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Structural Studies of Substituted 6,7-Benzomorphan Compounds. II. Absolute Configurations of (−)-2-Cyclobutylmethyl-5-ethyl-2′-hydroxy-9,9-dimethyl-6,7-benzomorphan Hydrobromide (NCBME) and (−)-5-Ethyl-2′-hydroxy-2,9,9-trimethyl-6,7-benzomorphan Hydrobromide Dihydrate (NME)

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Abstract

NCBME, $C_{21}H_{32}NO.Br$, crystallizes in the orthorhombic space group $P2_12_12_1$ with $a = 11{\cdot}379$ (1), $b = 15{\cdot}314$ (1), $c = 11{\cdot}657$ (1) Å and $Z = 4$. The structure was solved from a Patterson synthesis and refined to $R = 0{\cdot}036$ for 1808 independent reflections. NME, $C_{17}H_{26}NO.Br.2H_2O$, has orthorhombic symmetry, $P2_12_12_1$, with $a = 7{\cdot}146$ (1), $b = 12{\cdot}867$ (1), $c = 19{\cdot}899$ (1) Å and $Z = 4$. The structure was solved from a Patterson synthesis and refined to $R = 0{\cdot}039$ for 1561 independent reflections. The absolute configuration of the two compounds was determined by coordinate inversion. Hydrogen bonds between Br, O and N atoms link the molecules in the crystal. In NME an extensive network of hydrogen bonds is built up by the presence of the two water molecules.

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Introduction

The title structures were solved as part of a study on the structure–activity relationship in the 6,7-benzomorphan series. (−)-2-Cyclobutylmethyl-5-ethyl-2′-hydroxy-9,9-dimethyl-6,7-benzomorphan hydrobromide (US Patent 3764606, 1970), hereafter abbreviated as NCBME,† appears to be an active agonist/antagonist of the narcotic analgesics, whilst (−)-5-ethyl-2′-hydroxy-2,9,9-trimethyl-6,7-benzomorphan hydrobromide dihydrate, abbreviated as NME,† is an active morphinomimetic, with about 20 times the analgesic potency of morphine, and having only weak

† *Chemical Abstracts* name for NCBME: (−)-3-cyclobutylmethyl-6-ethyl-1,2,3,4,5,6-hexahydro-11,11-dimethyl-2,6-methano-[3]-benzazocin-8-ol hydrobromide; for NME: (−)-6-ethyl-1,2,3,4,5,6-hexahydro-3,11,11-trimethyl-2,6-methano-[3]-benzazocin-8-ol hydrobromide dihydrate.

antagonistic activity.* The present compounds can be compared with the structurally related antagonist (−)-gemazocine hydrobromide (Gelders, De Ranter & Schenk, 1979) and with other benzomorphans studied previously (Karle, Gilardi, Fratini & Karle, 1969; Fedeli, Giacomello, Cerrini & Vaciago, 1970; Cochran & Abola, 1975). A reasonable comparison can also be made between NCBME and nalbuphine hydrochloride dihydrate (Sime, Dobler & Sime, 1976), a compound of the morphine series, which also displays a mixed agonist/antagonist effect on the opiate receptor.

Experimental and structure determination

Crystal data are given in Table 1.

Prismatic crystals of NCBME and needle-shaped crystals of NME were obtained from solutions in methanol/water. The space groups of both compounds were determined from photographs which showed orthorhombic symmetry and systematic absences for $h00$, $0k0$ and $00l$ with h, k and l odd respectively. The cell parameters were obtained from a least-squares calculation of the setting angles of 30 reflections measured on a Nonius CAD-4 automatic diffractometer using Cu $K\alpha$ radiation ($\lambda = 1{\cdot}54178$ Å) and a θ–2θ scan.

