THE MOLECULAR AND CRYSTAL STRUCTURE OF BUPRENORPHINE HYDROCHLORIDE, A MORPHINE ANALOGUE

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The structure of buprenorphine hydrochloride {(6*R*,7*R*,14*S*)-17-cyclopropylmethyl-7,8-dihydro-7-[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6-*O*-methyl-6,14-ethano-17-normorphine hydrochloride} was solved by direct methods and refined anisotropically to the *R* value of 0.062 for 3 049 observed reflections. The substance crystallizes in the tetragonal space group $P4_32_12$, $a = b = 11.513(2)$ Å, $c = 42.054(8)$ Å, $V = 5\ 574(2)$ Å^3, $Z = 8$, $D_{calc} = 1.201$ g cm^{-3}, μ(MoKα) = 0.17 mm^{-1}. The compound is the first morphine derivative with a 6,14-ethano bridge whose molecular structure has been solved.

Many synthetic and semisynthetic morphine derivatives have been reported but only a few of them have found widespread use, such as butorphanol (*I*), a strong non-addictive injectable analgesic, naloxon (*II*), a morphine antagonist, and buprenorphine (*III*), a strong analgesic used per os. These morphinans are produced semisynthetically from the natural opiate alkaloid (–)-thebaine[1]. Morphinans are assumed to exist in the *N*-protonized form at the physiological pH. An “anionic” site of the receptor which accomodates the tertiary amine nitrogen plays an important role in the majority of models of opioid receptors. Since crystallographic studies of morphinans have mostly been carried out on the free bases, detailed structural information of their protonized forms is required.

The molecule of *III* differs from those of *I* and *II*, which have been studied by X-ray structural methods[2,3], by the presence of the 6,14-ethano bridge. Inspection of the Cambridge structural database identified 11 morphinan structures[4–14] involving the skeleton of morphine rings A, B, C and D, with the 6,14-etheno bridge only. Thus the X-ray

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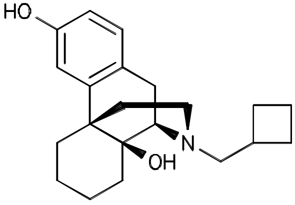
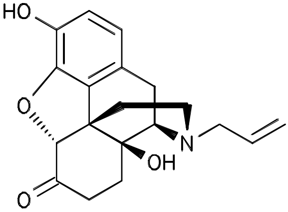
structural study of the *N*-protonized molecule of buprenorphine in the form of its hydrochloride, reported here, is the first example of a morphinan with the 6,14-ethano junction.



I



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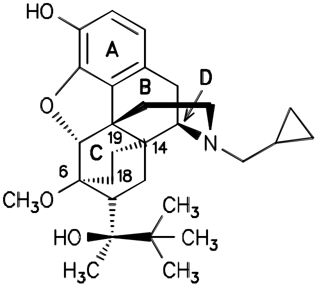

III

EXPERIMENTAL

Crystal Preparation

Buprenorphine hydrochloride (140 mg, Galena Co., The Czech Republic) was dissolved in acetone/methanol mixture at 50 °C (6 ml, 2 : 1 v/v). The solution was filtered and allowed to stand overnight. Crystals were filtered out, washed with acetone and dried in air.

Crystal Structure Determination

Buprenorphine hydrochloride, *III*, $C_{29}H_{42}NO_4Cl$, $M_r = 504.16$, space group $P4_32_12$, $a = b = 11.513(2)$ Å, $c = 42.054(8)$ Å, $V = 5\ 574(2)$ Å^3, $Z = 8$, $D_{calc} = 1.201$ g cm^{-3}, μ(MoKα) = 0.17 mm^{-1}, $F(000) = 2\ 176$.

