X-RAY CRYSTAL STRUCTURES OF POTENT OPIOID RECEPTOR LIGANDS: ETONITAZENE, *cis*-(+)-3-METHYLFENTANYL, ETORPHINE, DIPRENORPHINE, AND BUPRENORPHINE

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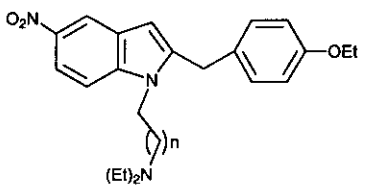
Abstract - As a prelude to molecular modeling and other studies of the newly cloned and expressed μ, δ and κ opioid receptor subtypes, X-Ray crystal structures were determined for etonitazene, (1) cis-(+)-3-methylfentanyl (4) and etorphine (6), three extremely potent opioid agonists. X-Ray crystal structures were also determined for diprenorphine (7), a potent opioid antagonist, and buprenorphine (8), a clinically useful mixed agonist-antagonist. Agonists (1), (4) and (6) are structurally diverse but have similar profiles while (7) and (8) have substantially different pharmacological profiles but differ structurally by only a methyl vs. a *tert*-butyl function. The present results should facilitate studies toward understanding the differences which underlie these observations on a molecular basis.

INTRODUCTION

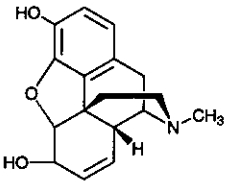
The opioid receptor endorphin system consists of saturable, enantioselective, high affinity μ, δ and κ opioid receptor types (and at least two subtypes of each) located in anatomically well defined areas of the

mammalian central nervous system (CNS) and the numerous endogenous opioid peptides (endorphins) which subserve these receptors.[1-9] This system mediates the analgesic, euphoric and addictive effects of narcotic drugs and regulates numerous physiologic and behavioral functions in its normal state, whereas, its dysfunction likely results in a number of CNS disorders. For example, the level of dopamine in the nucleus acumbens, a brain region thought to involve the human perception of reward (elevated dopamine), has been shown to be under control of tonically opposing endogenous opioid systems.[10-11] Thus, the "opiatergic tone of the CNS" is elevated by endogenous and exogenous μ agonists and depleted by endogenous and exogenous κ agonists. Conversely, exogenous μ and κ antagonists deplete and elevate respectively the opiatergic tone of the CNS, presumably by antagonism of endogenous ligands for these sites. Recently, chronic cocaine use in humans has been recognized to deplete μ opioid receptors and enkephalin mRNA associated with euphoria while increasing κ opioid receptors and the mRNA for dynorphin associated with dysphoria.[12] Collectively, these results indicate chemical alteration of the opiatergic tone by cocaine and suggest that some of the dysphoria associated with cocaine withdrawal in chronic users may result from this alteration. Other studies have suggested a role of δ opioid receptors in the mediation of μ receptor analgesia,[13] the development of morphine tolerance and dependence,[14,15] and in expression of the acute effects of cocaine.[16-18]

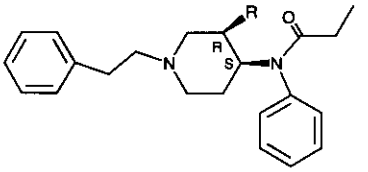
It is clear that production of the pharmacological effects of the opioids, cocaine, and diverse classes of drugs requires drug-receptor interaction as a first step. For the opioid system, it would be ideal to have drugs which act specifically at each of the receptor subtypes with profiles ranging from full agonists to pure antagonists. Such drugs alone or in combination could be used to activate or deactivate opioid receptor subtypes to achieve the desired pharmacological response. Elucidation of the molecular structure of opioid agonists and antagonist-receptor complexes will provide new opportunities for the design of new drugs useful in many clinical situations. Such elucidation will also enable understanding of the mechanism of action of these ligand-receptor systems which will provide new insight into disorders which are now little-understood. The recent elucidation of the amino acid sequences of the μ, δ and κ opioid receptors through cloning techniques and their expression[19-25] are major advances which will enable studies aimed at understanding differences in the binding of opioids with varying pharmacological and receptor subtype binding profiles. For example, the cloned δ receptor appears to require an aspartic acid 95 residue for high affinity agonist binding whereas antagonist binding does not require this residue.[26] Future drug and receptor molecular modeling studies will employ opioid drugs of different structures and pharmacological profiles and utilize their X-ray crystal structures.



