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The Crystal Structure of a Narcotic Antagonist: Naloxone Hydrochloride Dihydrate

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Naloxone hydrochloride dihydrate ($C_{19}H_{21}NO_4.HCl.2H_2O$) is orthorhombic, space group $P2_12_12_1$, with $a=7{\cdot}833$ (3), $b=13{\cdot}185$ (5), $c=18{\cdot}569$ (5) Å, $Z=4$. The structure was refined to a weighted R_2 of 0·084 ($R=0{\cdot}091$) for 1156 observed reflections. The structure of naloxone is similar to that of morphine. The two H_2O molecules are involved in hydrogen bonding with naloxone and Cl^-.

Introduction

Although differing only slightly from narcotics such as morphine and heroin, the antagonist naloxone can completely block the analgesic and euphoric effects of agonists. In clinical studies with human subjects, naloxone was found to have essentially no pharmacological properties of its own (Jasinski, Martin & Haertzen, 1967), but it abolishes the euphoria, respiratory depression, nausea, convulsions, and other effects produced by a variety of opiate narcotics. A clinically useful antagonist should not only block the euphorogenic and dependence-producing effects of narcotics, but should have a long duration of action and be free of unpleasant side effects; unfortunately, naxolone has a relatively short duration of action (Fink, Zaks, Sharoff, Mora, Bruner, Levit & Freedman, 1968). On the other hand, the narcotic antagonist cyclozocine, while longer-lasting than naloxone, is accompanied by unpleasant side effects in clinically effective dosages, including dizziness, headaches, and hallucinations (Jaffe & Brill, 1966). Cyclozocine (Karle, Gilardi, Fratini & Karle, 1969), like naloxone, is structurally similar to morphine itself (Mackay & Hodgkin, 1955). In recent years several narcotic antagonists have been clinically tested; their effectiveness generally lies between that of naloxone and cyclozocine (Maugh, 1972).

Experimental

Naloxone hydrochloride dihydrate forms colourless sturdy square prisms. The crystal used for intensity measurements was about 0·3 mm on edge. Systematic extinctions and preliminary cell dimensions were determined from Weissenberg and precession films. The systematic extinctions, $h00$, h odd; $0k0$, k odd; $00l$, l odd, indicate unambiguously space group $P2_12_12_1$.

For accurate determination of cell dimensions and for the collection of intensities, the crystal was transferred to a card-controlled General Electric XRD-5 diffractometer equipped with scintillation counter, pulse-height discriminator, and a quarter-circle Eulerian-cradle goniostat. The X-ray source was Zr-filtered Mo $K\alpha$ radiation ($\lambda=0{\cdot}70926$ Å). Cell constants were determined with a 1·0° take-off angle and hand measurement of 2θ for several high-order reflections. These data were refined by least-squares calculations* to give $a=7{\cdot}833$ (3), $b=13{\cdot}185$ (5), $c=$

* The following computer programs were furnished by A. Zalkin, University of California Radiation Laboratory, Berkeley, California: *LSCELL* (cell dimensions); *MAGPIK* (net intensities); *INCOR* (F_o's); *FORDAP* (Patterson and Fourier functions); *LSLONG* (refinement); *HFINDR* (location of H atoms); *LIST* (table of F_o's and F_c's). The programs, written for a CDC6600 (118K core), were adapted to a CDC3150 (16K core).

18·569 (5) Å. The density, measured by flotation in CCl_4/C_6H_6, is 1·35 g cm^{-3}; the calculated density is 1·385 g cm^{-3} for $Z=4(C_{19}H_{21}NO_4.HCl.2H_2O)$.

The integrated intensity of each reflection was measured by scanning in 2θ across the peak beginning 0·75° below the 2θ value for diffraction of $K\alpha_1$, at a rate of 1° min^{-1} until 2θ reached 0·75° above the 2θ value at which the $K\alpha_2$ beam was diffracted. Ten second background counts were taken with the apparatus stationary, 0·5° below and above the 2θ scan limits. To check for systematic variations in the intensities, two standard reflections were measured after every 50 reflections. No systematic variations were observed. 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 of I is

$$\sigma(I)=[C+(T_c/2T_b)^2(B_1+B_2)+(qI)^2]^{1/2}$$

in which q is an arbitrary factor of 0·04 used to prevent the relative error in large counts from becoming unrealistically small. The standard deviation in a structure factor is given by

$$\sigma(F)=F_o-[F_o^2-S\sigma(I)/\mathrm{Lp}]^{1/2}$$

in which S is the scaling factor in the equation

$$F_o=(SI/\mathrm{Lp})^{1/2}$$

and Lp are the Lorentz and polarization factors. No correction for absorption was made.