The structure was solved by direct methods. All non-hydrogen atoms were refined anisotropically by block-diagonal least-squares based on the F values. The H atoms were included in the calculated positions with fixed U_{iso} values equivalent to the U_{eq} values of the attached atoms, except for H(-O1), H(-O4) and H(-N) which were localized by the difference synthesis and fixed with $U_{iso} = 0.05$. The terminal C20-H_3 methyl group was found disordered, therefore two carbon positions, designated C201 and C202, were refined. The sum of their occupancy factors was held at 1 and both $U_{iso} = 0.1$. The O3–C201 (O3–C202) distances were restrained using the value of 1.43 Å with the weight corresponding to e.s.d. 0.01 Å (see program CRYSTALS). Flack's enantiopole parameter[15] was calculated by using the equation $|F(\boldsymbol{h},x)|^2 = (1 - x)\ |F(\boldsymbol{h})|^2 + x\ |F(-\boldsymbol{h})|^2$. Relevant data concerning the crystal structure analysis are listed in Table I.

RESULTS AND DISCUSSION

The final positional and thermal parameters of the non-H atoms of *III* are summarized in Table II. The bond distances and angles are listed in Table III. Figure 1 shows the rigid morphine-like cage of the typical opiate T-shape. The title molecule is depicted in Fig. 2. The atom numbering system with the nitrogen atom at position 17 was chosen.

The buprenorphine phenyl ring A (C1,C2,C3,C4,C12,C11) with O1 is almost planar, rings B, C and D are puckered. Ring B (C12,C13,C14,C9,C10,C11) possesses an envelope ^3E conformation [Cremer and Pople's puckering parameters[21] are: Q = 0.553(6) Å, ϕ = 109.9(9)° and θ = 51.6(7)°] with the C14 atom displaced by 0.743(6) Å above the mean plane. Ring C (C8,C14,C13,C5,C6,C7) has a boat $^{2,5}B$ form distorted towards an envelope ^5E [Q = 0.809(7) Å, ϕ = 64.1(4)°, θ = 91.6(4)°] with displacements of the atoms C14 [–0.657(6) Å] and C6 [–0.831(7) Å]. The piperidine ring D (C13,C14,C9,N,C16,C15) adopts a chair $^1C_4$ shape [Q = 0.611(6) Å, ϕ = 101.0(4)°, θ = 8.10(5)°] with C13 –0.689(5) Å below and nitrogen 0.704(5) Å above the plane of the remaining four atoms.

The X-ray analysis gave evidence that there is no significant difference in the ring conformations between the 6,14-ethano bridged buprenorphine molecule, its precursors thevinol[13] and cyanothevinol[14], other 6,14-etheno bridged morphinans[4–12] and

TABLE I
Data collection and refinement parameters

Crystal dimensions	0.8 × 0.8 × 0.9 mm
Diffractometer and radiation used	Enraf–Nonius CAD4, MoKα, λ = 0.71073 Å
Scan technique	ω
Temperature	293 K
No. and θ range of reflection for lattice parameter refinement	20; 19 – 20°
Range of h, k, and l	0 → 12, 0 → 12, 0 → 46
Standard reflections monitored in intervals; intensity fluctuation	120 min; –0.6%
Total number of reflections measured; 2θ range	4 116; 0 – 46°
No. of observed reflections	3 049
Criterion for observed reflections	$I \geq 1.96\ \sigma(I)$
Function minimized	$\Sigma w(\lvert F_o\rvert - \lvert F_c\rvert)^2$
Weighting scheme	$w = [\sigma^2(F_o)]^{-1}$
Parameters refined	316
Values of R, wR and S	0.062; 0.060; 1.96
Ratio of max. least-squares shift to e.s.d. in the last cycle	0.01
Max. and min. heights in final $\Delta\rho$ map	0.48, –0.34 e Å^{-3}
Source of atomic scattering factors	International Tables for X-Ray Crystallography[16]
Programs used	CRYSTALS (ref.[17]), SDP (ref.[18]), SHELXS86 (ref.[19]), PARST (ref.[20])
Computer used	PDP 11/73, PC 386

TABLE II
Final atomic parameters with e.s.d's in parentheses. $U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* \boldsymbol{a}_i \cdot \boldsymbol{a}_j$