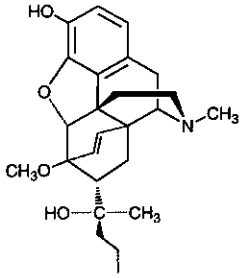
1: n = 1, ETONITAZENE
3: n = 2



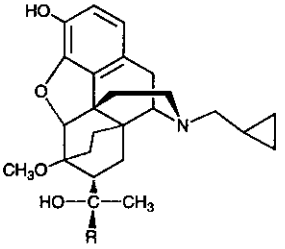
2: MORPHINE



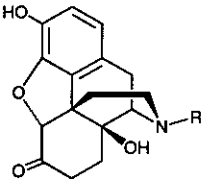
4: R = CH_3
5: R = H, FENTANYL



6: ETORPHINE



7: R = CH_3, DIPRENORPHINE
8: R = t-Bu, BUPRENORPHINE
9: R = *n*-Pr



10: R = CH_3, OXYMORPHONE
11: R = ALLYL, NALOXONE

Here we report the X-ray structures of three extremely potent, structurally diverse opioid agonists, and a mixed agonist-antagonist as well as an antagonist based on the endoethanomorphinan carbon-nitrogen skeleton. The benzimidazole etonitazene (1)[27,28] bears little resemblance to other extremely potent agonists yet is about 1200 times as potent as morphine (2) in mice and was for a time the most potent opioid known in vivo.[29] Recent work[30] has shown that etonitazene is a highly selective μ1 ligand with 976 fold more selectivity and 2500 fold higher affinity than morphine for this receptor subtype. It was also shown[30] to have less affinity than morphine for the δ and κ receptor subtypes. Since etonitazene is the result of a series carefully optimized for potency and very sensitive to small changes in structure, this series should be of significant value in understanding the requirements for receptor binding on a molecular basis. As examples, a 500-fold loss of potency results from replacement of the ethoxy group in etonitazene by hydrogen while addition of one methylene group to the aminoethyl side chain of etonitazene results in a 5000-fold activity decrease of the resulting diethylaminopropyl analog (3).[27] The extremely potent opioid agonist cis-(+)-3-methylfentanyl (4)[31] of known 3R, 4S absolute configuration[32] shows nearly 7000 times the in vivo potency of morphine in the rat. In this case, introduction of the 3-methyl substituent into fentanyl (5) results in a 16 fold potency increase for the cis-(+)-enantiomer which is 120 fold more potent in a tail withdrawal assay than its enantiomer.[31] A recent theoretical study has addressed

the molecular determinants of μ receptor recognition for other fentanyl derivatives.[33] Etorphine (6),[34] also known as M-99, is the third potent agonist examined in this study and is an endoethenooripavine which is approximately 8600-times as potent as morphine in the guinea pig and is utilized in veterinary medicine to sedate large animals. In contrast, the unnatural (+)-etorphine available by the NIH Opiate Total Synthesis[35] does not bind to opioid receptors and shows no opioid activity.[36]

We also determined the crystal structures of diprenorphine (7),[34,37] a potent narcotic antagonist which is used to reverse the effects of etorphine in veterinary practice. Finally, we studied buprenorphine (8),[34,37] a clinically useful mixed agonist-antagonist which is about 25 times as potent as morphine in human postoperative pain. This drug produces much less physical dependence than morphine and has been studied as an agent to detoxify heroin and cocaine addicts. The antinociceptive activity[37] of these structures is exquisitely sensitive to small changes in structure. For example, the ED_{50} of diprenorphine as an agonist exceeds 100 mg/kg in the rat tail pressure test while substitution of a methyl group in the carbinol function of this compound with a *tert*-butyl group affords buprenorphine which is about 75 times more potent than morphine (> 4000 potency increase relative to 7). Furthermore, the corresponding n-propyl derivative 9 is 225 times as potent (> 12,500 fold increase relative to 7) as morphine in this test. Future molecular modeling studies of the compounds described above and others, together with the individual receptors subtypes should provide considerable insight into the drug receptor interactions on a molecular basis which underlie these remarkable differences in activity. Similar studies should be useful in resolution of the long-standing question of why substitution of the *N*-methyl in potent 3-hydroxymorphinan based narcotic agonists with allyl or cyclopropylmethyl generally gives potent morphine antagonists. A familiar example is the replacement[38] of the *N*-methyl in oxymorphone (10) (10 times as potent as morphine) with *N*-allyl which affords the pure narcotic antagonist naloxone (11), a drug extensively utilized clinically as a life saving antidote for narcotic overdose.

