Acta Cryst. (1975). B31, 2919

N-Methyl-*D*-normorphinan Hydrobromide

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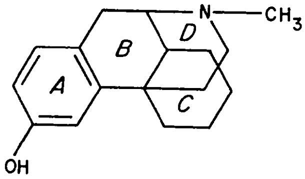
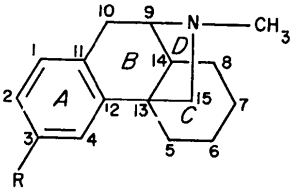
(*Received* 18 *July* 1975; *accepted* 21 *July* 1975)

Abstract. $[C_{16}H_{22}N]^+Br^-$, F. W. 308·26, orthorhombic, $Pna2_1$, $a=16·580$ (3), $b=11·710$ (1), $c=7·411$ (1) Å, $Z=4$, $D_x=1·423$, $D_m=1·427$ g cm^{-3}. The structure was determined by the heavy-atom method, and refined by block-diagonal least-squares calculations. The final R is 0·060 for 1070 observed reflexions. The lone pair electrons of N are facing the side of the benzene ring, and hence are not freely available for interaction with the opiate receptor surface. This is also interpreted as the principal cause for biological inactivity of 3-hydroxy-*N*-methyl-*D*-normorphinan.

Introduction. Synthetic substances possessing morphine-like analgesic activity were described by Braenden, Eddy & Halbach (1955) as having the following features in common: (1) a tertiary N with the group on it relatively small, (2) a quaternary C, separated from N by two methylene groups, (3) a benzene nucleus attached to the quaternary C. These features were categorized as necessary, but not sufficient for analgesic action. *dl*-3-Hydroxy-*N*-methylmorphinan (racemorphan), (I), contains the above features and has analgesic action equivalent to that of morphine. Its five-membered ring *D* analogues, (II*a*) and (II*b*), have been synthesized by Belleau, Conway & Doyle (1973), and are seen to lack the second feature listed above. They are found to be inactive as analgesics or antagonists, and exhibit no side effects characteristic of narcotics (Belleau, Conway, Ahmed & Hardy, 1974).



(I)



(II*a*) R=H
(II*b*) R=OH

The present study of the hydrobromide of (II*a*) has been undertaken in order to determine the stereochemistry of the molecule, especially that of ring *D*, and so establish the reason for the obliteration of analgesic activity. A crystal of the hydrobromide of (II*a*) was assumed to contain left- and right-handed molecules, but it was found to be non-centrosymmetric and to contain only one molecule in the asymmetric unit. On this basis it was concluded that the crystals were not a racemate, but probably a racemic mixture.

Intensities were measured on a four-circle diffractometer with Cu radiation and Ni filter. 1215 reflexions within $\sin\theta/\lambda=0·57$ were scanned, but only 1070 were classified as observed. The data were scaled with the

Table 1. *Fractional coordinates and thermal parameters*

$T=\exp\,[-(U_{11}a^{*2}h^2+\ldots+2U_{23}b^*c^*kl+\ldots)]$. All quantities are $\times 10^4$.