For NCBME, 1904 reflections were collected, of which 93 were rejected for their low intensities ($I_o < 3\sigma$). They were corrected for Lorentz and polarization factors but not for absorption. A Patterson synthesis and a fourfold superposition (minimum function) gave the coordinates of the non-hydrogen atoms of the molecule. Subsequent isotropic and anisotropic refinements by block-diagonal least-squares methods using the XRAY program system (Stewart, Kruger, Ammon, Dickinson & Hall, 1976) lowered the R value to 0·064. A difference synthesis at this stage gave the coordinates of the H atoms, which were given the isotropic thermal parameters of the atoms to which they were attached. Although not refined, they were included in the following calculations. At an agreement index R of 0·044 the absolute configuration of the molecule was determined by coordinate inversion (Ibers & Hamilton, 1964). Two refinement cycles were performed, one with $\bar{x},\bar{y},\bar{z}$ yielding $R = 0{\cdot}048$ and one with the appropriate coordinates resulting in $R = 0{\cdot}039$, so that the exact structure could be accepted even at the 0·5% level of significance (Hamilton, 1965). Three reflections suffering from extinction were eliminated and the final refinement yielded an R value of 0·036 for 1808 contributing reflections. The atomic coordinates of the non-hydrogen atoms are given in Table 2;* the positional parameters of the H atoms with their isotropic temperature factors are given in Table 3.

For NME, 1699 reflections were collected of which 133 were rejected because of their low intensities ($I_o < 3\sigma$). They were also corrected for Lorentz and polarization factors but not for absorption. The structure of NME was solved by an identical procedure as for NCBME. At an agreement index R of 0·045 the absolute configuration of the molecule was determined by coordinate inversion (Ibers & Hamilton, 1964). Two refinement cycles were performed, one with $\bar{x},\bar{y},\bar{z}$

* Private communication from ACF Chemiefarma NV.

Table 1. *Crystal data*

	NCBME	NME
Formula	$C_{21}H_{32}NO.Br$	$C_{17}H_{26}NO.Br.2H_2O$
M_r	394·41	376·34
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell a	11·379 (1) Å	7·146 (1) Å
b	15·314 (1)	12·867 (1)
c	11·657 (1)	19·899 (1)
V	2031 Å^3	1830 Å^3
Z	4	4
D_c	1·289 Mg m^{-3}	1·366 Mg m^{-3}
D_m	1·283	1·362
$F(000)$	832	792
μ(Cu $K\alpha$)	3·043 mm^{-1}	3·329 mm^{-1}

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34129 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Atomic coordinates for the non-hydrogen atoms of NCBME with e.s.d.'s in parentheses*

	x	y	z
Br	0·3607 (0)	−0·0920 (0)	0·7652 (0)
O(2′)	0·5166 (3)	−0·1478 (2)	−0·0171 (3)
C(1)	0·5194 (4)	0·0553 (3)	0·4718 (4)
N	0·4099 (3)	0·0175 (2)	0·5290 (3)
C(3)	0·3608 (4)	−0·0573 (3)	0·4634 (3)
C(4)	0·4560 (4)	−0·1259 (3)	0·4475 (4)
C(5)	0·5706 (4)	−0·0929 (3)	0·3946 (3)
C(6)	0·5422 (4)	−0·0598 (3)	0·2733 (4)
C(7)	0·5020 (4)	0·0254 (2)	0·2572 (4)
C(8)	0·4916 (4)	0·0921 (3)	0·3525 (4)
C(9)	0·6166 (4)	−0·0146 (3)	0·4681 (4)
C(10)	0·6561 (5)	−0·1726 (3)	0·3940 (4)
C(11)	0·7735 (5)	−0·1684 (4)	0·3383 (6)
C(12)	0·6506 (5)	−0·0407 (3)	0·5927 (4)
C(13)	0·7257 (4)	0·0303 (3)	0·4176 (5)
C(14)	0·3144 (4)	0·0844 (3)	0·5530 (4)
C(15)	0·3564 (5)	0·1649 (3)	0·6115 (4)
C(16)	0·2599 (6)	0·2205 (4)	0·6678 (7)
C(17)	0·3342 (9)	0·2293 (6)	0·7684 (8)
C(18)	0·4195 (7)	0·1600 (4)	0·7248 (6)
C(1′)	0·5453 (4)	−0·1163 (3)	0·1797 (4)
C(2′)	0·5115 (4)	−0·0880 (3)	0·0710 (4)
C(3′)	0·4764 (4)	−0·0037 (3)	0·0529 (4)
C(4′)	0·4722 (4)	0·0530 (3)	0·1463 (4)

