated, washed with ethanol and dried in air.

Crystal Structure Determination

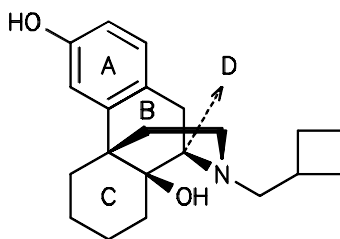
$C_{21}H_{29}NO_2 \cdot C_4H_6O_6$ ($M_r = 477.6$), triclinic system, space group *PI* (No. 1), $a = 7.620(1)$, $b = 9.140(1)$, $c = 9.591(1)$ Å, $\alpha = 105.48(1)$, $\beta = 112.91(1)$, $\gamma = 84.29(1)^\circ$, $V = 593.0(1)$ Å³, $Z = 1$, $D_{\text{calc}} = 1.34$ g cm⁻³, $\mu(\text{MoK}\alpha) = 0.93$ cm⁻¹, $F(000) = 256$.

The structure was solved by direct methods and anisotropically refined by block-diagonal least-squares. The hydrogen atoms were found from difference synthesis and from expected geometry. Absorption was neglected. Data collection and structure refinement parameters are listed in Table I.

DISCUSSION

The final positional and thermal parameters of the non-H atoms are summarized in Table II. Interatomic distances and angles are listed in Table III. Figure 1 shows the butorphanol molecule and the unit-cell contents is presented in Fig. 2. Though the absolute configuration was not determined from anomalous dispersion due to the absence of a heavy atom, the presence of the hydrogen tartrate anion of known chirality makes this unambiguous assignment possible. The standard numbering for morphine was chosen with the nitrogen atom at the position 17.

The molecule of butorphanol resembles in many ways the characteristic T-shape of classical opiates^{8,9}, with the piperidine ring D and ring C comprising the short arms of the T and the aromatic ring A, and the ring B forming the stalk of the T. The ring A is nearly planar with the maximal deviation of $-0.031(2)$ Å for C3 atom. The relatively large torsion angle $C2-C3-C4-C12 = -4.0(3)^\circ$ has the opposite sign compared with these found in compounds having ether bridge^{10,11}. The O1 atom lies $-0.115(2)$ Å ap-



SCHEME 1

TABLE I

Data collection and refinement parameters

Crystal dimensions	0.45 × 0.40 × 0.25 mm
Diffractometer and radiation used	Enraf–Nonius CAD4, MoK α , $\lambda = 0.71073 \text{ \AA}$
Scan technique	$\omega/2\theta$
Temperature	293 K
Number and θ range of reflections for lattice parameter refinement	23; 20.02 – 20.92°
Range of h , k and l	-9 → 9, -10 → 10, -11 → 11
Standard reflections monitored in interval; intensity fluctuation	120 min; -2.4%
Total number of reflections measured; 2θ range	4 114; 0 – 50°
Value of R_{int}	0.010
Number of unique observed reflections	2 018
Criterion for observed reflections	$I \geq 1.96 \sigma(I)$
Function minimized	$\sum w (F_o - F_c)^2$
Weighting scheme	$w = 1/[\sigma(F)^2 + 0.0009 F^2]$
Parameters refined	450
Value of R , wR and S	0.029; 0.030; 0.98
Ratio of max. LS shift to e.s.d. in the last cycle	0.007
Max. and min. heights in final $\Delta\rho$ map	0.12, -0.18 e \AA^{-3}
Source of atomic scattering factors	SHELX76 (ref. ³) and International Tables for X-Ray Crystallography (ref. ⁴)
Programs used	SDP (ref. ⁵), SHELX76 (ref. ³), SHELXS86 (ref. ⁶), PARST (ref. ⁷)
Computer used	PDP 11/73, PC AT 486

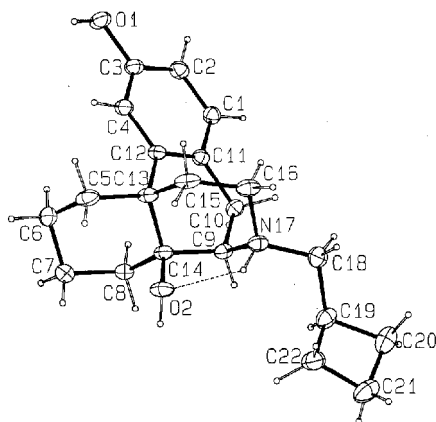


FIG. 1

ORTEP drawing of the butorphanol molecule, showing 50% probability ellipsoids and atom-labelling schemes

TABLE II

Atomic coordinates ($\cdot 10^4$) for non-H atoms and their equivalent isotropic thermal parameters ($\cdot 10^4$).
 $U_{\text{eq}} = 1/3 [U_{11} + U_{22} + U_{33} + 2 (U_{12} \cos \gamma + U_{13} \cos \beta + U_{23} \cos \alpha)]$