EXPERIMENTAL

Data for all 5 compounds was collected on an automated Siemens R3/mV diffractometer equipped with an incident beam monochromator. Lattice parameters were determined from a least-squares fit of the experimentally determined coordinates of 25 high angle reflections. Data were collected in the $\theta/2\theta$ scan mode, with scan a width of $[2\theta(K_{\alpha 1}) - 1.0]$ to $[2\theta(K_{\alpha 2}) + 1.0]°$ and a variable scan rate depending on intensity (except for 1 for which data was collected in Wykoff scan mode with a constant scan rate). Three standard reflections, measured after every 97 new data points, showed only minor random fluctuations indicating that the crystals remained stable during data collection. Data were corrected for Lorentz and

polarization effects. Absorption corrections were applied for compounds (1, 7 and 8) All five structures were solved with the aid of the SHELXTL system of programs[39] and refined, with the full-matrix least-squares program SHELXL-93,[40] on F^2 values using all the unique data. Parameters refined included atom coordinates and anisotropic thermal parameters for all non-H atoms and coordinates for hydroxyl hydrogens. All other H atoms were included in the refinement using a riding model [coordinate shifts of C applied to attached H atoms, C-H distance set to 0.96 Å, H angles idealized, $U_{iso}(H)$ set to 1.1 $U_{eq}(C)$ or, if methyl, 1.2 $U_{eq}(C)$]. Final residuals quoted in Table 1 are R_1 which is the traditional R-factor based on F values and wR_2 which is based on F^2 values For statistical reasons wR_2 is generally about twice as large as R_1. The least-squares program also calculates a 'racemic twinning parameter' [41] as a check on whether or not the absolute configuration could be determined from the experimental data. A value near 0.0 for this parameter indicates the correct hand. Pertinent physical data are presented in Table 1. The results of the X-ray studies on 1, 4, 6, 7 and 8 are illustrated in figures 1, 3 and 4. The figures have been drawn using the experimentally determined coordinates with thermal parameters at the 20% probability level. All atoms in the asymmetric unit have been included. Hydrogen bonds in the asymmetric unit have been shown as dashed bonds. Tables of atomic coordinates, bond distances and angles have been deposited with the Cambridge Crystallographic Data Base.[42]

RESULTS AND DISCUSSION

The structure of etonitazene (1) is illustrated in Figure 1. The molecule is made up of three components; (a) the nitro-benzimidazoyl moiety (planar to within 0.08 Å), (b) the ethoxyphenyl methyl group (planar to within 0.05 Å) and (c) the *N, N*-diethylethanamine chain. Both (b) and (c) are approximately perpendicular to the fused ring system (a) with interplanar angles of 81° between (a) and (b) and 104° between (a) and (c). (b) and (c) are almost parallel to one another (angle between planes is 22°). An earlier X-ray study of etonitazene hydrochloride has been reported[43] in which the compound co-crystallized with one molecule of acetic acid instead of with 4 molecules of water as in the present study. The overall conformation of 1 is the same in both studies, however, in the present study C10b is rotated by approximately 130° about the N10-C10a bond and the ethoxyphenyl group is rotated by approx 15° around the C2-C11 bond. This is not unusual since a large degree of rotational freedom would be expected around these single bonds. There are also differences in the hydrogen bonding schemes of the two structures. Both crystals have an N10-H . . . Cl hydrogen bond but in the earlier study N3 is also an acceptor in a hydrogen bond from an acetic acid molecule while in the present study N3 does not participate in any hydrogen bonding at all. All the remaining hydrogen atoms available as donors are

