The Crystal Structure of a Narcotic Analgesic: Oxymorphone Hydrate

By Rodney J. Sime,* Max Dobler and Ruth Lewin Sime

Laboratory of Organic Chemistry, Swiss Federal Institute of Technology, 8006 Zurich, Switzerland

Oxymorphone (*N*-methyl-7,8-dihydro-14-hydroxynormorphinone) crystallizes with one water molecule in the space group $P2_12_12_1$, $a = 13\cdot199$ (3), $b = 14\cdot766$ (4), $c = 8\cdot078$ (2) Å and contains four formula units, $C_{17}H_{19}NO_4 . H_2O$. Packing is determined by intermolecular hydrogen bonding and bridging water molecules.

Introduction

Oxymorphone, a narcotic agonist more potent than morphine, is the precursor of two of the most effective narcotic antagonists known: naloxone (Jasinski, Martin & Haertzen, 1967; Maugh, 1972) and naltrexone (Resnick, Volavka, Freedman & Thomas, 1974). Naltrexone, more potent as an antagonist and longer lasting in its effect than naloxone (Martin, Jasinski & Mansky, 1973), differs structurally from nolaxone only by the substitution of an *N*-cyclopropyl group for an *N*-allyl group (Sime, Forehand & Sime, 1975).

Experimental

Oxymorphone forms colourless prisms upon slow crystallization from 50% water/acetone. The crystal used for the intensity measurements was of edge ~0·35 mm. No correction for absorption effects was deemed necessary ($\mu = 1\cdot1$ cm^{-1}). Systematic extinctions and cell dimensions were determined from precession films. The systematic extinctions, $h00$, h odd; $0k0$, k odd; $00l$, l odd, indicate unambiguously space group $P2_12_12_1$. Intensities and accurate cell dimensions were measured with a computer-controlled automatic diffractometer (Enraf–Nonius CAD-4). Cell dimensions, determined by least-squares refinement of eight high-angle reflexions, are $a = 13\cdot199$ (3), $b = 14\cdot766$ (4), $c = 8\cdot078$ (2) Å. The density, measured by flotation in CCl_4/C_6H_6, is 1·340 g cm^{-3}, while the density calculated for $Z = 4$ ($C_{17}H_{19}NO_4H_2O$) is 1·343 g cm^{-3}.

A Mo tube and graphite monochromater were used to produce the Mo $K\alpha$ radiation ($\lambda = 0\cdot71069$ Å) for measurement of intensities by the $\omega/2\theta$ scan method. The net intensity was calculated from $I = C - (B_1 + B_2)(T_c/2T_b)$, in which C is the total recorded count in scan time T_c, and B_1 and B_2 are background counts for time T_b each. The standard deviation in I is $\sigma(I) = [C + (T_c/2T_b)^2(B_1 + B_2)]^{1/2}$. Of the 1606 intensities measured, exactly 1500 had $I > 3\sigma(I)$.

The program *MULTAN* (Germain, Main & Woolfson, 1971) was used to solve the structure and *ORTEP* (Johnson, 1965) to produce the illustrations. Two local unpublished programs written by D. Schwarzenbach were used to process the intensities and backgrounds (program *CADIV*) and to analyse the behaviour of the standard reflexions, to average the intensities of symmetrically equivalent reflexions and to sort and merge reflexions when necessary (program *INTENS*). All other calculations were carried out with the X-RAY 72 series of programs (Stewart, Kruger, Ammon, Dickinson & Hall, 1972).

The full-matrix least-squares program minimizes $\sum w(\Delta F)^2$ in $R_2^2 = \sum w(\Delta F)^2/\sum wF_o^2$, where ΔF is the difference between the magnitudes of F_o and F_c. The weighting factor w was set equal to $1/(\sigma F_o)^2$. The scattering factor for H was taken from Stewart, Davidson & Simpson (1965) and those for the remaining atoms from Cromer & Waber (1965).

Determination and refinement of the structure

The structure was solved by direct methods with the program *MULTAN*, using 242 normalized structure factors ($E > 1\cdot40$). The largest absolute figure of merit (1·08) indicated the correct solution. Three successive Fourier maps permitted location of all the non-H atoms. After calculation of the positions of all H atoms bonded to non-methyl C atoms, the positions of the remaining seven H atoms were located in an $(F_o - F_c)$ Fourier map. The refinement was completed by refining the H atoms (one cycle, isotropic temperature factors, full matrix) and then the non-H atoms (two cycles, anisotropic, full matrix). The final weighted and unweighted R values, based on the 1500 reflexions with $I > 3\sigma(I)$, were 3·6 and 3·9% respectively.† The average shift/sigma value in the final cycle was 16%.