Atom	x	y	z	U_{eq}, Å^2
C1	0.2008(1)	0.7139(2)	0.86951(4)	0.0542(7)
O1	0.9856(4)	0.7640(5)	0.9099(1)	0.060(2)
O2	0.7459(3)	0.7690(4)	0.9307(1)	0.050(2)
O3	0.6084(4)	0.8684(5)	0.9842(1)	0.056(2)
O4	0.4031(4)	0.9051(5)	1.0043(1)	0.055(2)
N	0.4204(4)	0.8392(4)	0.8441(1)	0.034(2)
C1	0.8261(6)	0.8970(6)	0.8416(2)	0.057(3)
C2	0.9168(6)	0.8512(6)	0.8607(2)	0.053(3)
C3	0.8994(6)	0.8052(7)	0.8904(2)	0.052(3)
C4	0.7834(6)	0.7979(6)	0.9009(2)	0.045(3)
C5	0.6188(5)	0.7882(6)	0.9309(1)	0.045(3)
C6	0.5778(6)	0.8881(6)	0.9517(2)	0.047(3)
C7	0.4404(5)	0.8836(6)	0.9481(1)	0.040(3)
C8	0.4061(5)	0.9184(5)	0.9136(1)	0.038(2)
C9	0.4940(5)	0.9385(5)	0.8567(1)	0.037(2)
C10	0.6081(5)	0.9493(5)	0.8369(2)	0.046(3)
C11	0.7114(6)	0.8863(5)	0.8519(2)	0.040(3)
C12	0.6973(5)	0.8298(5)	0.8803(2)	0.039(2)
C13	0.5833(5)	0.8105(6)	0.8963(1)	0.035(2)
C14	0.5127(5)	0.9234(5)	0.8924(1)	0.033(2)
C15	0.5176(5)	0.7069(5)	0.8820(1)	0.038(2)
C16	0.4841(5)	0.7256(6)	0.8475(1)	0.040(3)
C18	0.6295(6)	1.0010(7)	0.9391(2)	0.055(3)
C19	0.5846(6)	1.0259(6)	0.9054(2)	0.049(3)
C21	0.3656(6)	0.9444(6)	0.9743(2)	0.043(3)
C22	0.3789(6)	1.0774(6)	0.9738(2)	0.063(3)
C23	0.2306(6)	0.9089(6)	0.9723(2)	0.050(3)
C24	0.1633(6)	0.9760(7)	0.9462(2)	0.064(3)
C25	0.1697(6)	0.9380(6)	1.0039(2)	0.061(3)
C26	0.2169(6)	0.7786(6)	0.9667(2)	0.068(3)
C27	0.3770(6)	0.8527(6)	0.8111(1)	0.047(3)
C28	0.3102(6)	0.9651(6)	0.8054(2)	0.052(3)
C29	0.2001(7)	0.9621(7)	0.7871(2)	0.075(4)
C30	0.2004(7)	0.9875(7)	0.8217(2)	0.066(3)
C201[a]	0.716(1)	0.910(1)	0.9963(3)	0.1[b]
C202[a]	0.595(2)	0.753(1)	0.9988(4)	0.1[b]

[a] Occupation factor refined: 0.555(8) for C201 and 0.445(8) for C202. [b] Fixed.