	x	y	z	U_{11}	U_{22}	U_{33}	$2U_{23}$	$2U_{13}$	$2U_{12}$
Br^-	1706 (1)	1748 (1)	5005 (4)	564 (6)	329 (5)	559 (6)	−229 (17)	−371 (16)	−95 (11)
N^+	2628 (5)	8277 (7)	3274 (12)	282 (42)	234 (40)	343 (48)	−17 (79)	122 (76)	74 (68)
C(1)	1542 (6)	4939 (8)	3462 (17)	416 (58)	229 (49)	453 (70)	−214 (102)	407 (110)	101 (88)
C(2)	868(7)	4586 (9)	2560 (18)	479 (67)	288 (53)	508 (76)	−153 (114)	209 (124)	−201 (97)
C(3)	323 (7)	5381 (11)	1959 (18)	371 (61)	646 (77)	434 (70)	−294 (133)	14 (118)	−564 (122)
C(4)	440 (6)	6530 (9)	2374 (16)	295 (56)	434 (62)	326 (59)	58 (103)	36 (101)	−77 (92)
C(5)	430 (6)	8827 (9)	4095 (19)	279 (53)	207 (48)	651 (77)	182 (106)	−95 (111)	121 (86)
C(6)	−56 (7)	8417 (11)	5760 (20)	325 (57)	469 (68)	718 (94)	88 (127)	261 (121)	166 (104)
C(7)	433 (8)	8429 (9)	7447 (21)	591 (79)	326 (60)	690 (93)	−218 (128)	741 (150)	102 (110)
C(8)	1237 (8)	7740 (9)	7248 (18)	702 (79)	191 (51)	433 (70)	−106 (101)	108 (136)	−34 (108)
C(9)	2497 (5)	7720 (7)	5109 (20)	339 (46)	283 (43)	247 (48)	37 (129)	−62 (120)	7 (78)
C(10)	2422 (5)	6435 (7)	4907 (23)	255 (43)	263 (42)	427 (60)	−83 (150)	−135 (131)	128 (69)
C(11)	1662 (6)	6090 (8)	3897 (15)	314 (49)	218 (45)	292 (53)	−100 (92)	143 (98)	−9 (82)
C(12)	1104 (5)	6906 (7)	3367 (13)	202 (45)	173 (42)	239 (50)	9 (82)	205 (77)	48 (73)
C(13)	1221 (6)	8153 (7)	3924 (17)	254 (47)	50 (38)	568 (69)	48 (95)	8 (100)	−2 (71)
C(14)	1697 (6)	8233 (8)	5677 (15)	360 (53)	227 (46)	418 (61)	44 (92)	−188 (97)	−17 (92)
C(15)	1821 (6)	8716 (9)	2638 (17)	236 (53)	351 (53)	432 (65)	383 (109)	−37 (99)	−7 (86)
C(16)	3245 (6)	9201 (10)	3357 (18)	273 (53)	405 (57)	494 (73)	199 (113)	5 (113)	−211 (95)

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* NRCC Postdoctoral Fellow, 1972–1974.

† NRCC Publication No. 14980.

aid of (111), and Lp corrections applied. Absorption corrections were omitted since the crystal used was an irregular fragment 0·10 × 0·17 × 0·23 mm [μ(Cu $K\alpha$) = 41·3 cm^{-1}], and high accuracy was not necessary for this study.

The positions of the non-hydrogen atoms were derived from Patterson and electron density maps, and the H atoms were located from a subsequent difference map. The H positions were not refined, and the parameters of the other atoms were refined by block-diagonal least-squares cycles minimizing $\sum w(\Delta F)^2$, where $w = 1/\{1 + [(|F_o| - 25)/25]^4\}$ and $3{\cdot}4 \le |F_o| \le 149{\cdot}3$. In the final cycle, mean $(\Delta/\sigma) = 0{\cdot}1$, maximum $(\Delta/\sigma) = 0{\cdot}5$, $[\sum w\Delta^2/(m-n)]^{1/2} = 1{\cdot}75$, $R = 0{\cdot}060$ and $R_w = 0{\cdot}07$ for the observed reflexions. 201, which is the strongest reflexion, and those classified as unobserved were excluded. The residual electron density in the final difference map was within −0·9 and 0·6 e Å^{-3} near Br, and within ±0·4 e Å^{-3} elsewhere, where $\sigma(\Delta\varrho) = 0{\cdot}35$ e Å^{-3}.

Table 2. *Fractional coordinates of the* H *atoms* (× 10^3)

Thermal motion assumed isotropic, $B = 3{\cdot}0$ Å^2.

	x	y	z
H(1)	200	437	379
H(2)	77	365	257
H(3)	−16	509	135
H(4)	6	714	190
H(5,1)	66	960	425
H(5,2)	0	885	315
H(6,1)	−24	756	508
H(6,2)	−50	910	517
H(7,1)	0	805	828
H(7,2)	57	925	774
H(8,1)	109	709	724
H(8,2)	134	793	846
H(9)	284	792	634
H(10,1)	284	612	423
H(10,2)	241	616	621
H(14)	184	908	580
H(15,1)	182	858	126
H(15,2)	182	962	224
H(16,1)	380	901	382
H(16,2)	303	997	430
H(16,3)	329	944	193
H(17)	295	789	255

