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The Crystal Structure of Morphine Hydrate

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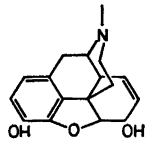
The crystal and molecular structure of the monohydrate of morphine has been determined by X-ray methods. The compound crystallizes in space group $P2_12_12_1$, with $a=7.438(1)$, $b=13.751(3)$, $c=14.901(3)$ Å. The structure was determined by direct methods and refined by full-matrix least-squares methods to an R-value of 0.045 for 1150 observed reflections. The e.s.d.'s for non-hydrogen atoms are 0.005 – 0.006 Å and 0.3 – 0.4° in bond lengths and angles, respectively.

The morphine molecule has the usual T-shape with an angle of 86.6° between the two "planar" parts. The water molecule bridges the phenolic and hydroxylic oxygen atoms through two O–H···O bonds acting as a donor in both. There is an extensive network of hydrogen bonds throughout the molecular crystal, including chains of morphine molecules parallel to the b-axis formed by a strong O–H···N hydrogen bond of 2.635 Å. A common structural feature of narcotic analgetics and phenethylamines is discussed.

Morphine (*1*) is one of the most familiar narcotic analgetics and is widely used as a medicinal agent against severe pain. It has been the central compound in the synthesis and the development of other analgetics, for example methadone (*2*).



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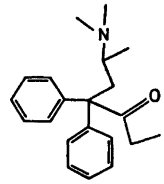

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Intensive structural and conformational studies have been performed on analgetics during the last 25 years to elucidate the mechanism of analgesic action. Analgetics, their receptor(s) and structure activity relationships between these compounds have been reviewed recently,[2] however, a complete understanding of the mechanism of analgesia is still not achieved.

The constitution of the alkaloid (*1*) has been known for 50 years [1] although not confirmed until 1952.[3] The structure of morphine was verified by Mackay *et al.*[4] in 1955 and the absolute configuration established in 1962 by Kartha *et al.*[5] Morphine is a rigid molecule and may serve as a model compound for a large class of narcotic agonists and their antagonists acting on the central nervous system. The model may give valuable information about the receptor topography assuming stereospecific receptor interactions.[3,6]

The present crystallographic investigation was part of a research program on analgetics * particularly for comparison with the structure of (–)-morphine.HCl.$3H_2O$ [7] and methadone base,[8] which has recently been studied in this laboratory.

EXPERIMENTAL

Commercial (–)-morphine hydrate was obtained as transparent, colourless single crystals and a specimen of dimensions $0.2\times0.2\times0.4$ mm[3] was used for the experiments. Photographic investigations indicated orthorhombic symmetry; systematic absences are compatible with space group $P2_12_12_1$. Unit cell dimensions were determined on a SYNTEX $P\bar{1}$ diffractometer with graphite crystal monochromated Mo$K\alpha$-radiation ($\lambda=0.71069$ Å).

Intensities were collected with the $2\theta-\theta$ autocollection program using variable scan rate (2 – 8° min^{-1}). The scan range was from

* Previous paper in this series: E. Bye, *Acta Chem. Scand. B 30* (1976) 323.

0.9° below $2\theta(\alpha_1)$ to 0.9° above $2\theta(\alpha_2)$ and the background was counted for 0.35 times the scan time at each end of the scan range. Three periodically measured reflections showed no systematic variation. E.s.d.'s in the intensities were taken as the square root of the total counts with a 2 % addition (of the net counts) for instrumental instability.

1593 independent reflections with $\sin\theta/\lambda \leq 0.60$ were recorded; 1150 with $I \geq 2\sigma_I$ were considered as observed. All calculations were performed in a CYBER-74 computer utilizing the programs in Ref. 9, except for the phase determination.[10] Atomic form factors were those of Hanson *et al.*[11] for O, N, C and of Stewart *et al.*[12] for H.

CRYSTAL DATA

(−)-Morphine hydrate, $C_{17}H_{19}NO_3.H_2O$, orthorhombic.

$a = 7.438(1)$ Å, $b = 13.751(3)$ Å, $c = 14.901(3)$ Å.

$V = 1524.1$ Å^3, $M = 303.17$, $Z = 4$.

$D_o = 1.31$ g cm^{-3} (flotation), $D_c = 1.32$ g cm^{-3}.

Systematic absences: $h00$, $0k0$, $00l$ for odd indices; space group $P2_12_12_1$.