The final positional parameters of the non-H atoms

---

* Address for correspondence: Department of Chemistry, California State University, Sacramento, California 95819, U.S.A.

Table 1. *Positional coordinates of the non-hydrogen atoms* $(\times 10^4)$

Numbers in parentheses here and in subsequent tables are the estimated standard deviations of the last digits.

	x	y	z		x	y	z
C(1)	722 (2)	3743 (2)	11458 (4)	C(13)	143 (2)	3153 (2)	6940 (4)
C(2)	−255 (3)	4116 (2)	11332 (4)	C(14)	1758 (2)	2328 (2)	7120 (5)
C(3)	−773 (2)	4127 (2)	9851 (4)	C(15)	1626 (2)	3948 (2)	6159 (4)
C(4)	−296 (2)	3749 (2)	8503 (4)	C(16)	2576 (2)	4170 (2)	7142 (5)
C(5)	−1 (2)	2990 (2)	6123 (4)	C(17)	4135 (2)	3584 (3)	8223 (6)
C(6)	−430 (2)	2049 (2)	6437 (4)	N	3168 (2)	3346 (2)	7448 (4)
C(7)	312 (3)	1280 (2)	6519 (5)	O(1)	−1742 (1)	4455 (1)	9680 (3)
C(8)	1181 (2)	1498 (2)	7692 (6)	O(2)	−675 (1)	3663 (1)	6903 (3)
C(9)	2600 (2)	2635 (2)	8331 (5)	O(3)	−1341 (2)	1936 (2)	6599 (3)
C(10)	2214 (2)	2887 (2)	10077 (5)	O(4)	2211 (1)	2106 (2)	5568 (3)
C(11)	1201 (2)	3376 (2)	10094 (4)	O(5)	1999 (1)	756 (2)	3141 (3)
C(12)	681 (2)	3422 (2)	8621 (4)				

Table 2. *Anisotropic thermal parameters* $(\times 10^2)$

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	589 (22)	592 (23)	308 (18)	−94 (19)	−63 (19)	−13 (20)
C(2)	546 (22)	472 (21)	377 (20)	−8 (18)	86 (19)	−65 (19)
C(3)	417 (18)	328 (18)	418 (20)	1 (15)	4 (17)	22 (17)
C(4)	450 (19)	365 (18)	311 (18)	52 (15)	−26 (16)	66 (17)
C(5)	413 (19)	589 (24)	349 (19)	74 (18)	−40 (16)	−88 (19)
C(6)	463 (20)	633 (23)	357 (19)	−51 (18)	16 (17)	−156 (20)
C(7)	461 (21)	504 (22)	931 (33)	−48 (18)	−126 (24)	−181 (26)
C(8)	450 (20)	397 (21)	857 (29)	16 (17)	24 (22)	−14 (22)
C(9)	386 (18)	415 (19)	594 (25)	48 (16)	−56 (19)	14 (18)
C(10)	487 (20)	547 (22)	522 (23)	55 (18)	−130 (20)	113 (21)
C(11)	446 (18)	432 (20)	334 (19)	9 (17)	−51 (17)	71 (16)
C(12)	416 (18)	336 (17)	337 (17)	8 (14)	−40 (16)	13 (18)
C(13)	359 (17)	401 (19)	466 (19)	19 (14)	−18 (16)	−20 (16)
C(14)	372 (17)	377 (18)	619 (24)	39 (15)	14 (19)	−43 (19)
C(15)	531 (21)	532 (22)	401 (20)	−19 (18)	−49 (19)	34 (18)
C(16)	532 (21)	514 (20)	556 (24)	−142 (18)	−10 (20)	23 (21)
C(17)	419 (20)	858 (30)	967 (34)	−110 (21)	−133 (24)	−19 (31)
N	364 (15)	531 (17)	646 (20)	−28 (14)	−39 (16)	−20 (17)
O(1)	492 (13)	468 (13)	565 (15)	89 (12)	28 (13)	−74 (13)
O(2)	430 (12)	604 (14)	395 (13)	153 (11)	−93 (11)	−41 (13)
O(3)	375 (12)	904 (19)	695 (17)	−53 (13)	−13 (14)	−62 (18)
O(4)	442 (12)	630 (15)	692 (16)	−55 (12)	133 (13)	−254 (14)
O(5)	678 (15)	558 (13)	619 (16)	−173 (12)	181 (14)	−54 (14)

