

The Crystal Structure of a Narcotic Agonist/Antagonist: Nalbuphine Hydrochloride Dihydrate

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Nalbuphine (*N*-cyclobutylmethyl-7,8-dihydro-14-hydroxynormorphine) crystallizes as the hydrochloride dihydrate in space group $P2_12_12_1$, with $a = 11.576$, $b = 12.336$, $c = 14.658$ Å, $Z = 4$ ($C_{21}H_{27}NO_4 \cdot HCl \cdot 2H_2O$). Packing is largely determined by extensive hydrogen bonding involving H_2O and Cl^- .

Introduction

Nalbuphine, considered potentially useful as an analgesic (Elliot, Navarro & Nomof, 1970), also exhibits antagonist properties. As an antagonist, it is about $\frac{1}{10}$ as effective as naloxone, but as an agonist, it is four to five times as potent as morphine (Jasinski & Mansky, 1972). The dual behaviour of nalbuphine appears consistent with the two receptor theory proposed by Martin (1967). The structure of nalbuphine may be considered intermediate between that of the pure antagonist naloxone (Sime, Forehand & Sime, 1975) and the potent agonist morphine (MacKay & Hodgkin, 1955).

Experimental

Nalbuphine hydrochloride crystallizes from 50% water/ethanol as colourless, bright prisms containing two water molecules of hydration. The crystal used for intensity measurements was about 0.3 mm on edge, and no correction for absorption was made ($\mu = 2.3$ cm⁻¹). Systematic extinctions determined from precession films ($h00$, h odd; $0k0$, k odd; $00l$, l odd) indicate

unambiguously the space group $P2_12_12_1$. Intensities and cell dimensions were determined with an Enraf-Nonius CAD-4 computer-controlled automatic diffractometer. Cell dimensions, determined by least-squares refinement of several high-angle reflexions, are $a = 11.576$, $b = 12.336$, $c = 14.658$ Å. The density, measured by flotation in CCl_4/C_6H_6 , is 1.354, while the density calculated for $Z = 4$ ($C_{21}H_{27}NO_4 \cdot HCl \cdot 2H_2O$) is 1.364 g cm⁻³.

Nalbuphine base was also crystallized, but the crystals obtained were judged to be of too poor quality to justify attempting a structure analysis. The systematic extinction $0k0$, k odd indicates the monoclinic space group $P2_1$ (unambiguously for an optically active compound) with $a = 7.699$, $b = 9.009$, $c = 26.146$ Å and $\beta = 97.84^\circ$. The measured density, 1.33 g cm⁻³, indicates $Z = 4$ (two molecules per asymmetric unit).

An Mo tube and graphite monochromator were used to produce the Mo $K\alpha$ radiation ($\lambda = 0.71069$ Å) for the 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 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 2688 reflexions measured, 1850 had $I \geq 3\sigma(I)$.

The structure was solved with *MULTAN* (Germain,

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

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

| | <i>x</i> | <i>y</i> | <i>z</i> | | <i>x</i> | <i>y</i> | <i>z</i> |
|------|----------|----------|----------|-------|----------|----------|-----------|
| Cl | 2182 (1) | 2139 (1) | 2316 (1) | C(8) | 3729 (3) | 3992 (3) | 7567 (3) |
| N | 2715 (3) | 1299 (2) | 8584 (2) | C(9) | 3545 (4) | 2030 (3) | 8070 (2) |
| O(1) | 1753 (3) | 3393 (2) | 4103 (2) | C(10) | 3996 (4) | 1499 (3) | 7183 (3) |
| O(2) | 1091 (2) | 3796 (2) | 5960 (2) | C(11) | 3356 (4) | 1853 (3) | 6334 (3) |
| O(3) | 1327 (2) | 5839 (2) | 6699 (2) | C(12) | 2410 (3) | 2511 (3) | 6421 (3) |
| O(4) | 2418 (2) | 3430 (2) | 8796 (2) | C(13) | 1883 (3) | 2908 (3) | 7296 (2) |
| O(5) | 4100 (3) | 4308 (3) | -140 (2) | C(14) | 2893 (3) | 3127 (3) | 7942 (2) |
| O(6) | 1412 (3) | 1542 (3) | 247 (2) | C(15) | 1045 (4) | 2081 (3) | 7734 (3) |
| C(1) | 3745 (4) | 1656 (4) | 5445 (3) | C(16) | 1647 (4) | 1055 (3) | 8018 (3) |
| C(2) | 3200 (4) | 2131 (4) | 4700 (3) | C(17) | 3255 (4) | 266 (3) | 8949 (3) |
| C(3) | 2274 (4) | 2855 (4) | 4815 (3) | C(18) | 4377 (4) | 454 (4) | 9435 (3) |
| C(4) | 1907 (4) | 3036 (3) | 5697 (3) | C(19) | 4372 (4) | 1142 (4) | 10302 (4) |
| C(5) | 1211 (4) | 3931 (4) | 6970 (3) | C(20) | 4547 (9) | 174 (7) | 10811 (5) |
| C(6) | 1855 (4) | 4958 (3) | 7184 (3) | C(21) | 4743 (5) | -546 (5) | 10007 (4) |
| C(7) | 3128 (4) | 4880 (4) | 6984 (3) | | | | |