STRUCTURE DETERMINATION

The structure was determined by direct methods using the program MULTAN.[10] The most probable phase-set based on the 194 highest normalized structure factors ($E \geq 1.42$) gave an E-map which revealed all the 22 non-hydrogen atoms. Isotropic full-matrix least-squares refinement gave $R = 0.10$, and approximate positional parameters of all the hydrogen atoms were calculated from stereochemical considerations, except for the four hydroxyl hydrogen atoms. These were localized in a difference Fourier-map and subsequently all the hydrogen positional parameters were refined. The hydrogen atoms were ascribed B-values equal to the isotropic temperature factors of the heavy atoms to which they are bonded.

The refinement converged at $R = 0.045$ ($R_w = 0.032$) for the 1150 observed reflections and the final parameters are listed in Table 1.

A list of the observed and calculated structure factors may be obtained from this Department.

DISCUSSION

Molecular structure. Bond distances, angles and torsional angles are listed in Tables 2 and 3 with e.s.d.'s as calculated from the correlation matrix. A schematic view of the morphine hydrate unit is given in Fig. 1 which shows the correct absolute configuration of (−)-morphine

Table 1. Final atomic parameters (e.s.d.'s in parenthesis). The anisotropic temperature factors are given by $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + U_{12}hka^*b^* + U_{13}hla^*c^* + U_{23}klb^*c^*)]$.

ATOM	X	Y	Z	U11	U22	U33	U12	U13	U23
C1	.3869(7)	.2821(3)	.0811(3)	.0556(33)	.0427(26)	.0326(24)	-.0013(27)	.0132(27)	-.0085(22)
C2	.3663(6)	.2934(3)	.1266(3)	.0411(29)	.0355(25)	.0561(30)	.0039(25)	.0107(28)	-.0144(24)
C3	.3472(6)	.1777(3)	.2134(3)	.0336(24)	.0288(22)	.0475(26)	-.0045(24)	-.0048(24)	-.0027(23)
C4	.1795(5)	.2401(3)	.2492(3)	.0264(23)	.0301(22)	.0417(26)	-.0027(21)	.0023(23)	-.0033(21)
C5	.2434(6)	.3344(3)	.3554(3)	.0297(24)	.0318(24)	.0344(26)	.0056(22)	.0070(22)	.0019(21)
C6	.1747(6)	.3979(3)	.4078(3)	.0337(27)	.0451(25)	.0294(23)	.0020(25)	.0021(23)	-.0054(22)
C7	.2974(6)	.4569(3)	.3484(3)	.0288(26)	.0430(25)	.0408(28)	-.0047(23)	.0043(24)	-.0093(22)
C8	.2366(6)	.4099(3)	.2759(3)	.0335(25)	.0333(22)	.0343(25)	-.0062(22)	-.0007(22)	.0026(21)
C9	.0131(6)	.5068(3)	.1473(3)	.0400(27)	.0298(24)	.0353(26)	-.0002(23)	-.0003(23)	.0048(23)
C10	.1324(7)	.4442(3)	.0840(3)	.0493(34)	.0534(29)	.0332(25)	.0036(28)	.0040(28)	.0083(25)
C11	.1796(6)	.3439(3)	.1196(3)	.0424(29)	.0497(26)	.0302(24)	-.0011(25)	.0020(24)	-.0066(24)
C12	.1139(6)	.3179(3)	.2023(3)	.0268(23)	.0278(21)	.0337(23)	-.0019(22)	-.0042(20)	-.0046(21)
C13	-.0472(5)	.3773(3)	.2623(3)	.0243(22)	.0276(20)	.0361(26)	.0033(20)	-.0004(21)	-.0043(20)
C14	.0456(5)	.4843(3)	.2468(3)	.0293(23)	.0331(24)	.0332(25)	-.0045(20)	-.0000(22)	-.0079(21)
C15	-.2079(6)	.3648(3)	.2395(3)	.0357(27)	.0338(24)	.0516(30)	-.0042(22)	.0029(25)	-.0016(23)
C16	-.2404(7)	.3998(4)	.1449(4)	.0385(29)	.0462(29)	.0543(33)	-.0064(26)	-.0175(27)	.0074(24)
C17	-.2332(8)	.5345(4)	.0485(4)	.0609(39)	.0521(31)	.0522(33)	.0110(32)	-.0137(31)	.0031(26)
O1	.3838(4)	.1943(2)	.2647(2)	.0355(17)	.0347(16)	.0718(22)	.0110(17)	.0044(19)	.0113(16)
O2	.2792(4)	.3451(2)	.4783(2)	.0467(23)	.0695(23)	.0324(19)	-.0006(18)	-.0036(18)	.0102(16)
O3	.1231(4)	.2385(2)	.3374(2)	.0451(19)	.0349(16)	.0323(16)	.0033(16)	.0062(15)	.0055(13)
O4	.5544(5)	.2269(3)	.4047(2)	.0478(25)	.0809(32)	.0606(28)	.0054(21)	-.0074(21)	.0051(21)
N	-.1620(5)	.4995(2)	.1305(2)	.0398(21)	.0365(19)	.0495(21)	.0010(21)	-.0108(19)	.0007(19)