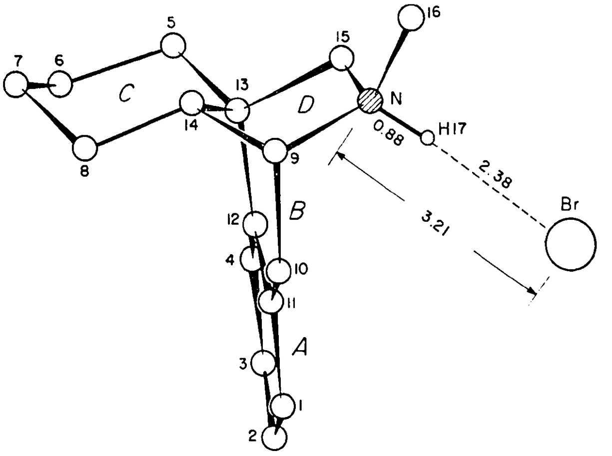

Fig. 1. A perspective view of *N*-methyl-*D*-normorphinan hydrobromide, showing its conformation and the N···Br hydrogen bond. The distances are in Å.

Table 3. *Bond lengths* (Å) *and valency angles* (°)

N–C		C(1)—C(2)-C(3)	119·5 (11)
N-C(9)	1·52 (2)	C(2)—C(3)—C(4)	119·5 (11)
N-C(15)	1·51 (1)	C(3)—C(4)—C(12)	122·0 (10)
N-C(16)	1·49 (1)	C(6)—C(5)—C(13)	110·5 (9)
C–C aromatic		C(5)—C(6)—C(7)	112·4 (10)
C(1)—C(2)	1·37 (2)	C(6)—C(7)—C(8)	112·3 (11)
C(1)—C(11)	1·40 (1)	C(7)—C(8)—C(14)	107·9 (10)
C(2)—C(3)	1·37 (2)	N——C(9)—C(10)	110·3 (9)
C(3)—C(4)	1·39 (2)	N——C(9)—C(14)	101·7 (8)*
C(4)—C(12)	1·39 (1)	C(10)-C(9)—C(14)	110·5 (9)
C(11)-C(12)	1·39 (1)	C(9)—C(10)-C(11)	112·3 (9)
C–C single		C(1)—C(11)-C(10)	119·1 (9)
C(5)—C(6)	1·55 (2)	C(1)—C(11)-C(12)	120·2 (9)
C(5)—C(13)	1·54 (1)	C(10)-C(11)-C(12)	120·6 (9)
C(6)—C(7)	1·49 (2)	C(4)—C(12)-C(11)	117·3 (9)
C(7)—C(8)	1·56 (2)	C(4)—C(12)-C(13)	122·9 (9)
C(8)—C(14)	1·51 (2)	C(11)-C(12)-C(13)	119·7 (8)
C(9)—C(10)	1·52 (1)	C(5)—C(13)-C(12)	113·8 (8)
C(9)—C(14)	1·52 (1)	C(5)—C(13)-C(14)	109·9 (8)
C(10)-C(11)	1·52 (1)	C(5)—C(13)-C(15)	112·7 (9)
C(12)-C(13)	1·53 (1)	C(12)-C(13)-C(14)	110·8 (8)
C(13)-C(14)	1·52 (2)	C(12)-C(13)-C(15)	109·1 (8)
C(13)-C(15)	1·53 (2)	C(14)-C(13)-C(15)	99·8 (8)*
		C(8)—C(14)-C(9)	120·4 (9)
C(9)—N—C(15)	107·4 (8)*	C(8)—C(14)-C(13)	111·9 (9)
C(9)—N—C(16)	111·8 (8)	C(9)—C(14)-C(13)	101·1 (8)*
C(15)-N—C(16)	112·0 (8)	N——C(15)-C(13)	103·6 (8)*
C(2)—C(1)-C(11)	121·3 (10)		

* Angles of the five-membered ring.