The full-matrix least-squares program minimizes $R_2^2=\sum w(\Delta F)^2/\sum wF_o^2$. For each reflection w was $1/F_o$ with the exception that $w=0$ when I(net count) $<\sigma(I)$. Of the 1423 measured reflections, the number for which $w\neq 0$ was 1156. $R=\sum|\Delta F|/\sum|F_o|$ was also calculated. The scattering factor for H was taken from *International Tables for X-ray Crystallography* (1962) and for the remaining atoms from Cromer & Waber (1965).

Table 1. *Anisotropic thermal parameters* ($\times 10^2$)

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	518 (12)	373 (9)	461 (12)	9 (11)	−96 (12)	−37 (11)
N	511 (31)	249 (24)	406 (26)	−23 (22)	11 (28)	−65 (23)
O(1)	385 (28)	477 (30)	319 (27)	80 (28)	−5 (24)	−51 (28)
O(2)	628 (31)	301 (23)	322 (28)	13 (25)	−65 (25)	−22 (24)
O(3)	927 (45)	452 (29)	314 (29)	−131 (34)	−38 (33)	141 (29)
O(4)	248 (23)	343 (26)	417 (24)	21 (27)	79 (24)	−1 (24)
O(5)	729 (41)	384 (27)	479 (34)	−140 (33)	−105 (33)	36 (29)
O(6)	520 (33)	380 (24)	411 (29)	−47 (28)	88 (29)	1 (25)
C(1)	492 (22)	283 (20)	331 (23)	39 (23)	11 (26)	81 (26)
C(2)	490 (27)	285 (25)	353 (33)	40 (29)	48 (25)	−67 (27)
C(3)	162 (26)	317 (29)	485 (27)	−7 (21)	34 (27)	−22 (22)
C(4)	248 (27)	237 (22)	317 (30)	129 (29)	−87 (30)	15 (26)
C(5)	549 (30)	309 (25)	151 (27)	−59 (34)	54 (34)	−40 (30)
C(6)	440 (34)	248 (37)	349 (24)	129 (28)	−100 (25)	93 (25)
C(7)	455 (33)	252 (27)	526 (39)	−116 (32)	129 (31)	−13 (27)
C(8)	363 (30)	356 (25)	461 (34)	−114 (23)	108 (27)	−46 (22)
C(9)	270 (25)	339 (35)	253 (28)	−19 (26)	−85 (22)	−76 (26)
C(10)	335 (24)	338 (27)	354 (25)	41 (21)	−93 (26)	117 (21)
C(11)	325 (32)	289 (28)	452 (28)	−3 (24)	126 (30)	59 (25)
C(12)	159 (30)	213 (22)	426 (28)	−15 (30)	−76 (26)	37 (30)
C(13)	211 (22)	299 (30)	421 (29)	63 (27)	−15 (27)	25 (26)
C(14)	320 (29)	313 (31)	259 (28)	−36 (36)	−42 (33)	8 (29)
C(15)	313 (31)	415 (24)	368 (27)	−31 (29)	−75 (26)	−36 (26)
C(16)	656 (31)	334 (24)	487 (23)	−111 (31)	−1 (31)	−76 (27)
C(17)	773 (38)	337 (23)	328 (24)	−61 (26)	2 (27)	−37 (23)
C(18)	851 (42)	583 (23)	351 (23)	−72 (24)	−2 (27)	154 (27)
C(19)	890 (37)	824 (34)	716 (23)	−355 (29)	−110 (25)	−17 (27)

Table 2. *Positional coordinates of the non-hydrogen atoms* ($\times 10^4$)