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

Atoms	Distances	Atoms	Distances
O1–C3	1.372(8)	C8–C14	1.518(8)
O2–C4	1.366(7)	C9–C10	1.559(8)
O2–C5	1.480(7)	C9–C14	1.525(7)
O3–C6	1.431(7)	C10–C11	1.529(8)
O3–C201	1.415(8)	C11–C12	1.367(8)
O3–C202	1.472(9)	C12–C13	1.492(8)
O4–C21	1.410(8)	C13–C14	1.542(8)
N–C9	1.518(7)	C13–C15	1.535(8)
N–C16	1.507(7)	C14–C19	1.542(8)
N–C27	1.486(7)	C15–C16	1.516(8)
C1–C2	1.42(1)	C18–C19	1.535(8)
C1–C11	1.396(8)	C21–C22	1.540(8)
C2–C3	1.373(9)	C21–C23	1.609(9)
C3–C4	1.408(9)	C23–C24	1.551(9)
C4–C12	1.367(8)	C23–C25	1.536(9)
C5–C6	1.521(9)	C23–C26	1.527(9)
C5–C13	1.532(8)	C27–C28	1.524(8)
C6–C7	1.590(8)	C28–C29	1.48(1)
C6–C18	1.526(9)	C28–C30	1.46(1)
C7–C8	1.560(8)	C29–C30	1.481(9)
C7–C21	1.561(8)		

Atoms	Angles	Atoms	Angles
C5–O2–C4	106.4(5)	C13–C12–C4	108.2(6)
C201–O3–C6	120.3(8)	C13–C12–C11	124.7(6)
C202–O3–C6	121.0(9)	C12–C13–C5	102.7(6)
C202–O3–C201	104.0(10)	C14–C13–C5	112.6(5)
C16–N–C9	110.4(4)	C14–C13–C12	106.8(5)
C27–N–C9	115.8(5)	C15–C13–C5	112.0(5)
C27–N–C16	110.0(5)	C15–C13–C12	111.8(5)
C11–C1–C2	119.2(7)	C15–C13–C14	110.6(5)
C3–C2–C1	123.4(7)	C9–C14–C8	117.9(5)
C2–C3–O1	124.8(7)	C13–C14–C8	109.4(5)
C4–C3–O1	118.6(7)	C13–C14–C9	106.1(5)
C4–C3–C2	116.5(7)	C19–C14–C8	104.7(5)
C3–C4–O2	126.9(6)	C19–C14–C9	109.7(5)
C12–C4–O2	114.6(6)	C19–C14–C13	108.9(5)

TABLE III
(*Continued*)

Atoms	Angles	Atoms	Angles
C12–C4–C3	118.3(6)	C16–C15–C13	113.0(6)
C6–C5–O2	115.0(5)	C15–C16–N	109.6(5)
C13–C5–O2	106.4(5)	C19–C18–C6	110.4(6)
C13–C5–C6	109.7(5)	C18–C19–C14	111.5(6)
C5–C6–O3	110.7(6)	C7–C21–O4	108.5(5)
C7–C6–O3	109.3(5)	C22–C21–O4	107.5(6)
C7–C6–C5	103.3(5)	C22–C21–C7	112.4(6)
C18–C6–O3	111.8(6)	C23–C21–O4	105.0(6)
C18–C6–C5	108.8(6)	C23–C21–C7	112.6(5)
C18–C6–C7	112.6(6)	C23–C21–C22	110.3(6)
C8–C7–C6	109.3(5)	C24–C23–C21	113.1(6)
C21–C7–C6	117.9(5)	C25–C23–C21	110.0(6)
C21–C7–C8	113.7(5)	C25–C23–C24	106.0(6)
C14–C8–C7	110.7(5)	C26–C23–C21	110.9(6)
C10–C9–N	110.2(5)	C26–C23–C24	109.1(6)
C14–C9–N	109.6(5)	C26–C23–C25	107.6(6)
C14–C9–C10	114.5(5)	C28–C27–N	113.8(5)
C11–C10–C9	113.4(5)	C29-C28-C27	119.5(6)
C10–C11–C1	124.4(6)	C30–28–C27	120.9(6)
C12–C11–C1	115.2(7)	C30–C28–C29	60.4(5)
C12–C11–C10	119.6(6)	C30–C29–C28	59.1(5)
C11–C12–C4	126.5(6)	C29–C30–C28	60.5(5)

morphine[22] and codeine[23] (see Table IV). Ring B assumes generally enveloped conformation, ring C has the form of a slightly distorted ${}^{2,5}B$ boat and ring D possesses the chair conformation. Only, the 6,14-etheno bridged morphinan molecules containing the 4,5-epoxy bridge have lower values of the total puckering amplitudes for ring C as compared with those without the O-bridge mentioned.