Atom	x	y	z	$U_{\text{eq}}, \text{\AA}^2$
N17	-1882(2)	333(2)	-1419(2)	299(5)
O1	2388(2)	771(2)	6723(2)	380(5)
O2	-410(2)	3034(2)	-590(2)	366(5)
O3	7055(2)	5062(2)	-2559(2)	423(5)
O4	7873(2)	6715(2)	-216(2)	520(6)
O5	4866(3)	6094(3)	231(2)	658(8)
O6	3168(3)	6920(2)	-2745(2)	450(6)
O7	1486(2)	3668(2)	-2232(2)	342(4)
O8	178(2)	5886(2)	-2605(2)	448(5)
C1	1893(3)	-1415(2)	2829(2)	292(6)
C2	2214(3)	-1063(2)	4407(2)	304(6)
C3	1946(3)	414(2)	5139(2)	278(5)
C4	1244(3)	1493(3)	4281(2)	276(5)
C5	447(4)	3960(2)	2705(3)	414(8)
C6	2560(4)	4336(2)	3324(3)	468(8)
C7	3274(5)	4060(3)	1989(3)	469(9)
C8	2841(3)	2428(2)	997(2)	339(6)
C9	282(2)	433(2)	-620(2)	261(5)
C10	1132(3)	-773(2)	281(2)	271(5)
C11	1289(2)	-336(2)	1960(2)	245(5)
C12	906(2)	1138(2)	2689(2)	244(5)
C13	-9(3)	2305(2)	1726(2)	300(6)
C14	719(3)	2067(2)	380(2)	274(5)
C15	-2183(3)	2001(3)	996(2)	367(7)
C16	-2785(3)	508(3)	-231(2)	368(7)
C18	-2603(3)	-1013(3)	-2789(2)	370(7)
C19	-2059(3)	-916(3)	-4121(2)	386(7)
C20	-2934(4)	-2103(3)	-5699(3)	502(8)
C21	-3173(4)	-850(4)	-6536(3)	547(9)
C22	-2938(4)	335(3)	-4992(3)	475(8)
C23	6824(3)	5759(2)	-1265(3)	357(6)
C24	5051(3)	5266(3)	-1161(2)	330(6)
C25	3298(2)	5427(2)	-2572(2)	273(5)
C26	1508(3)	4952(2)	-2448(2)	271(5)

TABLE III
Bond distances (Å) and angles (°) with e.s.d.'s in parentheses

Atoms	Distances	Atoms	Distances
N17-C9	1.524(2)	C6-C7	1.531(5)
N17-C16	1.513(3)	C7-C8	1.528(3)
N17-C18	1.501(3)	C8-C14	1.527(3)
O1-C3	1.374(3)	C9-C10	1.521(3)
O2-C14	1.432(3)	C9-C14	1.532(2)
O3-C23	1.305(3)	C10-C11	1.511(3)
O4-C23	1.208(2)	C11-C12	1.403(2)
O5-C24	1.400(3)	C12-C13	1.534(3)
O6-C25	1.407(3)	C13-C14	1.551(3)
O7-C26	1.248(3)	C13-C15	1.548(3)
O8-C26	1.248(3)	C15-C16	1.518(3)
C1-C2	1.386(3)	C18-C19	1.514(4)
C1-C11	1.389(3)	C19-C20	1.547(3)
C2-C3	1.381(2)	C19-C22	1.541(4)
C3-C4	1.386(3)	C20-C21	1.525(5)
C4-C12	1.396(3)	C21-C22	1.542(4)
C5-C6	1.523(4)	C23-C24	1.513(4)
C5-C13	1.544(2)	C24-C25	1.516(2)
		C25-C26	1.528(3)
Atoms	Angles	Atoms	Angles
C16-N17-C18	113.9(2)	C14-C13-C15	108.3(2)
C9-N17-C18	114.3(2)	C9-C14-C13	109.0(2)
C9-N17-C16	110.7(1)	C8-C14-C13	111.8(2)
C2-C1-C11	122.1(2)	C8-C14-C9	111.3(2)
C1-C2-C3	118.8(2)	O2-C14-C13	106.2(2)
O1-C3-C2	118.2(2)	O2-C14-C9	106.7(2)
C2-C3-C4	120.2(2)	O2-C14-C8	111.7(2)
O1-C3-C4	121.6(2)	C13-C15-C16	114.5(2)
C3-C4-C12	121.0(2)	N17-C16-C15	110.5(2)
C6-C5-C13	112.4(2)	N17-C18-C19	111.6(2)
C5-C6-C7	111.2(2)	C18-C19-C22	119.3(2)
C6-C7-C8	110.1(2)	C18-C19-C20	117.7(2)
C7-C8-C14	111.3(2)	C20-C19-C22	88.2(2)
N17-C9-C14	105.6(2)	C19-C20-C21	88.8(2)
N17-C9-C10	113.1(2)	C20-C21-C22	89.0(2)
C10-C9-C14	114.3(2)	C19-C22-C21	88.5(2)