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

	x	y	z		x	y	z
Cl	709 (4)	5495 (2)	4738 (1)	C(6)	−1194 (8)	3099 (5)	2331 (4)
N	833 (6)	5483 (4)	246 (3)	C(7)	−1719 (9)	2694 (5)	1597 (3)
O(1)	−2111 (8)	6089 (5)	3754 (3)	C(8)	−2140 (11)	3540 (4)	1064 (3)
O(2)	−26 (8)	4623 (4)	2896 (3)	C(9)	−815 (7)	5045 (6)	410 (3)
O(3)	−1638 (11)	2821 (5)	2890 (3)	C(10)	−2202 (9)	5848 (5)	696 (3)
O(4)	726 (7)	3528 (4)	631 (3)	C(11)	−2064 (9)	5966 (4)	1495 (4)
O(5)	−240 (9)	3267 (4)	4302 (4)	C(12)	−1093 (8)	5390 (4)	1914 (4)
O(6)	4400 (8)	2411 (4)	551 (3)	C(13)	176 (6)	4600 (5)	1622 (3)
C(1)	−3216 (8)	6662 (5)	1890 (4)	C(14)	−476 (6)	4152 (4)	933 (3)
C(2)	−3120 (8)	6666 (4)	2632 (3)	C(15)	−1908 (9)	5103 (4)	1469 (3)
C(3)	−1999 (7)	6028 (4)	3024 (3)	C(16)	1720 (8)	5920 (4)	914 (3)
C(4)	−1086 (6)	5373 (4)	2637 (4)	C(17)	800 (9)	6272 (4)	−385 (4)
C(5)	260 (9)	3936 (5)	2294 (3)	C(18)	−15 (6)	5877 (5)	−1002 (4)
				C(19)	737 (6)	5527 (4)	−1560 (3)

Real and imaginary corrections for anomalous dispersion by the Cl^- ion were from Cromer (1965).

Determination and refinement of the structure

The Cl atom was located from a Patterson function and the C, N, and O atoms of naloxone by successive Fourier syntheses. Two extra persistent peaks were assumed to be O atoms in two molecules of hydrate water. Three cycles of diagonal least-squares refinement with all temperature factors isotropic except that of Cl^- resulted in $R_2=18{\cdot}9$. The anisotropic temperature factors have the form $\exp(-\beta_{11}h^2-\beta_{22}k^2-\beta_{33}l^2-2\beta_{12}hk-2\beta_{13}hl-2\beta_{23}kl)$. In reporting the thermal parameters (Table 1) we have converted β_{ij} to B_{ij} ($4\beta_{ij}=a_i^*a_j^*B_{ij}$).

Because of core limitations the atoms were grouped into sets of seven, and two cycles of full-matrix least-squares calculations were carried out until all atoms had been refined at least once, resulting in $R_2=0{\cdot}112$. Since a difference map at this stage revealed only a few H atoms, their positions were calculated. The positions of the four water H atoms were obtained by assuming that each was located $\frac{1}{3}$ of the hydrogen-bonding distance from the O atom to which it is bonded (Hamilton & Ibers, 1968). With the H atom coordinates held constant, two cycles of full-matrix least-squares refinement on successive groups of seven atoms were repeated several times until no positional parameter shift was more than 6% of its standard deviation (mean = 3·4%). At the end of the refinement, R_2 was 0·084 and R 0·091. The standard deviation of an observation of unit weight was 1·7.

The final positional parameters of the non-hydrogen atoms are given in Table 2 and of the H atoms in Table 3. The latter were calculated from the non-hydrogen atom coordinates about half-way through the last stages of refinement, *i.e.* when R_2 stood at 0·112. Subsequently the positions of the H atoms were held constant at the values reported in Table 3, while the refinement of the remaining atoms proceeded. The thermal parameters of all H atoms were held constant at $B=4{\cdot}0$ Å^2. A list of structure factors is given in Table 4.

Description of the structure

A stereo view (Johnson, 1965) of the cation is shown in Fig. 1. The numbering is the standard numbering for morphine (which follows that for phenanthrene). Naloxone differs structurally from oxymorphone, a narcotic analgesic about ten times as active as morphine, only by substitution of an allyl group for the *N*-methyl group. In addition, naloxone differs from morphine by a keto group instead of an OH group at