Main & Woolfson, 1971). The stereoscopic illustrations were produced with *ORTEP* (Johnson, 1965). Two local unpublished programs written by D. Schwarzenback 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 $R_2^2 = \sum w(\Delta F)^2 / \sum wF_o^2$ where $\Delta F = F_o - F_c$ and w is a weighting factor described in X-RAY 72 as the 'University of Washington weighting scheme'. The scattering factor for H was taken from Stewart, Davidson & Simpson (1965); for the remaining atoms from Cromer & Waber (1965). Real and imaginary corrections for anomalous dispersion were from Cromer (1965).

Determination and refinement of the structure

MULTAN was used to determine the phases of 344 normalized structure factors ($E > 1.5$). The correct solution was indicated by the largest figure of merit: 1.19. Several successive Fourier maps revealed all non-hydrogen atoms. After calculating the positions of those H bonded to non-methyl C atoms, the positions of the eight remaining H [bonded to N, O(1), O(3), O(4), O(5) and O(6)] were located in a difference map. The refinement was completed by refining the H atoms (one cycle, isotropic temperature factors, full matrix)

and then the non-hydrogen atoms (two cycles, anisotropic, full matrix). These three cycles were then repeated a second time. The final R_w and R based on the 1850 reflexions with $I > 3\sigma(I)$ were 3.5 and 3.8%, respectively.*

The final positional parameters of the non-hydrogen atoms are in Table 1 and their thermal parameters in Table 2. The thermal and positional parameters of the H atoms are in Table 3. Bond distances and angles are in Tables 4 and 5, respectively. Hydrogen-bonding distances are in Table 6.

Description of the structure

Nalbuphine is structurally related to morphine. It differs by the cyclobutylmethyl substitution on N, by the OH substitution at C(14) and by hydrogenation of the C(7), C(8) double bond. Generally, substitution of a larger group for the methyl group on the N of morphine (or similar agonists) tends to bring out antagonist activity (Eddy, 1972). Presence of the C(14)-OH group appears in general to decrease disorienting side effects (Pachter, 1974).

Like morphine, nalbuphine possesses asymmetric centres at positions 5, 6, 9, 13 and 14. The absolute configurations of nalbuphine and morphine are be-

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31268 (23 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