The chair conformation of ring C in butorphanol (without a 6,14-ethano bridge) is an exception.

The absolute configurations at chiral centres C6(*R*), C7(*R*) and C14(*S*) were confirmed by X-ray data as followed from the calculated value of Flack's enantiopole parameter, $x = -0.1(2)$.

The nitrogen atom is protonized and the Cl atom is joined through the enforced N–H...Cl hydrogen bridge [N...Cl = 3.101(5) Å, N–H...Cl = 133°]. Buprenorphine

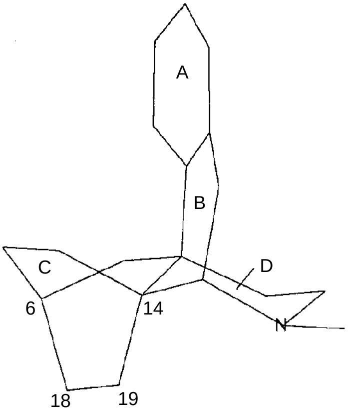

FIG. 1
The typical T-shape of buprenorphine molecule

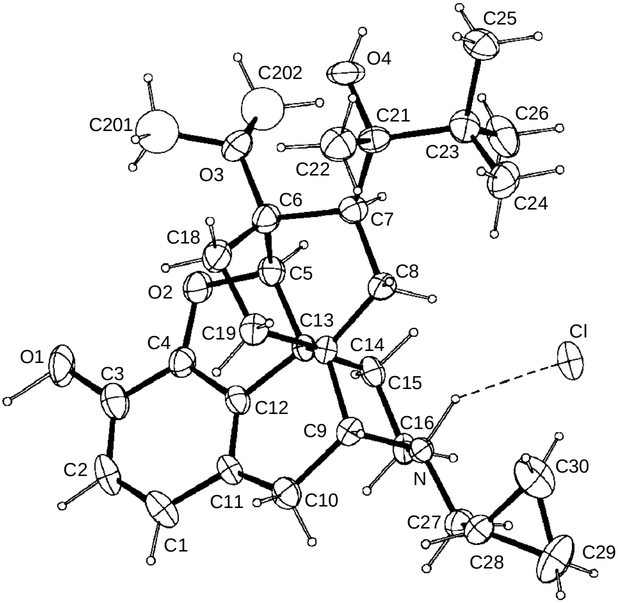

FIG. 2
Ortep drawing of buprenorphine hydrochloride (*III*) with the atom numbering and the N–H...Cl hydrogen bridge (dotted line)

TABLE IV
Comparison of puckering parameters of opiate rings B, C and D for morphine, codeine and some related morphinans

Compound	Ring B			Ring C			Ring D			Ref.
	Q, Å	φ, °	θ, °	*Q*, Å	φ, °	θ, °	*Q*, Å	φ, °	θ, °	
THEBAN[ay]	0.565	109.8	51.3	0.750	57.9	91.3	0.595	128.1	5.5	4
CAWGOW[an]	0.558	137.9	52.1	0.878	59.1	92.0	0.595	41.2	8.4	5
CIDTAK[ay]	0.601	110.4	56.1	0.764	60.6	89.0	0.602	103.9	11.5	6
COMFIT[an]	0.538	137.1	49.7	0.868	57.1	91.2	0.603	52.1	7.0	7
FOMXEK[an]	0.548	136.7	50.1	0.888	56.4	89.3	0.600	48.0	8.1	8
FUGTEG[an]	0.563	120.1	52.9	0.892	68.6	92.0	0.602	112.5	7.3	9
KELBEI[ay]	0.599	115.0	55.6	0.763	59.0	89.1	0.574	80.3	15.4	10
KELBIM[ay]	0.615	113.6	55.0	0.772	58.8	90.0	0.574	82.0	15.2	10
JAGMUZ[ay]	0.601	112.7	54.7	0.768	62.1	89.0	0.582	79.3	13.5	11
JAGNAG[ay]	0.627	112.4	55.1	0.782	59.2	89.8	0.567	88.8	13.8	11
KICPAN[ay]	0.572	109.1	54.7	0.761	59.0	89.3	0.606	83.4	9.5	12
THEVIN[y]	0.607	113.0	55.6	0.772	59.5	89.6	0.597	108.5	8.4	13
CNTHEV[y]	0.587	109.5	54.2	0.775	57.9	89.2	0.606	93.7	8.8	14
BUPRCL[y]	0.553	109.9	51.6	0.809	64.1	91.6	0.611	101.0	8.1	here
BUTART[n]	0.491	116.1	46.5	0.586	99.4	1.5	0.623	106.9	12.3	2
MORPHC[ay]	0.541	111.6	55.4	0.572	71.5	83.4	0.645	86.3	9.7	22
CODEIN[ay]	0.561	117.9	54.3	0.522	73.6	82.5	0.620	79.6	9.3	23