Table 3. *Approximate positional parameters* ($\times 10^3$) *for the hydrogen atoms in naloxone hydrochloride dihydrate*

	x	*y*	*z*
H(N)	124	478	15
H(1)	−399	711	162
H(2)	−388	713	289
H(5)	102	341	210
H(7)1	−74	229	143
H(7)2	−269	224	168
H(8)1	−256	313	66
H(8)2	−312	384	132
H(9)1	−66	499	−11
H(9)2	−258	642	40
H(10)	−308	532	69
H(15)1	274	526	184
H(15)2	239	457	115
H(16)1	123	651	115
H(16)2	294	605	82
H(17)1	202	632	−45
H(17)2	37	690	−16
H(18)	−114	598	−138
H(19)1	195	562	−148
H(19)2	78	527	−208
H(O1)	−134	592	385
H(O4)	206	352	59
H(O5)1	−72	311	374
H(O5)2	11	387	456
H(O6)1	435	287	42
H(O6)2	320	217	57

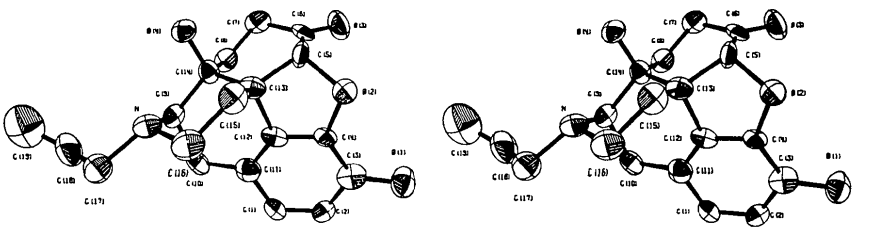

Fig. 1. Stereo view of the cation, $C_{19}H_{22}NO_4^+$.

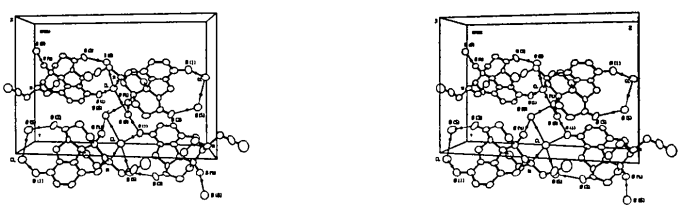

Fig. 2. Stereoscopic packing diagram, with possible hydrogen bonds indicated.

position 6, by an OH group instead of an H atom at position 14, and by saturation of the 7, 8 double bond. While morphine possesses asymmetric centers at positions 5, 6, 9, 13 and 14, position 6 in naloxone (the keto position) is not asymmetric. The 5, 6, 7, 8, 13, 14 ring in naloxone adopts the boat conformation, while this ring in morphine has the chair conformation. Otherwise, the absolute configurations of naloxone and morphine are believed to be the same (Harris, 1971). Bond lengths and angles are shown in Tables 5 and 6.

Packing of the naloxone cation and Cl^- anion is determined primarily by hydrogen bonding. A suggested scheme is shown in Fig. 2. Both OH groups, the NH^+, and two water molecules appear to be involved, for a total of seven hydrogen bonds per asymmetric unit (Table 7). The quaternary N atom has its H atom directed towards the Cl^- ion: $NH^+\cdots Cl^-$ is 3·14 Å, compared with 3·07 Å in cocaine hydrochloride (Gabe & Barnes, 1963) and an average of 3·21 Å (Stout & Jensen, 1968). This bond and the three intramolecular bonds of the N atom are nearly tetrahedrally arranged. In addition, Cl^- is

Table 5. *Interatomic distances* (Å)

O(1)—C(3)	1·363	C(8)—C(7)	1·527
C(3)—C(2)	1·416	C(7)—C(6)	1·520
C(2)—C(1)	1·380	C(6)—C(5)	1·588
C(1)—C(11)	1·482	C(6)—O(3)	1·156
C(11)-C(12)	1·327	C(14)-C(9)	1·549
C(12)-C(4)	1·343	C(9)—C(10)	1·607
C(4)—C(3)	1·332	C(10)-C(11)	1·496
O(2)—C(4)	1·377	C(13)-C(15)	1·537
O(2)—C(5)	1·455	C(15)-C(16)	1·498
C(5)—C(13)	1·527	N———C(16)	1·534
C(13)-C(12)	1·538	N———C(9)	1·446
C(13)-C(14)	1·498	N———C(17)	1·568
O(4)—C(14)	1·372	C(17)-C(18)	1·412
C(14)-C(8)	1·553	C(18)-C(19)	1·277