Table 3. *Positional parameters* $(\times 10^3)$ *and thermal parameters* $(\times 10)$ *for hydrogen atoms*

	x	y	z	B
H(1)	104	374	1248	33
H(2)	−54	442	1228	43
H(5)	1	312	474	68
H(7,1)	−13	69	684	103
H(7,2)	55	121	536	85
H(8,1)	94	159	885	64
H(8,2)	167	95	773	91
H(9)	307	208	842	59
H(10,1)	211	255	1066	62
H(10,2)	268	329	1068	65
H(15,1)	179	379	497	44
H(15,2)	118	453	605	37
H(16,1)	306	461	652	49
H(16,2)	241	451	832	63
H(17,1)	447	305	826	62
H(17,2)	420	347	923	150
H(17,3)	457	404	725	137
H(O1)	−178	483	1039	56
H(O4)	272	265	519	160
H(O5,1)	244	67	221	155
H(O5,2)	219	112	375	70

are in Table 1 and their thermal parameters in Table 2. Thermal and positional parameters of the H atoms are in Table 3. Bond distances and angles are in Tables 4 and 5 respectively. Hydrogen-bond distances and angles are in Table 6.

Table 4. *Interatomic distances* (Å)

O(1)—C(3)	1·374 (4)	C(14)–C(8)	1·516 (4)
C(3)—C(2)	1·378 (5)	C(8)—C(7)	1·522 (5)
C(2)—C(1)	1·406 (5)	C(7)—C(6)	1·501 (5)
C(1)—C(11)	1·381 (5)	C(6)—C(5)	1·522 (5)
C(11)-C(12)	1·375 (4)	C(6)—O(3)	1·220 (4)
C(12)-C(4)	1·380 (4)	C(14)-C(9)	1·548 (5)
C(4)—C(3)	1·376 (4)	C(9)—C(10)	1·545 (5)
O(2)—C(4)	1·392 (4)	C(10)-C(11)	1·520 (4)
O(2)—C(5)	1·475 (4)	C(13)-C(15)	1·539 (5)
C(5)—C(13)	1·547 (4)	C(15)-C(16)	1·521 (5)
C(13)-C(12)	1·494 (5)	N——C(16)	1·467 (4)
C(13)-C(14)	1·547 (4)	N——C(9)	1·474 (4)
O(4)—C(14)	1·427 (4)	N——C(17)	1·465 (4)

Description of the structure

The molecular structure of oxymorphone is shown stereoscopically in Fig. 1, while the packing diagram is shown in Fig. 2. Oxymorphone, derived from thebain (Eddy & May, 1973), may be regarded as a derivative of phenanthrene bridged across the 4,5 positions by oxygen and the 9,13 positions by an ethanamine chain. The latter generates a six-membered piperidine ring, the basic centre of the molecule. The hydroxyl group at position 3 is phenolic, that at position 14 is not. The molecule possesses non-centrosymmetric centres at positions 5, 9, 13 and 14.

The pure narcotic agonist oxymorphone differs structurally from the pure narcotic antagonist naloxone only by substitution of an N-allyl group for an N-methyl group (Karle, 1974; Sime, Forehand & Sime, 1975). In Table 7 some selected distances and angles reported in these two determinations of the structure of naloxone are compared with each other as well as with the oxymorphone data of this paper, with morphine (Gylbert, 1973) and with codeine (Kartha, Ahmed & Barnes, 1962). In Table 7 only oxymorphone is the free base, the others are amine salts. The N–C(17) distance is seen to be considerably shorter in oxymorphone. The shorter N–C distance in the base was also reported in a structure determination of the free base and of the hydrobromide for cyclazocine (Karle, Gilardi, Fratini & Karle, 1968).

Table 5. *Bond angles* (°)