Table 1. Summary of Crystal Data and Refinement Parameters

Compound	Etonitazene (1)	*cis* -(+)-3-methylfentanyl (4)	Etorphine (6)	Diprenorphine (7)	Buprenorphine (8)
Empirical formula	$C_{22}H_{29}N_3O_3^+ Cl^- \cdot 4H_2O$	$C_{23}H_{31}N_2O^+ NO_3^- \cdot C_3H_8O$	$C_{25}H_{33}NO_3 \cdot 2\,H_2O$	$C_{26}H_{36}NO_4^+ Cl^-$	$C_{29}H_{42}NO_4^+ Cl^-$
Crystal Habit	colorless plate	colorless plate	colorless plate	colorless prism	colorless prism
Crystal system	triclinic	monoclinic	monoclinic	monoclinic	tetragonal
Space group	$P\bar{1}$	$P2_1$	$P2_1$	$P2_1$	$P4_32_12$
a, Å	7.380(2)	10.790(3)	11.011(5)	10.425(2)	11 523(1)
b, Å	9 932(3)	8.126(3)	12.882(3)	10.676(2)	11.523(1)
c, Å	18 60(6)	16 045(4)	16.002(4)	11.637(2)	43.025(7)
α, deg.	78 48(3)	90	90	90	90
β, deg.	81.09(3)	106.61(2)	99 26(3)	107 36(1)	90
γ, deg.	87.66(2)	90	90	90	90
V, Å	1319.9(4)	1348.1(7)	2240(1)	1236.2(4)	5581(1)
Z	2	2	4	2	8
formula weight / F(000)	505.0 / 540	473 6 / 512	429 54 / 928	462.0	504.1 / 2176
ρ(calc), g cm^{-3}	1.271	1.17	1.094	1.241	1.200
Radiation, Wavelength (Å)	(CuKα) 1 54178	(CuKα) 1.54178	(MoKα) 0 71073	(CuKα) 1.54178	(CuKα) 1.54178
Temp., K°	243	243	293	293	293
crystal dim. mm	0.21 x 0.34 x 0.42	0 04 x 0.16 x 0.58	0.05 x 0 40 x 0.64	0.24 x 0 40 x 0.40	0.13x 0 13 x 0.46
μ, absorp. coef., mm^{-1}	1.68	0 65	0.09	1.62	1 47
2θ max (deg)	112	112	45	112	112
Data Collected	3640	2056	3399	1928	4257
Independent data/ Rint.	3399(0.025)	1910 (0.016)	3098 (0.024)	1717 (0.022)	3655 (0.021)
Observed data ($I > 2\sigma I$)	2769	1618	2503	1611,	2691
Absorption Correction	face indexed	none	none	semi-empirical	semi-empirical
Max & Min transmission	0.832 / 0.537			0 897 / 0.748	0.653 / 0.626
Parameters refined	318	311	572	299	333
R-factors - observed data ($R1^a$, $wR2^b$)	0.072, 0 213	0 043, 0 101	0.052, 0.127	0.032, 0.089	0.056, 0.119
R-factors - all data	0084, 0.241	0.056, 0.111	0 074, 0.165	0.035, 0 092	0.086, 0 139
Goodness of fit[c] - all data	1 04	1 08	0.96	1.012	1 01
Absolute structure paramater	not applicable	indeterminate	indeterminate	0 01(2)	-.03(4)
Fourier differences, eÅ-3	0 40, -0.36	0.15, -0.16	0.27, -0.23	0.13, -0.14	0.15, -0.19

[a] $\Sigma|\Delta I/\Sigma|F_o|$ [b] $[\Sigma(w\Delta^2)/\Sigma)wF_o^2)]^{1/2}$ [c] $[\Sigma w(\Delta^2)/(N_o-N_p)]^{1/2}$

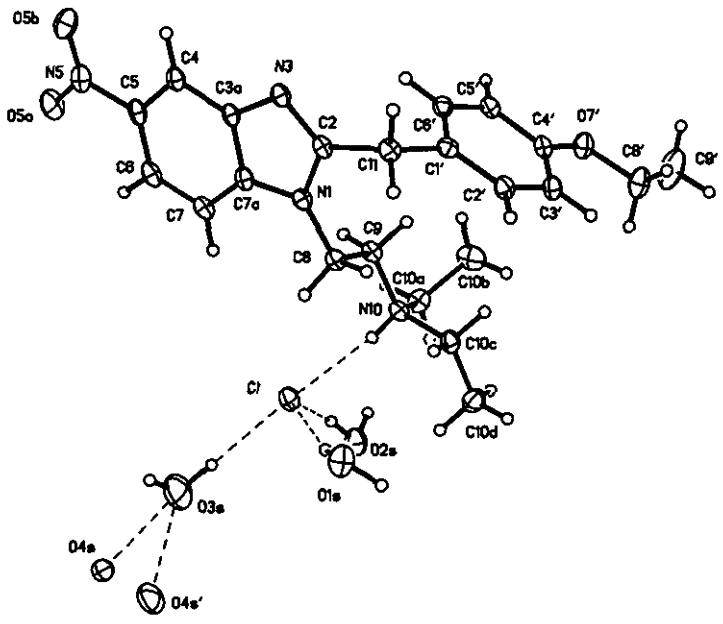


Figure 1: *Molecular structure and numbering scheme* for etonitazene (1)

involved in water . . . Cl or water . . .water interactions (see Table 2). Even though 1 bears no obvious resemblance to morphine it does have intramolecular charge site separations which are close to those found in morphine. In morphine the N1 . . .O1 separation is 7.14 Å and in 1 the N3 . . .O7' separation is 7.11 Å and the N1 . . .O7' distance is close at 6.47 Å. Other N . .O distances in the morphinoids range from 5.11 to 6.47 Å (see Table 3). In 1 there are five intramolecular N . . .O approaches between 5.14 and 6.26 Å. In fact,aligning the N3 . . .O7' vector in 1 with the N17 . . .O1 vector in morphine (Figure 2) shows that the two molecules appear to be able to present, at least in part, a similar charge distribution to a receptor.