Table 4. *Observed and calculated structure factors*

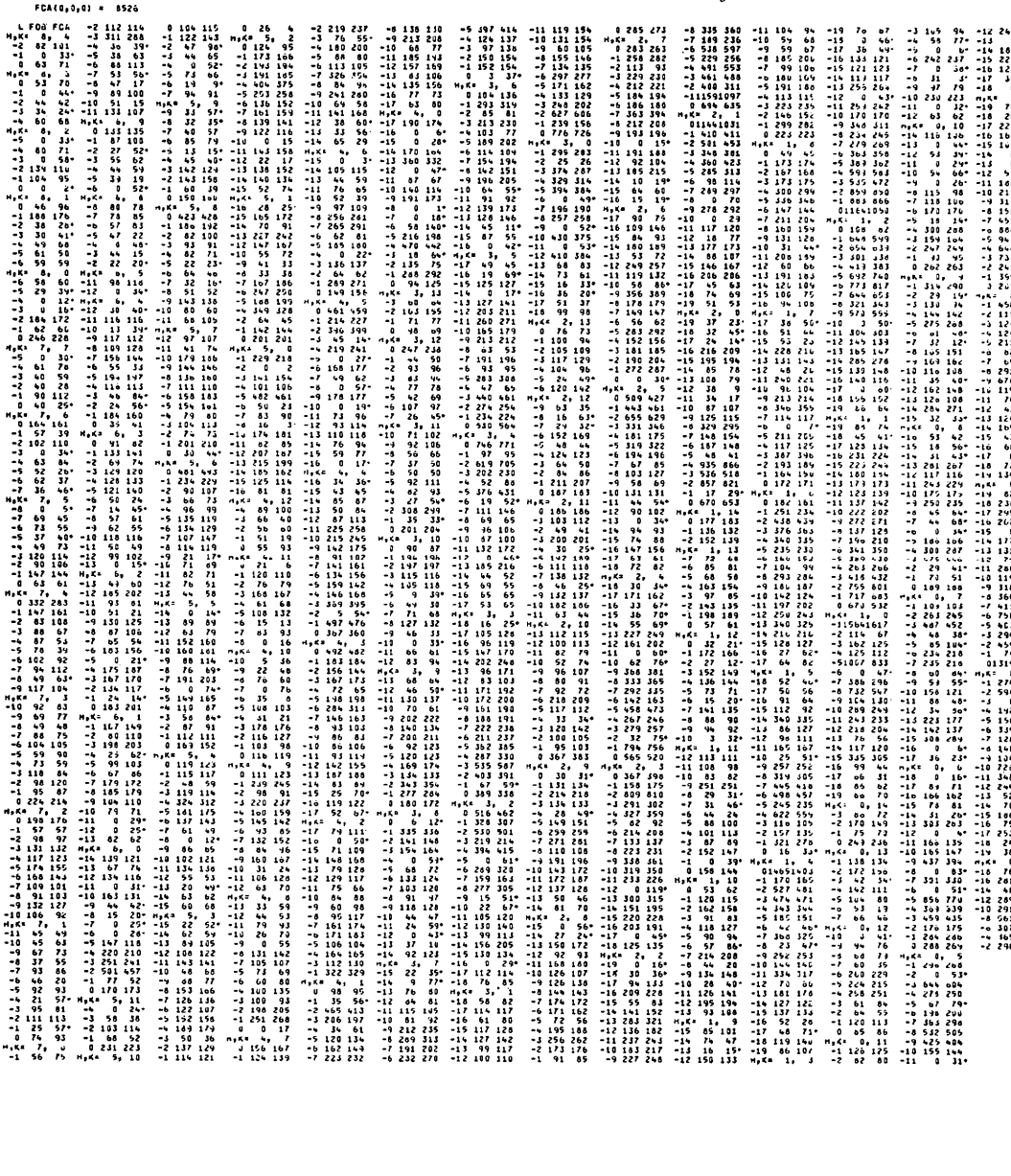

Table 6. *Bond angles* (°)