Table 3. *Atomic coordinates and isotropic thermal parameters U* ($\times 10^3$ Å^2) *for the hydrogen atoms of NCBME*

	x	*y*	*z*	*U*
H(1)	0·5378	0·1068	0·5278	41
H(N)	0·4321	−0·0094	0·6100	31
H(3,1)	0·3426	−0·0304	0·3862	45
H(3,2)	0·2836	−0·0652	0·5005	45
H(4,1)	0·4644	−0·1644	0·5129	44
H(4,2)	0·4132	−0·1699	0·3937	44
H(8,1)	0·4046	0·1139	0·3594	49
H(8,2)	0·5460	0·1491	0·3390	49
H(10,1)	0·6609	−0·1943	0·4626	61
H(10,2)	0·6172	−0·2268	0·3496	61
H(11,1)	0·8188	−0·1180	0·3850	78
H(11,2)	0·7692	−0·1214	0·2682	78
H(11,3)	0·8304	−0·2174	0·3650	78
H(12,1)	0·7225	−0·0652	0·5723	55
H(12,2)	0·6741	0·0099	0·6282	55
H(12,3)	0·6040	−0·0840	0·6193	55
H(13,1)	0·7375	0·0858	0·4506	55
H(13,2)	0·7166	0·0457	0·3535	55
H(13,3)	0·7918	0·0000	0·4242	55
H(14,1)	0·2696	0·0912	0·4750	59
H(14,2)	0·2674	0·0538	0·6038	59
H(15)	0·4180	0·1953	0·5550	64
H(16,1)	0·2401	0·2798	0·6259	143
H(16,2)	0·1801	0·1865	0·6822	143
H(17,1)	0·3763	0·2909	0·7809	144
H(17,2)	0·2966	0·2115	0·8494	144
H(18,1)	0·5068	0·1801	0·7234	86
H(18,2)	0·4107	0·1002	0·7660	86
H(1′)	0·5852	−0·1874	0·1929	42
H(O2′)	0·4953	−0·1087	0·9300	61
H(3′)	0·4500	0·0204	−0·0300	53
H(4′)	0·4159	0·1096	0·1293	40

Table 4. *Atomic coordinates for the non-hydrogen atoms of NME with e.s.d.'s in parentheses*

	x	*y*	*z*
Br	0·1925 (1)	0·0538 (0)	0·1140 (0)
O(2′)	0·9577 (6)	0·4087 (3)	0·2596 (2)
C(1)	0·4580 (8)	−0·0024 (4)	0·3262 (3)
N	0·5962 (7)	−0·0629 (3)	0·3694 (2)
C(3)	0·7634 (8)	0·0025 (4)	0·3885 (3)
C(4)	0·6962 (10)	0·0996 (4)	0·4232 (2)
C(5)	0·5493 (8)	0·1631 (4)	0·3826 (3)
C(6)	0·6488 (8)	0·1974 (4)	0·3190 (2)
C(7)	0·6525 (8)	0·1328 (4)	0·2624 (3)
C(8)	0·5512 (9)	0·0301 (4)	0·2595 (3)
C(9)	0·3798 (8)	0·0906 (4)	0·3648 (3)
C(10)	0·4929 (10)	0·2553 (4)	0·4300 (3)
C(11)	0·3673 (11)	0·3412 (5)	0·4005 (3)
C(12)	0·2747 (9)	0·0531 (5)	0·4272 (3)
C(13)	0·2332 (10)	0·1422 (5)	0·3195 (3)
C(14)	0·6519 (10)	−0·1648 (4)	0·3391 (4)
C(1′)	0·7525 (8)	0·2906 (4)	0·3170 (3)
C(2′)	0·8530 (8)	0·3180 (4)	0·2609 (3)
C(3′)	0·8615 (9)	0·2544 (5)	0·2062 (3)
C(4′)	0·7591 (9)	0·1622 (4)	0·2064 (3)
O(*W*1)	0·9256 (7)	0·1481 (3)	−0·0001 (2)
O(*W*2)	0·5344 (7)	0·1419 (4)	0·0220 (3)

yielding $R = 0{\cdot}053$ and one with the appropriate coordinates resulting in $R = 0{\cdot}042$, so that the correct structure could be accepted, even at the 0·5% level of significance (Hamilton, 1965). Five reflections strongly suffering from extinction were eliminated and the final refinement yielded an R value of 0·039 for 1561 contributing reflections. The atomic coordinates of the non-hydrogen atoms are given in Table 4; the positional parameters of the H atoms with their isotropic temperature factors appear in Table 5.