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

| | B_{11} | B_{22} | B_{33} | B_{12} | B_{13} | B_{23} |
|-------|------------|-----------|----------|-----------|-----------|----------|
| Cl | 1119 (11) | 563 (7) | 392 (7) | -81 (9) | 5 (8) | -30 (6) |
| N | 458 (23) | 386 (20) | 331 (18) | -46 (19) | -21 (18) | 29 (17) |
| O(1) | 673 (21) | 624 (21) | 304 (15) | 85 (20) | -10 (17) | 2 (16) |
| O(2) | 399 (16) | 474 (18) | 296 (15) | 101 (16) | -48 (14) | -50 (14) |
| O(3) | 533 (20) | 396 (17) | 501 (18) | 146 (17) | -28 (16) | -30 (16) |
| O(4) | 455 (18) | 453 (17) | 283 (14) | -18 (16) | -4 (14) | -41 (14) |
| O(5) | 609 (23) | 736 (23) | 536 (20) | -62 (19) | 10 (18) | -29 (19) |
| O(6) | 616 (22) | 1082 (30) | 605 (21) | -118 (23) | 68 (19) | -45 (22) |
| C(1) | 400 (26) | 433 (28) | 384 (26) | 43 (24) | 58 (23) | -94 (24) |
| C(2) | 448 (28) | 476 (29) | 320 (24) | -2 (28) | 30 (23) | -71 (25) |
| C(3) | 407 (27) | 397 (25) | 322 (25) | 17 (26) | 62 (23) | 15 (25) |
| C(4) | 312 (24) | 409 (28) | 286 (23) | -29 (24) | 16 (20) | -76 (20) |
| C(5) | 415 (26) | 463 (28) | 258 (22) | 47 (26) | 12 (22) | -32 (22) |
| C(6) | 384 (26) | 402 (26) | 416 (26) | 70 (24) | 23 (24) | -21 (24) |
| C(7) | 449 (29) | 400 (27) | 462 (26) | -97 (25) | 10 (25) | 1 (23) |
| C(8) | 323 (23) | 377 (23) | 390 (24) | -67 (21) | -60 (21) | 45 (22) |
| C(9) | 403 (24) | 375 (26) | 301 (22) | -45 (23) | -32 (20) | 50 (22) |
| C(10) | 468 (28) | 507 (29) | 364 (26) | 116 (25) | 36 (24) | 27 (25) |
| C(11) | 374 (26) | 375 (26) | 347 (24) | 27 (23) | 13 (21) | -21 (21) |
| C(12) | 339 (25) | 418 (25) | 272 (20) | -65 (22) | -48 (22) | -36 (19) |
| C(13) | 305 (22) | 371 (22) | 253 (14) | -57 (23) | 34 (20) | -1 (21) |
| C(14) | 332 (23) | 398 (25) | 319 (21) | 20 (21) | -13 (20) | -13 (20) |
| C(15) | 423 (25) | 434 (25) | 322 (22) | -67 (25) | 16 (22) | -25 (23) |
| C(16) | 515 (30) | 430 (27) | 359 (24) | -140 (26) | -49 (23) | -11 (23) |
| C(17) | 763 (36) | 382 (27) | 347 (26) | 43 (27) | -46 (27) | 19 (23) |
| C(18) | 674 (33) | 509 (31) | 445 (30) | 124 (28) | 8 (28) | 101 (26) |
| C(19) | 669 (34) | 772 (39) | 588 (34) | 54 (31) | -234 (31) | -99 (34) |
| C(20) | 3178 (121) | 1204 (67) | 616 (43) | -390 (79) | -783 (65) | 385 (49) |
| C(21) | 848 (44) | 756 (41) | 844 (44) | 115 (37) | -188 (39) | 393 (38) |

lieved to be the same (Harris, 1971). A stereo view of the cation is shown in Fig. 1.

In the crystal, packing of the cations is determined by a complex hydrogen-bonding network involving bridging water molecules and the Cl^- anion (Fig. 2). Fig. 3 shows in outline the hydrogen-bonding chains

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

| | <i>x</i> | <i>y</i> | <i>z</i> | <i>B</i> |
|---------|----------|----------|----------|----------|
| H(1) | 445 | 119 | 536 | 110 |
| H(2) | 343 | 199 | 403 | 54 |
| H(5) | 36 | 391 | 721 | 69 |
| H(6) | 168 | 507 | 789 | 41 |
| H(7,1) | 320 | 465 | 628 | 21 |
| H(7,2) | 347 | 552 | 706 | 57 |
| H(8,1) | 435 | 361 | 715 | 27 |
| H(8,2) | 413 | 430 | 808 | 54 |
| H(9) | 422 | 222 | 850 | 20 |
| H(10,1) | 485 | 180 | 715 | 72 |
| H(10,2) | 402 | 66 | 726 | 40 |
| H(15,1) | 70 | 246 | 833 | 71 |
| H(15,2) | 46 | 18 | 73 | 53 |
| H(16,1) | 117 | 56 | 854 | 74 |
| H(16,2) | 191 | 61 | 750 | 32 |
| H(17,1) | 263 | 11 | 942 | 44 |
| H(17,2) | 323 | -20 | 832 | 65 |
| N(18) | 497 | 81 | 902 | 102 |
| H(19,1) | 524 | 177 | 1042 | 189 |
| H(19,2) | 377 | 163 | 1039 | 87 |
| H(20,1) | 511 | 6 | 1132 | 152 |
| H(20,2) | 415 | 11 | 1110 | 268 |
| H(21,1) | 430 | -112 | 999 | 110 |
| H(21,2) | 559 | -59 | 1010 | 175 |
| H(O1) | 186 | 298 | 366 | 118 |
| H(O3) | 174 | 653 | 687 | 134 |
| H(O4) | 290 | 368 | 912 | 78 |
| H(O5,1) | 396 | 296 | -37 | 130 |
| H(O5,2) | 387 | 466 | 37 | 114 |
| H(O6,1) | 75 | 138 | 31 | 86 |
| H(O6,2) | 135 | 209 | 32 | 125 |
| H(N) | 242 | 168 | 906 | 46 |