ATOM	X	Y	Z	B	ATOM	X	Y	Z	B
HC1	.358(5)	.299(2)	.021(2)	4.5	HC2	.474(5)	.157(2)	.108(2)	3.5
HC5	-.078(5)	.321(2)	.386(2)	2.5	HC6	.080(5)	.444(2)	.440(2)	3.0
HC7	.426(5)	.465(2)	.368(2)	3.0	HC8	.319(5)	.548(2)	.243(2)	3.0
HC9	.042(5)	.583(2)	.137(2)	3.0	H1C10	.084(5)	.442(2)	.027(2)	4.0
H2C10	.259(6)	.478(3)	.074(2)	4.0	HC14	-.027(5)	.529(2)	.279(2)	3.0
H1C15	-.276(5)	.405(2)	.284(2)	3.0	H2C15	-.249(4)	.289(2)	.247(2)	3.0
H1C16	-.386(5)	.402(2)	.136(2)	3.0	H2C16	-.204(5)	.347(2)	.099(2)	3.0
H1C17	-.190(5)	.493(2)	-.010(2)	4.5	H2C17	-.368(6)	.548(3)	.044(2)	4.5
H3C17	-.192(6)	.601(3)	.034(2)	4.5	HO1	.292(5)	.063(2)	.381(2)	4.0
HO2	.224(5)	.328(3)	.508(2)	4.0	H104	.529(7)	.195(3)	.366(3)	5.0
H204	.481(6)	.264(3)	.428(2)	5.0					

Table 2. Bond lengths (Å) and angles (°) for morphine hydrate.

DISTANCE	(A)	DISTANCE	(A)	DISTANCE	(A)
C1 - C2	1,385(6)	C1 - C11	1,396(6)	C2 - C3	1,402(5)
C3 - O1	1,359(5)	C3 - C4	1,387(5)	C4 - C12	1,367(5)
C4 - O3	1,381(4)	C5 - O3	1,478(4)	C5 - C6	1,526(6)
C5 - C13	1,553(5)	C6 - O2	1,413(5)	C6 - C7	1,589(6)
C7 - C8	1,313(6)	C8 - C14	1,500(6)	C9 - C10	1,556(6)
C9 - C14	1,535(5)	C10 - C11	1,519(6)	C11 - C12	1,373(5)
C12 - C13	1,509(5)	C13 - C14	1,541(5)	C13 - C15	1,535(6)
C15 - C16	1,526(7)	N - C9	1,476(5)	N - C16	1,475(5)
N - C17	1,476(6)				

ANGLE	( )	ANGLE	( )
C1 - C2 - C3	122,2(4)	C2 - C3 - C4	115,5(4)
C2 - C3 - O1	120,9(4)	O1 - C3 - C4	123,3(4)
C3 - C4 - O3	124,3(4)	C3 - C4 - C12	122,2(4)
C12 - C4 - O3	113,8(3)	C11 - C12 - C4	122,4(4)
C13 - C12 - C4	109,5(3)	C11 - C12 - C13	127,1(4)
C10 - C11 - C12	117,9(4)	C1 - C11 - C12	116,9(4)
C1 - C11 - C10	124,4(4)	C11 - C1 - C2	120,6(4)
C4 - O3 - C5	106,3(3)	O3 - C5 - C6	110,4(3)
C13 - C5 - O3	106,8(3)	C13 - C5 - C6	113,3(3)
C5 - C13 - C12	100,3(3)	C5 - C13 - C14	115,7(3)
C5 - C13 - C15	112,8(4)	C12 - C13 - C14	106,8(3)
C12 - C13 - C15	112,5(4)	C14 - C13 - C15	109,1(3)
C5 - C6 - C7	113,2(3)	C5 - C6 - O2	113,3(3)
O2 - C6 - C7	109,3(4)	C6 - C7 - C8	121,2(4)
C7 - C8 - C14	119,9(4)	C8 - C14 - C13	109,6(4)
C8 - C14 - C9	113,5(4)	C13 - C14 - C9	107,3(3)
C9 - C10 - C11	115,8(4)	C10 - C9 - C14	112,6(4)
N - C9 - C10	114,9(4)	N - C9 - C14	107,7(3)
C13 - C15 - C16	111,5(4)	C15 - C16 - N	111,3(4)
C16 - N - C9	111,9(3)	C17 - N - C9	112,6(4)
C17 - N - C16	110,3(4)		

Table 3. Torsional angles (°).