Discussion

Molecular geometry

The atomic-numbering system of NCBME and NME, commonly accepted for the benzomorphan class, is given in Figs. 1 and 2 together with the bond lengths of the molecules. *ORTEP* stereopairs (Johnson, 1965) of the NCBME and NME cations are shown in Fig. 3. Bond angles are given in Table 6. For easy comparison the rings are named in the same way as in morphine (Gylbert, 1973). In the present substances the aromatic *A* ring is almost planar, the hydro-

Table 5. *Atomic coordinates and isotropic thermal parameters U* ($\times 10^3$ Å^2) *for the hydrogen atoms of NME*

	x	*y*	*z*	*U*
H(1)	0·3406	−0·0499	0·3137	22
H(N)	0·5559	−0·0676	0·4011	22
H(3,1)	0·8294	−0·0475	0·4199	38
H(3,2)	0·8123	0·0101	0·3373	38
H(4,1)	0·6501	0·0827	0·4678	33
H(4,2)	0·7879	0·1466	0·4318	33
H(8,1)	0·4545	0·0389	0·2195	37
H(8,2)	0·6935	−0·0265	0·2469	37
H(10,1)	0·5998	0·3126	0·4264	38
H(10,2)	0·4545	0·2124	0·4774	38
H(11,1)	0·2272	0·3125	0·4000	96
H(11,2)	0·3787	0·3697	0·3502	96
H(11,3)	0·3864	0·4218	0·4250	96
H(12,1)	0·2026	0·0961	0·4519	56
H(12,2)	0·1818	−0·0095	0·4207	56
H(12,3)	0·3128	0·0228	0·4488	56
H(13,1)	0·1907	0·1105	0·3009	60
H(13,2)	0·1364	0·1920	0·3456	60
H(13,3)	0·2727	0·1741	0·2843	60
H(14,1)	0·7273	−0·1562	0·3083	51
H(14,2)	0·7172	−0·2220	0·3718	51
H(14,3)	0·5000	−0·2176	0·3292	51
H(1′)	0·7287	0·3386	0·3537	16
H(O2′)	0·9322	0·4375	0·2955	47
H(3′)	0·8390	0·2767	0·1744	30
H(4′)	0·7599	0·1088	0·1633	44
H(*W*1,1)	0·8182	0·1523	0·0170	51
H(*W*1,2)	0·9545	0·1137	0·0341	51
H(*W*2,1)	0·4855	0·1064	0·0489	51
H(*W*2,2)	0·6142	0·1543	0·0378	51

aromatic *C* ring has the sofa form and the piperidine *E* ring shows a slightly distorted chair conformation, as can be deduced from the torsion angles listed in Table 7. In NCBME the acute angle between planes *A* and *E* is 87·2°, while it is 84·5° between the plane through *A* and *C* and that of *E*. In NME the acute angle between planes *A* and *E* is 83·9°, while the angle between the plane through *A* and *C* and that of *E* is 81·9°. Both cases confirm the T shape of the fairly rigid morphine-derived compounds. Fig. 4 gives selected Newman projections of the configuration around the chiral centres C(1) and C(5) and of the conformation around the more flexible side chains. The absolute configuration of these laevorotatory substances can thus be defined as 1*R*,5*R*. In the C(5)–C(10) projections the terminal C(11) of the ethyl side chains can be seen to be staggered with respect to C(4) and very slightly deviated towards C(6), probably under the repelling influence of the dimethyl group at the 9-position. This steric effect could also explain the values of the C(5)–C(10)–C(11) angles (121·9 in NCBME and 117·6° in NME) which are quite large for a normal tetrahedral bond angle. Although the bond lengths (Figs. 1 and 2) and bond angles (Table 6) are within the expected range, some special remarks have to be made. In NCBME the values of 1·486 (8) Å for the C(10)–C(11) bond and 1·452 (12) Å for the C(16)–C(17) bond are small and could be attributed to some disorder in the side chain resulting in very high thermal parameters for the atoms concerned, so that the bond distances computed for an average position are considerably in error. In NME the C(10)–C(11) bond