The results of the X-ray study on the *cis*-(+)3-methylfentanyl (4) are shown in Figure 3. The heterocyclic ring has a normal chair conformation with the 3-methyl substituent in an axial position. The remaining substituents ae in equatorial positions. The amide group is planar and approximately perpendicular to the *N*-phenyl ring (angle betwen planes of 84°). 4 co-crystallizes with a molecule of 2-propanol and a nitrate ion. The nitrate ion is an acceptor in a two-centered hydrogen bond with N1 (selected H-bond values are listed in Table 2) and from the hydroxyl oxygen of the propanol. A recent theoretical study by Loew *et al.*[33] detailed both the key chemical moieties and the specific steric relationships between them which are

Table 2. Selected Hydrogen Bond Parameters

Donor (D)	Acceptor (A)	D-H (Å)	H...A (Å)	D-H....A (°)	D....A (Å)	
Etorphine (6)						
O1	O1S	0.85	1.83	177.7	2.68	
O4	O2	0.88	1.85	151.4	2.65	Intramolecular
O1'	O2S	0.91	1.83	154.3	2.68	
O4'	O2'	0.88	1.94	135.0	2.64	Intramolecular
O1S	O4	1.03	1.89	177.8	2.87	
O1S	O1'	0.72	2.21	143.8	2.83	
O2S	O1	0.93	2.05	157.1	2.93	
O2S	O4'	0.97	2.15	166.6	2.90	
Diprenorphine (7)						
N17	Cl	0.81	2.34	156.9	3.10	
O1	Cl	0.64	2.45	164.6	3.11	
O4	O2	0.79	2.07	136.5	2.70	Intramolecular
Buprenorphine (8)						
N17	Cl	1.02	2.24	141.3	3.10	
O1	Cl	0.98	2.10	167.4	3.07	
O4	O2	0.87	1.79	155.5	2.60	Intramolecular
cis-(+)-3-Methylfentanyl (4)						
N1	O2a	0.94	2.23	142.8	3.03	
N1	O2b	0.94	2.06	145.0	2.82	
O1S	O2a	0.98	1.93	155.2	2.84	
Etonitazene (1)						
N10	Cl	0.83	2.23	172.3	3.05	
O1S	Cl	0.95	2.28	165.0	3.21	
O2S	Cl	0.95	2.31	155.5	3.20	
O3S	Cl	0.95	2.37	161.1	3.28	

necessary for receptor recognition of the ligands in the fentanyl family of compounds. In 4 the N1 . . .O15 distance (R2) is 5.16 Å, the distance between N1 and the centroid of the ethyl phenyl aromatic ring (R1) is 5.13 Å and the distance between O15 and the centroid of the N-phenyl aromatic ring (R3) is 4.89 Å. The angle between the vectors R1 and R2 is 138.4° and 75.0° between R2 and R3. Both angles and the distances R2 and R3 lie at the mid-point of the ranges predicted for these values for the bioactive conformers of this class of compounds.[33] R1 is at the high end of the predicted range (3.5 - 5.1 Å) of values in Loew's study.

Table 3: Selected charge site separations (in Angstroms) for the morphinoids

Compound	N17-O1	N17-O2	N17-O3	N17-O4	N17-X1*
Morphine[46] (2)	7.14	6.47	5.25		4.59
Oxymorphone[49]	6.92	6.34	5.11		4.44
Naloxone[50] (11)	6.98	6.37	5.14		4.46
Etorphine (6)	7.17	6.20	5.29	6.64	4.61
	7.13	6.19	5.25	6.65	4.59
Diprenorphine (7)	7.15	6.25	5.30	6.65	4.59
Buprenorphine (8)	7.12	6.29	5.28	6.82	4.58