DIHEDRAL ANGLE	( )	DIHEDRAL ANGLE	( )
O1 - C3 - C2 - C1	-171,9(4)	O1 - C3 - C4 - O3	3,9(6)
O1 - C3 - C4 - C12	175,2(4)	C3 - C4 - C12 - C13	-174,1(3)
C1 - C11 - C12 - C13	172,5(4)	C4 - C12 - C13 - C15	-105,9(4)
C11 - C12 - C13 - C15	85,8(5)	C4 - C12 - C13 - C5	14,2(4)
C11 - C12 - C13 - C5	-154,1(4)	C4 - C12 - C13 - C14	135,0(3)
C11 - C12 - C13 - C14	-33,4(5)	C12 - C13 - C15 - C16	-63,1(5)
C12 - C13 - C14 - C9	60,5(4)	C12 - C13 - C14 - C8	63,1(4)
C12 - C13 - C5 - O3	-21,8(4)	C12 - C13 - C5 - C6	100,2(4)
C2 - C1 - C11 - C10	167,7(4)	C1 - C11 - C10 - C9	-169,4(4)
C11 - C10 - C9 - N	-93,2(5)	C11 - C10 - C9 - C14	30,6(6)
C10 - C9 - N - C17	-62,6(5)	C10 - C9 - N - C16	62,4(5)
C10 - C9 - C14 - C8	58,7(5)	C10 - C9 - C14 - C13	-62,5(4)
C13 - C14 - C9 - N	65,2(4)	C13 - C14 - C8 - C7	-39,1(5)
C4 - O3 - C5 - C13	21,1(4)	C4 - O3 - C5 - C6	-102,8(4)
C14 - C9 - N - C16	-64,0(4)	C14 - C9 - N - C16	64,0(4)
C14 - C9 - N - C17	171,0(3)	C9 - N - C16 - C15	56,6(5)
C13 - C15 - C16 - N	-51,5(5)	C15 - C16 - N - C17	-176,9(4)
C8 - C7 - C6 - O2	168,9(4)	C8 - C7 - C6 - C5	41,5(6)
C7 - C6 - C5 - O3	89,6(4)	C14 - C13 - C5 - O3	-134,5(3)
C11 - C10 - C4 - C5	-176,9(6)	C12 - C11 - C10 - C9	,2(6)
C12 - C11 - C10 - C9	,2(6)		

along with the conventional atomic numbering. The average C–N bond length of 1.475 Å is normal for unprotonated amino groups. The three C–N bond distances are equal in the present case, contrary to the somewhat different $C-N^+$ distances reported for the crystal structures of morphine.HCl.$3H_2O$[7] and naloxone HCl.$2H_2O$.[13,14] There are, however, no obvious chemical reasons for any variation in these C–N bonds.

The C6–O2 distance of 1.415 Å is normal for such a C–O bond as compared to the value 1.457(8) Å found in morphine.HCl.$3H_2O$.[7] Other bond lengths and interbond angles have expected values including the lengthening of the C13–C single bonds and the large variation of the C–C13–C tetrahedral angles (105–116°). This clearly demonstrates the non-bonded interactions around C13, in agreement with earlier reports on acyclic compounds containing a quaternary carbon atom.[15] The C3–O1 bond length (1.361 Å) is slightly shorter than the value most frequently found in phenols. This may be due to the strong O–H···N hydrogen bond (see below).

Strain in the molecular skeleton of morphine is evident from the distortion of the aromatic ring A (Fig. 1). Deviations from some least-squares planes are listed in Table 4. This shows that C12 is displaced by 0.03 Å from plane I.