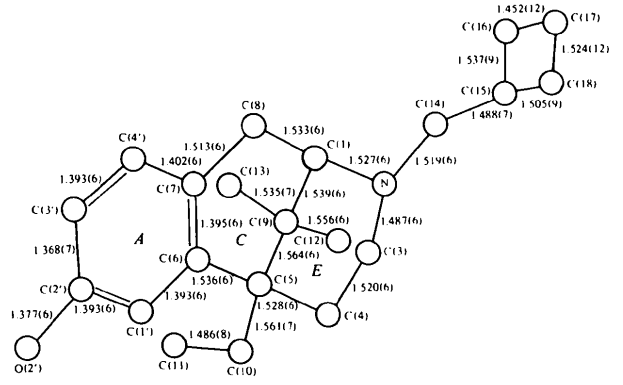

Fig. 1. Atomic numbering of the NCBME molecule with bond lengths (Å), and e.s.d.'s in parentheses.

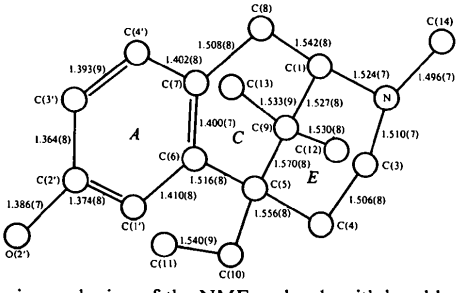

Fig. 2. Atomic numbering of the NME molecule with bond lengths (Å), and e.s.d.'s in parentheses.

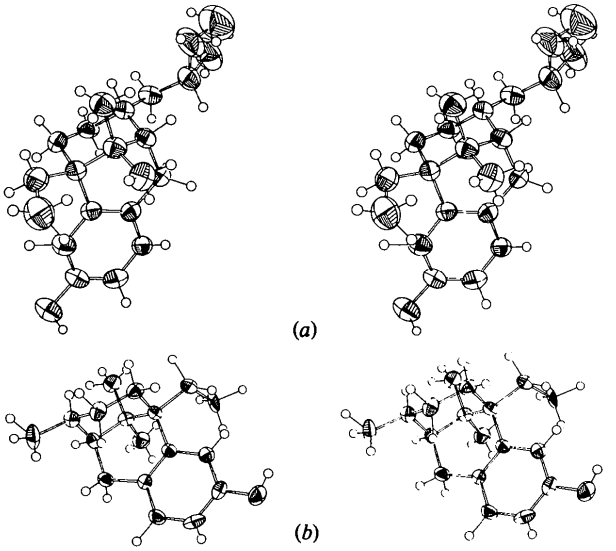

Fig. 3. Stereoscopic views of the protonated molecules (*a*) NCBME, (*b*) NME with 50% probability ellipsoids for the non-hydrogen atoms.

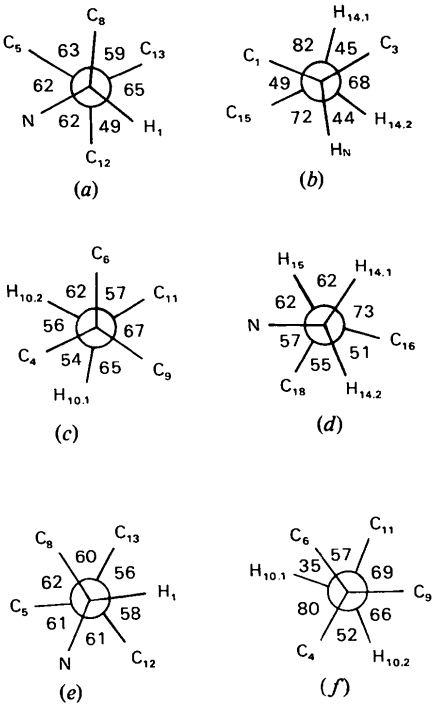

Fig. 4. Selected Newman projections. For NCBME: (*a*) along C(1)–C(9), (*b*) along N–C(14), (*c*) along C(5)–C(10), (*d*) along C(14)–C(15). For NME: (*e*) along C(1)–C(9), (*f*) along C(5)–C(10).