O(1)—C(3)—C(4)	127·5	C(12)–C(13)–C(15)	110·1
O(1)—C(3)—C(2)	115·9	C(13)–C(14)–C(8)	110·9
C(4)—C(3)—C(2)	116·3	C(13)–C(14)–C(9)	107·1
C(3)—C(2)—C(1)	123·0	C(8)—C(14)–C(9)	110·5
C(2)—C(1)—C(11)	117·6	C(8)—C(14)–O(4)	109·2
C(1)–C(11)—C(12)	114·5	C(13)–C(14)–O(4)	110·6
C(10)–C(11)–C(1)	120·8	C(9)—C(14)–O(4)	108·5
C(11)–C(12)–C(4)	126·7	C(13)–C(15)–C(16)	110·5
C(13)–C(12)–C(11)	123·5	C(15)–C(16)–N	109·3
C(13)–C(12)–C(4)	109·8	C(16)–N——C(9)	112·4
C(12)–C(4)—C(3)	121·7	C(16)–N——C(17)	111·2
C(12)–C(4)—O(2)	111·3	C(9)—N——C(17)	114·0
C(3)—C(4)—O(2)	127·0	N——C(9)—C(14)	106·3
C(4)—O(2)—C(5)	105·8	N——C(9)—C(10)	114·2
O(2)—C(5)—C(13)	105·3	C(9)—C(10)–C(11)	110·4
C(6)—C(5)—C(13)	113·7	C(5)—C(6)—O(3)	118·4
C(6)—C(5)—O(2)	106·8	C(7)—C(6)—O(3)	127·7
C(5)—C(13)–C(12)	97·3	C(5)—C(6)—C(7)	113·6
C(5)—C(13)–C(15)	111·1	C(6)—C(7)—C(8)	112·4
C(12)–C(13)–C(14)	110·3	C(7)—C(8)—C(14)	107·5
C(15)–C(13)–C(14)	108·3	N——C(17)–C(18)	111·6
C(5)—C(13)–C(14)	119·2	C(17)–C(18)–C(19)	125·7

Table 7. *Seven possible hydrogen bonds*

Type	Bond	Distance
Hydroxyl	O(1)–H···Cl^-	2·971 Å
	O(4)–H···O(6)	3·236
Quaternary amine	N^+–H···Cl^-	3·144
Hydrate water	H–O(5)–H···O(3)	2·901
	H–O(5)–H···Cl^-	3·136
	H–O(6)–H···Cl^-	3·148
	H–O(6)–H···O(1)	2·813

surrounded by three more hydrogen bonds, one to the OH group at position 6 (2·97 Å), and the other two to water molecules: $Cl^-\cdots$H–O(5) = 3·14, $Cl^-\cdots$H–O(6) = 3·15 Å. Three of the hydrogen bonds, O(1)···Cl, Cl···O(5) and O(5)···O(3) are in nine-membered rings, in the cavities of which lie the allyl groups. This is somewhat similar to the hydrogen bonding in valinomycin (Duax, Hauptman, Weeks & Norton, 1972) in which two hydrogen bonds are in 13-membered rings, into the cavities of which are directed two free carbonyl groups.

The chemical nature of the 'opiate receptor site' has not yet been established. Generally the receptor is believed to be located in protein, lipoprotein or glycoprotein (Smythies, 1970). Antagonist action is believed to arise from competitive interaction between agonist and antagonist at a single receptor site (Casy, 1971). Recently, a proteolipid fraction from mammalian brain has been isolated (Pert & Snyder, 1973), partially purified (Lowney, Schulz, Lowery & Goldstein, 1974), and in both cases the proteolipid fraction has been convincingly demonstrated to be the specific receptor for naloxone and for a variety of agonists.

It has been proposed that a molecule binds to a receptor by forming hydrophobic bonds with non-polar sites, through ion-pair formation with an anionic site (Beckett, 1956) and through hydrogen bonding with polar sites (Portoghese, 1965). The nature of hydrogen bonding between drug molecules and simple molecules which may be part of the proteolipid has been clearly demonstrated. For example, procaine forms a hydrogen-bonded complex with bis-*p*-nitrophenylphosphate (Sax & Pletcher, 1969), while phenobarbital forms hydrogen-bonded complexes with adenine derivatives (Kim & Rich, 1968). These hydrogen-bonded complexes may be prototypical of the way drugs are bonded to the receptor site.

Naloxone is capable of forming a variety of hydrogen bonds, not only with itself but with water molecules. It may be that bridging water molecules, hydrogen-bonded between drug and receptor, play an important role at the receptor site.

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