O(1)—C(3)—C(4)	119·3 (3)	C(5)—C(13)-C(14)	117·5 (3)
O(1)—C(3)—C(2)	123·5 (3)	C(12)-C(13)-C(15)	109·2 (3)
C(4)—C(3)—C(2)	117·1 (3)	C(13)-C(14)-C(8)	111·0 (2)
C(3)—C(2)—C(1)	121·5 (3)	C(13)-C(14)-C(9)	105·5 (2)
C(2)—C(1)—C(11)	121·1 (3)	C(8)—C(14)—C(9)	113·9 (3)
C(1)—C(11)-C(12)	116·2 (3)	C(8)—C(14)-O(4)	107·0 (3)
C(10)-C(11)-C(1)	126·6 (3)	C(13)-C(14)-O(4)	110·7 (3)
C(11)-C(12)-C(4)	122·9 (3)	C(9)—C(14)-O(4)	108·8 (2)
C(13)-C(12)-C(11)	127·8 (3)	C(13)-C(15)-C(16)	111·3 (3)
C(13)-C(12)-C(4)	109·2 (3)	C(15)-C(16)-N	110·3 (3)
C(12)-C(4)—C(3)	121·0 (3)	C(16)-N——C(9)	113·7 (2)
C(12)-C(4)—O(2)	111·6 (3)	C(16)-N——C(17)	109·7 (3)
C(3)—C(4)—O(2)	127·4 (3)	C(9)—N——C(17)	114·0 (3)
C(4)—O(2)—C(5)	103·9 (2)	N——C(9)—C(14)	105·5 (3)
O(2)—C(5)—C(13)	104·5 (2)	N——C(9)—C(10)	115·9 (3)
C(6)—C(5)—C(13)	113·8 (3)	C(9)—C(10)-C(11)	114·4 (3)
C(6)—C(5)—O(2)	108·6 (2)	C(5)—C(6)—O(3)	120·6 (3)
C(5)—C(13)-C(12)	98·3 (2)	C(7)—C(6)—O(3)	122·4 (3)
C(5)—C(13)-C(15)	112·9 (3)	C(5)—C(6)—C(7)	117·0 (3)
C(12)-C(13)-C(14)	108·6 (3)	C(6)—C(7)—C(8)	111·1 (3)
C(15)-C(13)-C(14)	109·5 (2)	C(7)—C(8)—C(14)	111·3 (3)

Table 6. *Hydrogen-bonding distances and angles*

1	2	3	1–2	2–3	1–3	Angles (°)	Symmetry equivalents of acceptor atoms
O(5)-H(1)···O(1)			0·9 (1)	1·9 (2)	2·815 (3)	175 (1)	$-\frac{1}{2}-x, 1-y, \frac{1}{2}+z$
O(5)-H(1)···O(4)			0·8 (1)	2·1 (2)	2·830 (3)	162 (1)	$-\frac{1}{2}+x, \frac{1}{2}-y, 1-z$
O(1)-H·····O(5)			0·8 (1)	1·9 (2)	2·648 (3)	174 (1)	$-\frac{1}{2}-x, 1-y, \frac{1}{2}+z$
O(4)-H·····N			1·1 (1)	2·2 (2)	2·693 (4)	106·5 (6)	$x, \quad y, \quad z$
O(4)-H·····O(3)			1·1 (1)	2·0 (2)	2·952 (3)	143·4 (9)	$\frac{1}{2}+x, \frac{1}{2}-y, 1-z$

Column header note: Distances (Å) span columns 1–2, 2–3, 1–3.

Table 7. *A comparison of selected distances and angles in related compounds*

	Naloxone[K]	Naloxone[S]	Oxymorphone	Morphine	Codeine
Distances (Å)					
N——C(17)	1·543	1·568	1·465	1·49	1·506
O(1)—C(3)	1·375	1·363	1·374	1·37	1·399
O(2)—C(4)	1·385	1·377	1·392	1·37	1·370
O(2)—C(5)	1·475	1·455	1·475	1·47	1·472
O(3)—C(6)	1·200	1·156	1·220	1·46	1·427
O(4)—C(14)	1·421	1·372	1·427	–	–
C(1)—C(11)	1·400	1·482	1·381	1·39	1·387
C(9)—C(10)	1·544	1·607	1·545	1·54	1·549
C(17)-C(18)	1·483	1·412	–	–	–
Average e.s.d.	0·004	0·009	0·004	0·01	0·021
Angles (°)					
O(1)-C(3)—C(2)	118·9	115·9	123·5	124·2	127·3
O(1)-C(3)—C(4)	123·4	127·5	119·3	118·3	114·5
C(4)-O(2)—C(5)	104·8	105·8	103·9	106·6	107·7
O(3)-C(6)—C(5)	119·8	118·4	120·6	111·2	112·5
O(3)-C(6)—C(7)	123·1	127·7	122·4	110·0	111·2
O(4)-C(14)-C(8)	110·0*	109·2	107·0	–	–
O(4)-C(14)-C(9)	107·9*	110·5	108·8	–	–
O(4)-C(14)-C(13)	108·3*	110·6	110·7	–	–
Average e.s.d.	0·3	0·6	0·3	0·6	1·2

* Calculated from Karle's (1974) data.