[a] Name of the compound in the Cambridge Structural Database. [yn] Presence of the 4,5-epoxy ring in the molecule, yes/not. THEBAN: 7α-(1-(*R*)-Hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrothebaine hydrobromide, [19-Propylthevinol hydrobromide]. CAWGOW: (–)-7α-Acetyl-3,6-dimethoxy-*N*-methyl-4-phenoxy-6,14-*exo*-ethenomorphinan. CIDTAK: (–)-7α-Acetyl-4,5α-epoxy-3-methoxy-*N*-methyl-6,14-ethenoisomorphinan. COMFIT: (+)-7β-Acetyl-3-methoxy-*N*-methyl-6,14-ethenomorphinan-4-ol. FOMXEK: (+)-8β-Acetyl-3-methoxy-17-methyl-4-phenoxy-6β,14β-ethenomorphinan. FUGTEG: (+)-3-Hydroxy-α,α,17-trimethyl-6β,14β-ethenomorphinan-7β-methanol. KELBEI: 7-(1-Cyclohexyl-1-hydroxyethyl)-16-methyl-6,14-*endo*-etheno-6,7,8,14-tetrahydro-3-oripavinyl methyl ether. KELBIM: 7-(1-Cyclohexyl-1-hydroxyethyl)-16-ethyl-6,14-*endo*-etheno-6,7,8,14-tetrahydro-3-oripavinyl methyl ether. JAGMUZ: 6,14-*endo*-Etheno-7α-(1-hydroxy-1-propyl)-16α-methyl-6,7,8,14-tetrahydrothebaine. JAGNAG: 6,14-*endo*-Etheno-7α-(1-hydroxy-1-propyl)-16α-ethyl-6,7,8,14-tetrahydrooripavine hemihydrate. KICPAN: *N*-(3,6-Dimethoxy-17-methyl-4,5-epoxy-6,14α-etheno-7α-somorphinanylcarbonyl)-L-phenylalanine ethyl ester hydrochloride. THEVIN: 7-(1-Hydroxy-1,2,2-trimethylpropyl)-6,14-etheno-6,7,8,14-tetrahydrothebain. CNTHEV: 17-cyano-7-(1-hydroxy-1,2,2-trimethylpropyl)-6,14-etheno-6,7,8,14-tetrahydro-17-northebain. BUPRCL: (6*R*,7*R*,14*S*)-17-Cyclopropylmethyl-7,8-dihydro-7-[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl-6-*O*-methyl-6,14-ethano-17-nonmorphine hydrochloride. BUTART: (–)-17-Cyclobutylmethyl-3,14β-dihydroxymorphinan hydrogen tartrate. MORPHC: Morphine hydrochloride trihydrate. CODEIN: Codeine.

molecules are connected in the crystal by the linkage O1–H...Cl′($x-1$, y, z) to form infinite chains [O1...Cl′ = 3.058(5) Å, O1–H...Cl′ = 151°].

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