Table 4. *Interatomic distances (\AA)*

| | | | |
|-------------|-------|-------------|-------|
| O(1)—C(3) | 1.377 | C(6)—C(5) | 1.504 |
| C(3)—C(2) | 1.402 | C(6)—O(3) | 1.435 |
| C(2)—C(1) | 1.391 | C(14)—C(9) | 1.560 |
| C(1)—C(11) | 1.400 | C(9)—C(10) | 1.547 |
| C(11)—C(12) | 1.369 | C(10)—C(11) | 1.512 |
| C(12)—C(4) | 1.373 | C(13)—C(15) | 1.547 |
| C(4)—C(3) | 1.381 | C(15)—C(16) | 1.504 |
| O(2)—C(4) | 1.385 | N—C(16) | 1.519 |
| O(2)—C(5) | 1.495 | N—C(9) | 1.519 |
| C(5)—C(13) | 1.557 | N—C(17) | 1.517 |
| C(13)—C(12) | 1.502 | C(17)—C(18) | 1.517 |
| C(13)—C(14) | 1.529 | C(18)—C(19) | 1.529 |
| O(4)—C(14) | 1.418 | C(18)—C(21) | 1.551 |
| C(14)—C(8) | 1.541 | C(19)—C(20) | 1.423 |
| C(8)—C(7) | 1.554 | C(20)—C(21) | 1.493 |
| C(7)—C(6) | 1.506 | | |

Table 5. *Bond angles ($^\circ$)*

| | | | |
|-------------------|-------|-------------------|-------|
| O(1)—C(3)—C(4) | 119.6 | C(13)—C(14)—C(9) | 107.0 |
| O(1)—C(3)—C(2) | 123.5 | C(8)—C(14)—C(9) | 109.9 |
| C(4)—C(3)—C(2) | 116.9 | C(8)—C(14)—O(4) | 112.0 |
| C(3)—C(2)—C(1) | 121.3 | C(13)—C(14)—O(4) | 107.3 |
| C(2)—C(1)—C(11) | 120.8 | C(9)—C(14)—O(4) | 108.1 |
| C(1)—C(11)—C(12) | 116.5 | C(13)—C(15)—C(16) | 112.3 |
| C(10)—C(11)—C(1) | 123.9 | C(15)—C(16)—N | 111.2 |
| C(11)—C(12)—C(4) | 123.2 | C(16)—N—C(9) | 111.2 |
| C(13)—C(12)—C(11) | 126.7 | C(16)—N—C(17) | 111.2 |
| C(13)—C(12)—C(4) | 109.5 | C(9)—N—C(17) | 114.4 |
| C(12)—C(4)—C(3) | 121.0 | N—C(9)—C(14) | 105.6 |
| C(12)—C(4)—O(2) | 113.2 | N—C(9)—C(10) | 112.2 |
| C(3)—C(4)—O(2) | 125.6 | C(9)—C(10)—C(11) | 113.8 |
| C(4)—O(2)—C(5) | 106.7 | C(5)—C(6)—O(3) | 108.9 |
| O(2)—C(5)—C(13) | 105.1 | C(7)—C(6)—O(3) | 111.7 |
| C(6)—C(5)—C(13) | 111.8 | C(5)—C(6)—C(7) | 113.0 |
| C(6)—C(5)—O(2) | 110.3 | C(6)—C(7)—C(8) | 112.1 |
| C(5)—C(13)—C(12) | 101.8 | C(7)—C(8)—C(14) | 113.8 |
| C(5)—C(13)—C(15) | 110.4 | N—C(17)—C(18) | 113.3 |
| C(12)—C(13)—C(14) | 106.0 | C(17)—C(18)—C(19) | 118.4 |
| C(15)—C(13)—C(14) | 109.8 | C(18)—C(19)—C(20) | 88.2 |
| C(5)—C(13)—C(14) | 115.4 | C(19)—C(20)—C(21) | 96.1 |
| C(12)—C(13)—C(15) | 113.2 | C(18)—C(21)—C(20) | 85.0 |
| C(13)—C(14)—C(8) | 112.4 | | |