has a normal length of 1·540 (9) Å. Because of the sp^2 hybridization of the C(6) and C(7) atoms that link the *C* ring with the benzene ring, somewhat shorter distances than normal for a C–C bond may be expected for the C(5)–C(6) and the C(7)–C(8) bonds. This has been shown to be the case for NCBME, but in NME this effect is less pronounced. The Newman projections along N–C(14) and C(14)–C(15) represent the conformation of the cyclobutylmethyl side chain of NCBME. This N substituent, which is believed to be very important for the pharmacological activity of the narcotic opiates displays a conformation which is acceptable on the basis of steric considerations.

Nalbuphine.HCl.$2H_2O$ (Sime *et al.*, 1976), a mixed agonist/antagonist of the morphine series, has the same cyclobutylmethyl substituent at N in a similar conformation, as shown by the torsion angles in Table 7, taking into account that the coordinates of nalbuphine.HCl.$2H_2O$ as given in the paper have to be inverted in order to be in the correct absolute configuration. In this respect it is also interesting to note that the given conformation approaches that of the

Table 6. *Bond angles* (°)

	NCBME	NME		NCBME	NME		NCBME	NME
N–C(1)–C(8)	111·5 (3)	110·1 (4)	C(5)–C(6)–C(7)	120·1 (4)	120·5 (5)	N–C(14)–C(15)	114·4 (4)	
N–C(1)–C(9)	109·6 (3)	110·7 (4)	C(5)–C(6)–C(1′)	120·7 (4)	121·2 (4)	C(14)–C(15)–C(16)	115·2 (5)	
C(8)–C(1)–C(9)	112·2 (4)	112·2 (4)	C(7)–C(6)–C(1′)	118·9 (4)	118·1 (5)	C(14)–C(15)–C(18)	120·9 (4)	
C(1)–N–C(3)	111·9 (3)	111·7 (4)	C(6)–C(7)–C(8)	123·9 (4)	122·7 (5)	C(16)–C(15)–C(18)	89·6 (5)	
C(1)–N–C(14)	114·2 (3)	113·1 (4)	C(6)–C(7)–C(4′)	119·0 (4)	119·3 (5)	C(15)–C(16)–C(17)	88·9 (6)	
C(3)–N–C(14)	110·2 (3)	112·3 (4)	C(8)–C(7)–C(4′)	117·0 (4)	117·9 (5)	C(16)–C(17)–C(18)	92·1 (6)	
N–C(3)–C(4)	109·1 (4)	109·0 (5)	C(1)–C(8)–C(7)	113·6 (4)	114·4 (4)	C(15)–C(18)–C(17)	87·4 (5)	
C(3)–C(4)–C(5)	115·4 (4)	114·4 (4)	C(1)–C(9)–C(5)	107·9 (3)	107·3 (4)	C(6)–C(1′)–C(2′)	120·8 (4)	121·1 (5)
C(4)–C(5)–C(6)	107·5 (3)	105·6 (5)	C(1)–C(9)–C(12)	109·3 (4)	109·9 (4)	O(2′)–C(2′)–C(1′)	117·4 (4)	120·9 (5)
C(4)–C(5)–C(9)	108·5 (3)	109·0 (4)	C(1)–C(9)–C(13)	106·3 (4)	107·1 (4)	O(2′)–C(2′)–C(3′)	121·7 (4)	117·8 (5)
C(4)–C(5)–C(10)	106·0 (4)	105·0 (4)	C(5)–C(9)–C(12)	113·4 (4)	112·5 (4)	C(1′)–C(2′)–C(3′)	120·9 (4)	121·1 (5)
C(6)–C(5)–C(9)	108·7 (3)	110·2 (4)	C(5)–C(9)–C(13)	113·8 (4)	113·7 (4)	C(2′)–C(3′)–C(4′)	118·5 (4)	119·1 (5)
C(6)–C(5)–C(10)	112·7 (3)	113·7 (4)	C(12)–C(9)–C(13)	105·8 (4)	106·2 (5)	C(7)–C(4′)–C(3′)	121·6 (4)	121·1 (5)
C(9)–C(5)–C(10)	113·1 (4)	112·8 (5)	C(5)–C(10)–C(11)	121·9 (4)	117·6 (5)			