TABLE III
 (Continued)

Atoms	Angles	Atoms	Angles
C9–C10–C11	115.2(2)	O3–C23–O4	125.8(2)
C1–C11–C10	119.0(2)	O4–C23–C24	120.6(2)
C10–C11–C12	122.2(2)	O3–C23–C24	113.6(2)
C1–C11–C12	118.7(2)	O5–C24–C23	110.3(2)
C4–C12–C11	119.0(2)	C23–C24–C25	110.9(2)
C11–C12–C13	120.4(2)	O5–C24–C25	111.2(2)
C4–C12–C13	120.5(2)	O6–C25–C24	110.2(2)
C5–C13–C12	112.9(2)	C24–C25–C26	110.7(2)
C12–C13–C15	107.0(2)	O6–C25–C26	111.9(2)
C12–C13–C14	110.0(2)	O8–C26–C25	116.3(2)
C5–C13–C15	111.1(2)	O7–C26–C25	117.8(2)
C5–C13–C14	107.6(2)	O7–C26–O8	125.9(2)

part the best A ring plane which may account for O1–H(O1) ... O7 hydrogen bond. Ring B (C12,C13,C14,C9,C10,C11) is very near to an envelope 3E conformation with a small component of 3H_2 , puckering parameters according to Cremer and Pople¹² are: $Q = 0.491(2)$ Å, $\phi = 116.1(3)^\circ$, $\theta = 46.5^\circ$ with C14 atom displaced by $0.661(2)$ Å above C13,C12,C11,C10,C9 mean plane. The ring C (C8,C14,C13,C5,C6,C7) has the regular chair conformation 1C_4 ($Q = 0.586(2)$ Å, $\phi = 99.4(8)^\circ$, $\theta = 1.5(2)^\circ$). Crystal structures of morphine and codeine have shown that the ring C in these molecules is in a boat

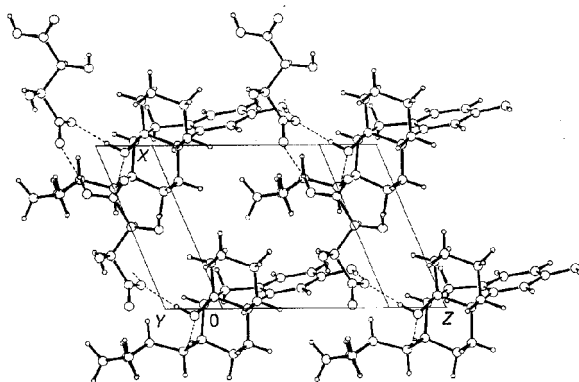


FIG. 2

Packing scheme. Dotted lines represent hydrogen bonds

form^{8,9,13-15}, this conformation preference has been attributed to the presence of the unsaturated linkage between C7 and C8 (see refs^{16,17}). The butorphanol D piperidine ring (C13,C14,C9,N17,C16,C15) possesses the regular chair conformation 1C_4 as has been observed in crystal structures of pentacyclic opiates ($Q = 0.623(2) \text{ \AA}$, $\phi = 106.9(9)^\circ$, $\theta = 12.3(2)^\circ$). The cyclobutylmethyl is in equatorial configuration, leaving the lone electron pair N-axial, as shown in Fig. 1.

Rotation about the single bonds are described by torsion angles C16–N17–C18–C19 = $165.3(2)^\circ$, N17–C18–C19–C20 = $-171.7(2)^\circ$. An enforced intramolecular hydrogen bond N17–H17 ... O2 ($d(\text{N17} \dots \text{O2}) = 2.61(3) \text{ \AA}$, angle N17–H17 ... O2 = $120(7)^\circ$) is observed in crystal structure of the title compound. The butorphanol and hydrogen tartrate molecules are connected by O2–H(O2) ... O7 ($d(\text{O2} \dots \text{O7}) = 2.71(3) \text{ \AA}$, angle O2–H(O2) ... O7 = $173(3)^\circ$, O1–H(O1) ... O7' ($x, y, z + 1$) ($d(\text{O1} \dots \text{O7}') = 2.69(2) \text{ \AA}$, angle O1–H(O1) ... O7' = $177(3)^\circ$) and O3–H(O3) ... O8'' ($x + 1, y, z$) ($d(\text{O3} \dots \text{O8}'') = 2.59(3) \text{ \AA}$, angle O3–H(O3) ... O8'' = $173(3)^\circ$) hydrogen bonds. The packing diagram given in Fig. 2 shows that each molecule participates in formation of hydrogen bond networks extending along the *ac* plane.

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