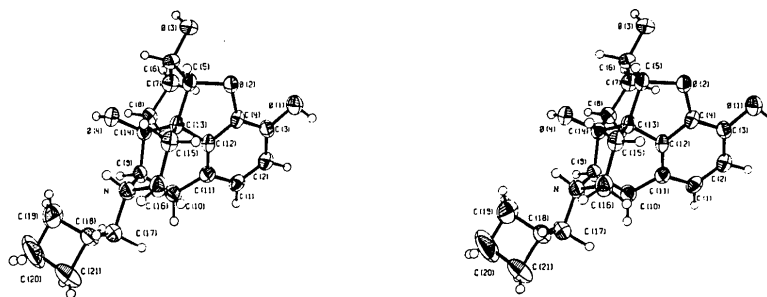


Fig. 1. Stereo view of the cation, $\text{C}_{21}\text{H}_{27}\text{NO}_4^+$.

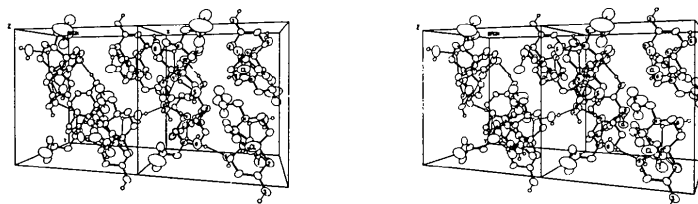


Fig. 2. Stereoscopic packing diagram, with hydrogen bonds indicated.

Table 6. *Hydrogen-bonding distances (Å)*

(a) In Fig. 3

| D | H | A | D-H | H...A | D...A |
|------|----|---------|-----|-------|-------|
| O(1) | -H | ...Cl | 0.8 | 2.3 | 3.083 |
| O(3) | -H | ...Cl | 1.0 | 2.2 | 3.166 |
| N | -H | ...O(6) | 0.9 | 2.1 | 2.882 |
| N | -H | ...O(4) | 0.9 | 2.2 | 2.670 |
| O(4) | -H | ...O(5) | 0.8 | 1.9 | 2.719 |

(b) Other O(5) and O(6)

| | | | | | |
|------|-------|---------|-----|-----|-------|
| O(5) | -H(1) | ...O(1) | 0.9 | 2.3 | 3.201 |
| O(5) | -H(2) | ...O(3) | 0.9 | 2.1 | 2.849 |
| O(6) | -H(1) | ...O(5) | 0.8 | 2.1 | 2.878 |
| O(6) | -H(2) | ...O(4) | 0.7 | 3.0 | 3.363 |

originating from a single cation. The associated bond distances are in Table 6. Though much investigated in recent years, the nature of the forces acting between drug and receptor site has not yet been established. Hydrogen bonding may play a significant role. Just as the water molecules and the Cl⁻ ion form an interface between the drug molecules they connect, so is it likely that a similar interface forms between drug and receptor. Such a drug-receptor interface (DRI) may well facilitate drug-receptor interaction.

The hydrogen-bonding distances agree well with generally accepted average values (Stout & Jensen, 1968) and quite closely with those in naloxone. HCl.2H₂O (Sime, Forehand & Sime, 1975). In naloxone, the Cl⁻ anion is more enclosed, being within hydrogen-bonding distance of O(1), O(5), O(6) and NH⁺, while in nalbuphine, the Cl⁻ is hydrogen bonded only to O(1) and O(3). In naloxone, O(3) is a keto oxygen and does not participate in hydrogen bonding.

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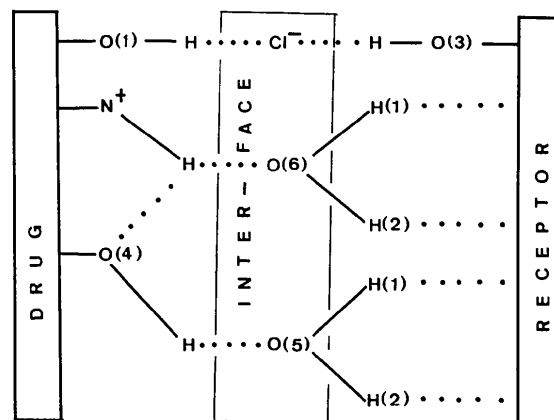


Fig. 3. Schematic diagram of hydrogen bonds from a single drug cation.

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