Table 7. *Torsional angles* (°) *with e.s.d.'s in parentheses for the comparative parts in five narcotic analgesics*: *NCBME* (I), *nalbuphine*.HCl.$2H_2O$ (II), *NME* (III), 2,9-*β*-*dimethyl*-6,7-*benzomorphan*.HCl (IV) *and morphine*.HCl.$3H_2O$ (V) *using the atomic numbering of NCBME*

	I	II	III	IV	V
Ring *A*					
C(7)–C(6)–C(1′)–C(2′)	1·4 (6)	5·6 (6)	0·6 (8)	−0·4 (5)	−2·1 (13)
C(6)–C(1′)–C(2′)–C(3′)	1·2 (7)	−1·5 (6)	−2·4 (9)	−1·4 (5)	−3·7 (9)
C(1′)–C(2′)–C(3′)–C(4′)	−1·6 (7)	−2·4 (7)	3·0 (9)	1·6 (5)	11·1 (11)
C(2′)–C(3′)–C(4′)–C(7)	−0·5 (7)	2·4 (7)	−1·9 (9)	0·0 (4)	−11·0 (15)
C(3′)–C(4′)–C(7)–C(6)	3·1 (7)	1·3 (6)	0·1 (7)	−1·9 (4)	−1·0 (10)
C(4′)–C(7)–C(6)–C(1′)	−3·5 (6)	−5·3 (6)	0·5 (8)	−2·0 (4)	5·4 (10)
Ring *C*					
C(8)–C(1)–C(9)–C(5)	−63·0 (4)	57·6 (4)	−62·2 (6)	−62·2 (2)	−57·8 (7)
C(1)–C(9)–C(5)–C(6)	59·8 (4)	−60·2 (3)	58·7 (5)	62·8 (2)	58·3 (6)
C(9)–C(5)–C(6)–C(7)	−32·0 (5)	37·2 (5)	−30·6 (7)	−35·7 (3)	−35·6 (9)
C(5)–C(6)–C(7)–C(8)	4·4 (6)	−2·5 (6)	3·4 (8)	6·4 (4)	2·8 (10)
C(6)–C(7)–C(8)–C(1)	−4·9 (6)	−5·3 (5)	−5·1 (8)	−4·7 (3)	3·2 (9)
C(7)–C(8)–C(1)–C(9)	34·6 (5)	−23·2 (5)	35·6 (7)	32·9 (3)	25·9 (8)
Ring *E*					
C(9)–C(1)–N–C(3)	−62·3 (4)	64·6 (3)	−62·2 (6)	−61·5 (2)	−65·3 (6)
C(1)–N–C(3)–C(4)	55·6 (4)	−56·9 (4)	55·8 (6)	55·6 (3)	57·6 (6)
N–C(3)–C(4)–C(5)	−53·4 (4)	50·3 (4)	−54·0 (6)	−52·8 (3)	−52·7 (6)
C(3)–C(4)–C(5)–C(9)	54·7 (5)	−54·5 (4)	55·7 (6)	55·8 (3)	57·7 (7)
C(4)–C(5)–C(9)–C(1)	−56·9 (4)	62·4 (3)	−56·8 (5)	−59·2 (3)	−64·0 (6)
C(5)–C(9)–C(1)–N	61·5 (4)	−67·0 (3)	61·3 (5)	62·1 (2)	66·3 (6)
N side chain					
C(1)–N–C(14)–C(15)	−49·0 (5)	47·3 (4)			
C(3)–N–C(14)–C(15)	−176·0 (4)	174·3 (3)			
N–C(14)–C(15)–C(16)	−162·9 (4)	165·3 (4)			
N–C(14)–C(15)–C(18)	−57·0 (6)	63·2 (5)			