* X1 = centroid of phenolic aromatic ring

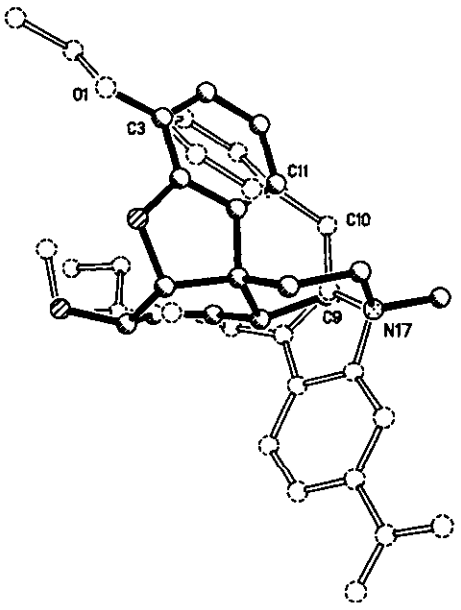


Figure 2: A least-squares fit of etonitazene (1) drawn with hollow bonds to morphine (2) drawn with solid bonds. The atoms in 2 used to do the fit have been labelled.

A similar overall molecular conformation was reported in an X-ray study of fentanyl itself.[44] As already seen in the two X-ray structures of etonitazene the only differences between the X-ray conformer of

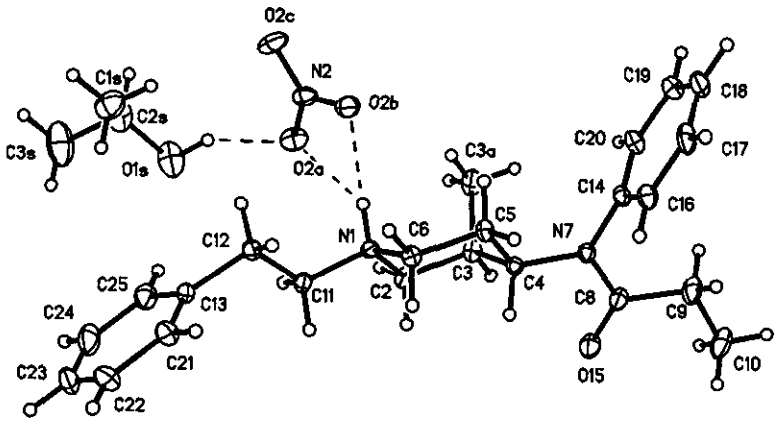


Figure 3: Molecular structure and numbering scheme for *cis*-(+)-3-methyl fentanyl (4)

fentanyl and that found here for the *cis*-(+)-3-methyl derivative 4 are in the rotations of the aromatic rings about their adjacent single bonds. The results of the X-ray study on etorphine (6) are illustrated in Figure 4 (top). It crystallized with two independent molecules of 6 and two water molecules in the asymmetric unit. 6 has a double bond in the fused ring system (C18-C19) as does morphine and the conformation of the ring system which is in common to both molecules is essentially the same (see Figure 5). In 6 there is an intramolecular hydrogen bond formed between the hydroxyl oxygen O4 and the methoxy oxygen O2. The 1-methylbutyl side chain is fully extended with the methyl group below the C7-C20-O4 plane and the remaining three atoms of the butyl group above the plane. The X-ray structure of 1-methoxyetorphine hydrobromide has been reported[44] and while the conformation of the etorphine nucleus is the same as it is in 6, including the intramolecular hydrogen bond, the packing environments are quite different. In the bromide salt the Br^- is an acceptor in a hydrogen bond from $N17^+$ and there are no other possible hydrogen bonds since the hydroxyl hydrogen on O1 has been replaced with a methyl and all remaining intermolecular separations are at least van der Waal's distances. In 6, which did not crystallize as a salt, one would still expect the lone pair on the uncharged N17 atom to be an acceptor in an OH . . .N hydrogen bond as has been seen in the structures of morphine monohydrate,[46] azidomorphine,[47] 14-OH azidomorphine[48] and oxymorphone.[49] However, the N17 atom in 6 does not participate in any hydrogen bonding. The molecules of 6 align themselves in columns such that neighboring columns have either