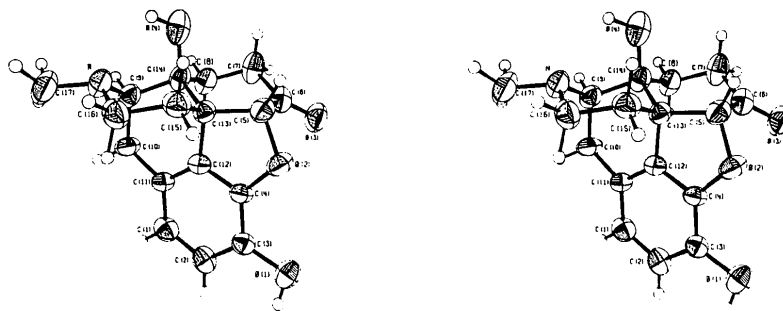(K) Karle (1974). (S) Sime, Forehand & Sime (1975).

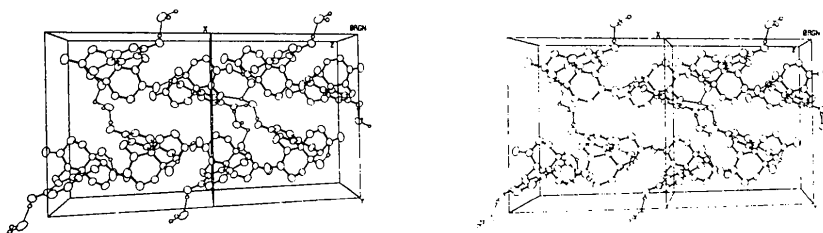Fig. 1. Stereo view of the oxymorphone molecule, $C_{17}H_{19}NO_4$.

Fig. 2. Stereoscopic packing diagram with hydrogen bonds and bridging water molecules indicated.

The O(1)–C(3)–C(2) and O(1)–C(3)–C(4) angles average 117 and 125° in naloxone. In oxymorphone, morphine and codeine the averages are the same but reversed: 125 and 117° respectively. In codeine, O(1) is a methoxy O, so the reversal of the values of these angles apparently must be attributed to packing rather than hydrogen bonding. Although the structure and hydrogen-bonding schemes for naloxone reported by Karle and by us are essentially the same, Karle's data for naloxone should be considered to be more accurate since our structure for naloxone was refined on a small computer, seven atoms at a time.

Packing of the molecules in the unit cell is determined largely by hydrogen bonding. Each water molecule bridges oxymorphone molecules between the two hydroxyl groups. The phenolic hydroxyl H is bonded to the water O atom, while the non-phenolic hydroxyl H is involved in a bifurcated hydrogen bond, intramolecularly to N and intermolecularly to O(3).

References

Cromer, D. T. & Waber, J. T. (1965). *Acta Cryst.* **18**, 104–109.

Eddy, N. B. & May, E. L. (1973). *Science*, **181**, 407–414.

Germain, G., Main, P. & Woolfson, M. M. (1971). *Acta Cryst.* **A27**, 368–376.

Gylbert, L. (1973). *Acta Cryst.* **B29**, 1630–1635.

Jasinski, D. R., Martin, W. R. & Haertzen, C. A. (1967). *J. Pharmacol. Exp. Ther.* **157**, 420–426.

Johnson, C. K. (1965). *ORTEP.* Oak Ridge National Laboratory Report ORNL-3794.

Karle, I. L. (1974). *Acta Cryst.* **B30**, 1682–1686.

Karle, I. L., Gilardi, R. D., Fratini, A. V. & Karle, J. (1969). *Acta Cryst.* **B25**, 1469–1479.

Kartha, G., Ahmed, F. R. & Barnes, W. H. (1962). *Acta Cryst.* **15**, 326–333.

Martin, W. R., Jasinski, D. R. & Mansky, P. A. (1973). *Arch. Gen. Psychiat.* **28**, 784–791.

Maugh, T. H. (1972). *Science*, **177**, 249–250.

Resnick, R. B., Volavka, J., Freedman, A. M. & Thomas, M. (1974). *Amer. J. Psychiat.* **131**, 646–650.

Sime, R. L., Forehand, R. & Sime, R. J. (1975). *Acta Cryst.* **B31**, 2326–2330.

Stewart, J. M., Kruger, G. J., Ammon, H. L., Dickinson, C. & Hall, S. R. (1972). The X-RAY system – version of June 1972. Tech. Rep. TR-192. Computer Science Center, Univ. of Maryland, College Park, Maryland.

Stewart, R. F., Davidson, E. R. & Simpson, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.