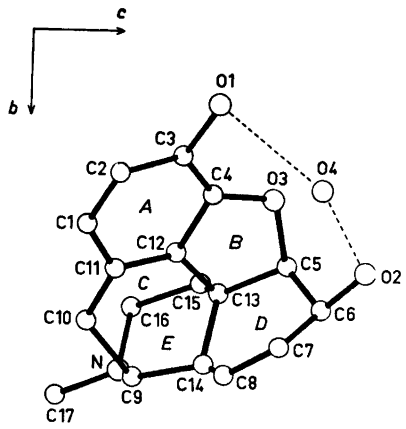


Fig. 1. The morphine hydrate unit.

Rings C and D both contain an unsaturated bond but differ markedly in conformations. The normal halfchair conformer is observed for ring C whereas D has adopted the boat form due to the oxygen-bridge in ring B. The overall conformation may be described by the interplanar angle between the least-squares planes through the atoms of rings A, B, C and D, E, respectively, (planes II and III in Table 4). The angle is 86.6°, as compared to 90.9 and 82.6° in the hydrochlorides of morphine [7] and naloxone,[13] respectively, giving the usual T-shaped molecule.

Table 4. Deviations (Å) of individual atoms from some least-squares planes.

Plane I, Benzene ring[a]			
C1	0.004	C11	0.022
C2	−0.021	C12	−0.031
C3	0.012	C10*	0.316
C4	0.014	C13*	0.130
O1*	0.151		
Plane II, Rings A, B, C			
C1	0.019	O3	−0.097
C2	0.079	C10	0.023
C3	0.008	C11	−0.161
C4	−0.186	C12	−0.315
C5	0.129	C13	−0.366
C9	0.020	C14	0.569
O1	0.233		
Plane III, Rings D, E			
C5	−0.130	C13	−0.342
C6	0.354	C14	0.255
C7	−0.111	C15	0.131
C8	−0.110	C16	−0.189
C9	−0.261	C17	0.043
O2	0.014	N	0.296

[a] Atoms with an asterisk do not define the plane.

It is of interest to compare some conformational features of the bases of morphine and methadone. With a near "cyclic" conformation as observed in methadone [8] the dimethylamino group is (−)-*syn-clinal* relative to the quaternary carbon atom C4, denoted C13 in this paper. A similar conformation is observed in morphine, properly described by the torsional angles C11−C12−C13−C15 (85.8°), C12−C13−C15−C16 (−63.1°), C13−C15−C16−N (−51.5°) and C14−C13−C15−C16 (54.3°). These are close to the corresponding values found in methadone (94.2, −61.5, −68.5, and 64.2°)[8] and the molecular geometry resembles the particular conformation proposed by Beckett *et al.*[6] based on the assumption that methadone interacts with the same receptor as morphine.

Molecular packing. The crystal structure of morphine hydrate is shown in Fig. 2. The alkaloid molecules are linked in chains along the *y*-direction through a strong O1−H···N hydrogen bond of 2.635 Å. This is close to the shortest value listed by Pimentel *et al.*,[16] although somewhat larger than those observed in *N*-(5-chlorosalicylidene)aniline [17] (2.584 Å) and in the alkaloid gerradine [18] (2.59 Å). These are, however, *intramolecular* bridges in donor-acceptor systems with rigid molecular structures. The strong character of the present O−H···N hydrogen bond agrees with the HO1···N distance of 1.57 Å and the O1−HO1 distance of 1.07 Å, which is long for such bonds.

An interesting feature of the present hydrate is the water molecule bridging the hydroxyl and phenolic oxygen atoms, O4 being the donor-atom in both hydrogen bonds. The distance O4···O2 of 2.798 Å is normal for an O···O interaction [16] whereas O4···O1 (3.004 Å) is a rather weak interaction. However, the localization of the H1O4 hydrogen atom in a difference map and the distances and angles given in Table 5 support the assumption of O4···O1 as a hydrogen bond. The interbond angle H1O4−O4−H2O4 of 122° is large compared with the values given by Ferraris *et al.*[20] for hydrates. (H−O−H bond angles are in the range 103−115°.) The water oxygen is