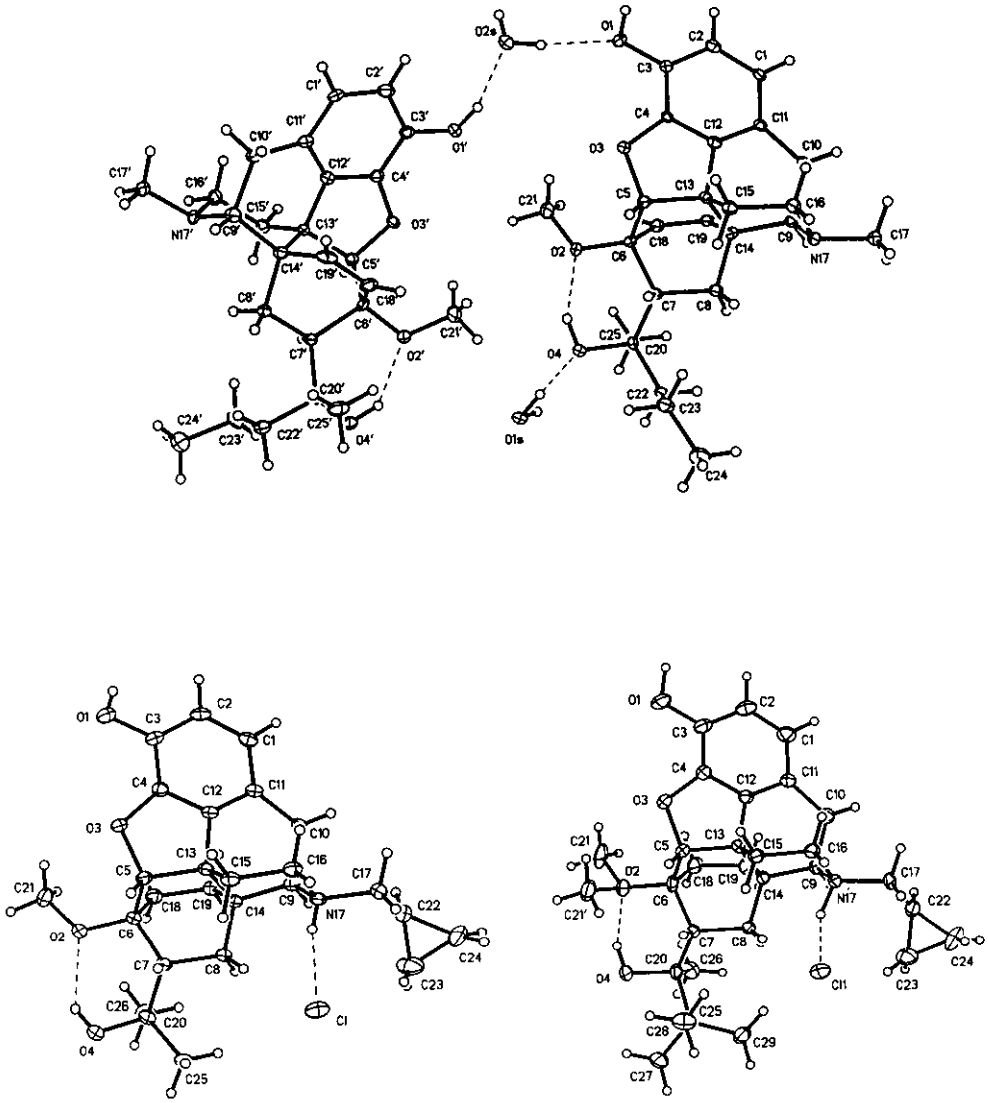


Figure 4: Molecular structure and numbering scheme for etorphine (6 -top), diprenorphine (7 - lower left) and buprenorphine (8 - lower right).

hydrophilic (all the oxygens aligned on the same side of the molecule) - water - hydrophilic interactions or hydrophobic-hydrophobic interactions where the closest approaches between columns of molecules are at least van der Waal's separations (see Figures 4 top and 6). There are "holes" in the unit cell where the halogen atoms normally sit in the salt crystals (Figure 6) but in this packing arrangement the holes are not quite large enough to hold a neutral hydrogen bonding donor (eg a water molecule).

The results of the X-ray studies on diprenorphine (7) and buprenorphine (8) are shown in Figure 4. 7 differs from 6 in that the C18-C19 bond is saturated rather than double, a cyclopropyl ring has been added to the methyl group on N17 and the 3 carbon side chain on C20 has been shortened to a single carbon. 8 differs from 7 only in having the equatorial methyl group on C20 replaced by a *t*-butyl group. As in 6 the conformation of the fused ring systems in 7 and 8 agree quite well with the conformation found for morphine even though the C18-C19 bond has been saturated (Figure 5). The solid state structure of 7 and 8 are almost identical. Both have an intramolecular O4H . . .O2 hydrogen bond, as was also seen in 6, and both form pairs of molecules connected by hydrogen bonds to a common Cl^- ion (Table 2). Even the side chains are similarly oriented and close to what was seen in 6. The presence of the bulky t-butyl group, rather than a methyl, on C20 does alter access to the lone pair on O4 and there is some "closure" of the space available to groups seeking access to N17. In 7 the closest C . . .C approach between the side chain on C20 and the propyl ring is 6.3 Å. In 8 the closest approach is apporximately 1 Å less at 5.2Å.