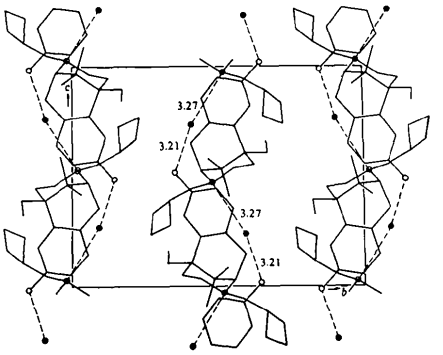

Fig. 5. Projection in the (100) plane of NCBME showing the packing and the hydrogen-bonding scheme. Filled, open and crossed circles represent Br, O and N atoms respectively.

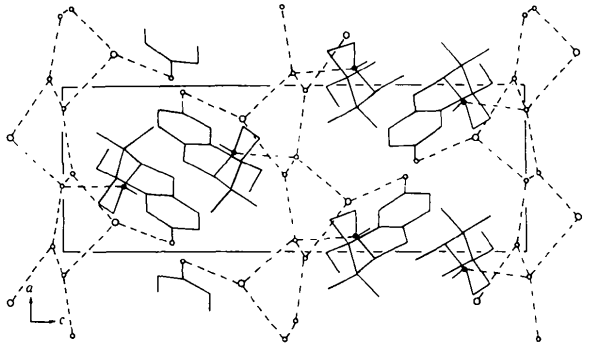

Fig. 6. Projection in the (010) plane of NME showing the packing and the hydrogen-bonding scheme. Large and small open circles represent Br and O atoms respectively. Filled circles represent N atoms.

cyclopropylmethyl group in the antagonist homologue (−)-gemazocine.HBr very well, rather than the conformation of the cyclazocine molecules (Gelders, De Ranter & Schenk, 1979). Furthermore the torsion angles listed in Table 7 describe the stereochemistry of the molecules and show similarity with comparative parts of some narcotic analgesic compounds.

Molecular packing and hydrogen bonds

In NCBME the packing of the molecules in the crystal is essentially achieved by hydrogen bonds between Br, O and N atoms. Each Br ion is bonded to a phenolic O of one molecule and a N atom of another molecule. Endless chains are thus formed parallel to the *c* axis (Fig. 5). The distances and angles listed in Table 8 represent favourable values for hydrogen-bond formation. As a result of the presence of the two water molecules in the NME crystal, an extensive network of hydrogen bonds is formed (Fig. 6), involving Br, O and N atoms. The Br ion is hydrogen bonded to the phenolic O atom and the two water molecules, which makes the situation distinct from that in (−)-codeine hydrobromide dihydrate (Kartha, Ahmed & Barnes, 1962) where the bromide is solely bonded to the solvent molecules. In this crystal, the distances and angles between donor and acceptor atoms, defining the hydrogen-bonding system (Table 8), also represent acceptable values. Although the N is protonated in NME the closest $N^+\cdots Br^-$ approach is 4·48 Å for this compound and thus out of range for being involved in a hydrogen bond. In both compounds no other short intermolecular distances with influence on the packing have been found.

Table 8. *Hydrogen-bond distances* (Å) *and angles* (°)

D–H···*A*	Angle	*D*–H	H···*A*	*D*···*A*
NCBME				
N–H(N)···Br	144·2	1·06	2·35	3·273 (3)
O(2′)–H(O2′)···Br	140·8	0·89	2·47	3·212 (3)
NME				
O(2′)–H(O2′)···Br	165·7	0·83	2·50	3·311 (4)
N–H(N)···O(*W*1)	144·6	0·70	2·22	2·822 (6)
O(*W*1)–H(*W*1,1)···O(*W*2)	157·6	0·84	2·03	2·831 (7)
O(*W*1)–H(*W*1,2)···Br	149·7	0·84	2·45	3·205 (4)
O(*W*2)–H(*W*2,1)···Br	149·8	0·78	2·55	3·256 (5)
O(*W*2)–H(*W*2,2)···O(*W*1)	130·3	0·67	2·35	2·845 (6)

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