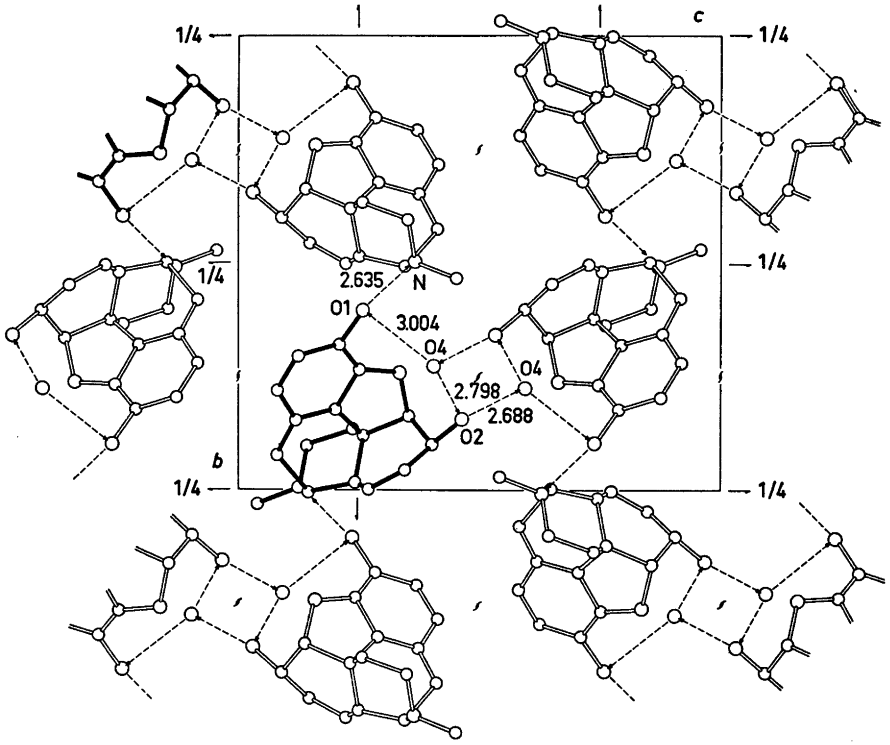


Fig. 2. The crystal structure of morphine hydrate as seen along the *a*-axis.

Table 5. Distances (Å) and angles (°) of the A—H···B hydrogen bonds. The letters (i) and (ii) give the symmetry code of the acceptor, whereas R and R′ denote the atoms which the donor and acceptor are bonded to, respectively.[a]

Atoms	Distances A···B	A—H	H···B	Angles ∠A—H···B
O1—HO1···N(i)	2.635	1.07	1.57	172
O2—HO2···O4(ii)	2.688	0.79	1.91	170
O4—H1O4···O1	3.004	0.74	2.28	166
O4—H2O4···O2	2.798	0.84	1.97	170
σ(average)	0.005	0.04	0.05	4

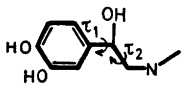
Atoms	Angles ∠R—A—H	∠H···B—R′
C3—O1—HO1···N—C17	115	106
C3—O1—HO1···N—C16		104
C3—O1—HO1···N—C9		111
C6—O2—HO2···O4—H1O4	114	120
C6—O2—HO2···O4—H2O4		110
H2O4—O4—H1O4···O1—C3	122	99
H2O4—O4—H2O4···O2—C6		120

[a] Reference molecule: x,y,z; (i) $-x,y-\frac{1}{2},\frac{1}{2}-z$; (ii) $x-\frac{1}{2},\frac{1}{2}-y,1-z$.

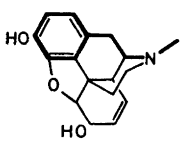
acceptor in a O – H···O hydrogen bond of 2.688 Å from a hydroxyl oxygen (O2) related by a 2-fold screw axis. The water oxygen atom is connected to two different morphine molecules in a hydrogen bond system between O2 and O4 to form a helix running along the *a*-axis (see Fig. 2).

CONCLUDING REMARKS

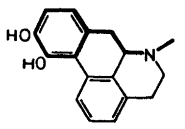
During the last twenty years extensive studies have been performed on structure activity relationships between narcotic analgetics. However, one point seems to have received little attention; there is a phenethylamine framework in the skeleton of morphine. This is exemplified below with adrenaline (*3*) and the heavy lines in morphine (*4*). It is still not known whether the phenethylamines have a maximally extended chain or not when interacting with their receptors. In a fully extended chain, the dihedral angles τ_1 and τ_2 (see *3*) are 90 and 180°, respectively, which is usually observed in crystal structures.[19,21] Apomorphine (*5*) is known to interact with dopamine receptors but lacks any analgesic activity. Giesecke [22] recently reported $\tau_1 =$



3



4



5

$-40°$ and $\tau_2 = 180°$ for apomorphine which means an extended chain, nearly coplanar with the aromatic nucleus. The present corresponding dihedral angles are 0 and $-93°$, respectively, and the two different τ_2 values of morphine and apomorphine, both being quite rigid molecules, may explain the inactivity of the latter as an analgetic.

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