The 6-14 endo additions to morphine which produced 6, 7 and 8 do not significantly alter most of the charge site separations listed in Table 3. The presence of the O4_H. . .O2 intramolecular hydrogen bond in the three compounds does pull the O-CH3 group away from the 5-membered ring increasing both the O2 . . .O3 and O2 . . . O1 intramolecular distances which are 2.7 and 4.6 Å in morphine to approximately 3.0 and 5.5Å for 6, 7 and 8. When looking at the comparison of the structures of 6, 7 and 8 in Figure 5 the only outstanding difference between 6, which acts only as an agonist, and 7 and 8, both of which have antagonist properties, is the addition of the cyclopropyl group on the *N*-methyl side chain which can have the effect of limiting the size of groups having access to the lone pair on the nitrogen atom. The change from pure antagonist activity in 7 to mixed agonist / antagonist activity in 8 is even more perplexing since the conformation of the two molecules is almost identical in the solid state. The O4-H. . .O2 intramolecular hydrogen bond somewhat limits the conformations available to the bulky side chains on C7. It would be interesting to model these compounds without that constraint to see if it would lead to low energy conformers with differences in the overall shape of the two compounds which may help account for the observed differences in activity. Valuable information has been gained from the combined pharmacological, molecular modeling and X-ray studies of these compounds making it clear that many more opioid receptor ligands should be studied in a similar manner to adequately support structural studies on the newly cloned receptor subtypes.

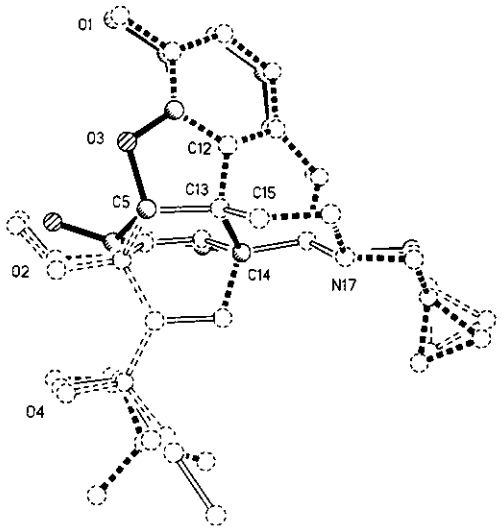


Figure 5 A least-squares fit of molecule 6, 7 and 8 to morphine (solid bonds). The carbon atoms used to perform the fit are labelled as are the oxygen and nitrogen positions

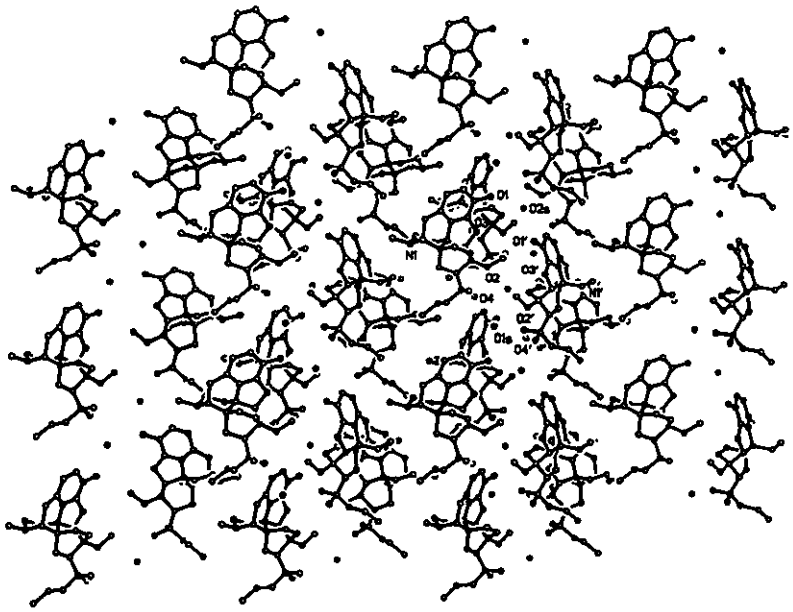


Figure 6 Packing diagram for 6. The figure, showing the hydrophilic-hydrophilic and hydrophobic-hydrophobic interactions between neighboring columns has been drawn looking down the a axis. Oxygen atoms are drawn as ⊙ and nitrogen atoms as ●.

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