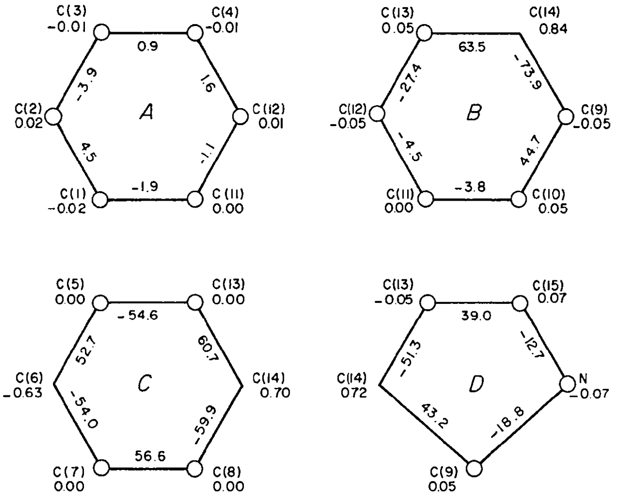

Fig. 2. Schematic drawing of the rings, showing the torsion angles (°), and deviations (Å) of the atoms from the mean planes of those identified by circles.

The scattering factors were those of Hanson, Herman, Lea & Skillman (1964) for C, N, Br, and of Stewart, Davidson & Simpson (1965) for H. Appropriate modifications were applied for the ionization of N and Br, and for $\Delta f'$ (Br). All computations were performed with the programs of Ahmed, Hall, Pippy & Huber (1973).

The atomic parameters are listed in Tables 1 and 2,* and a perspective view of the molecule is presented in Fig. 1. The conformations of the four rings, in terms of the torsion angles and the deviation of the atoms from selected mean planes, are given in Fig. 2. The aromatic ring *A* is planar, $\chi^2=9{\cdot}3$, ring *B* is distorted sofa, ring *C* is chair, and the five-membered ring *D* is half-chair. The molecule is T-shaped as for other morphine-like compounds, rings *C* and *D* forming one arm, and rings *A* and *B* [excluding C(14)] the other. The two arms join at C(9) and C(13), with an angle of 89·2° between their mean planes.

The bond lengths and angles, not corrected for thermal vibration, are listed in Table 3. The C–H lengths are in the range 0·80 to 1·19 Å, mean = 1·04 Å. The Br at $(\frac{1}{2}-x,\frac{1}{2}+y,z-\frac{1}{2})$ forms a hydrogen bond to N as shown in Fig. 1, and there are no other intermolecular distances shorter than the corresponding van der Waals contacts.

Discussion. The outstanding feature in this structure is the direction of the N–H···Br bond which indicates the approximate orientation of the N lone pair electrons when the HBr is absent. Thus, for a five-membered ring *D* in this type of compound, the lone pair electrons project from the same side of ring *D* as the benzene ring, and this presumably makes them unavailable for interaction with the opiate receptor surface. This result has led Belleau *et al.* (1974) to conclude that the orientation of the N lone pair is a key determinant of productive interactions with the morphine receptor. Consequently, Belleau & Morgan (1974) have proposed that clastic binding, which is tantamount to injecting electrons (from N) at the receptor level, may help create interneuronal connections, thus allowing for the multiplicity of biological effects associated with several classes of narcotics.

The important role of the N lone pair in the biological activity of drugs and narcotics was noted by Ahmed & De Camp (1972). Based on the structural studies which had been carried out in this laboratory on the isomeric prodines and the isomeric promedol alcohols, it was concluded that the potency of the 4-phenylpiperidines is enhanced when the 4-phenyl group is in axial conformation relative to the piperidine ring, similar to its conformation in morphine and codeine. In this orientation, the N lone pair electrons are *trans* to the phenyl ring and hence are available for free linkage to the receptor surface.

The authors are grateful to Professor B. Belleau of McGill University for proposing the crystallographic study, and to Mrs M. E. Pippy for assistance with the computations.

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31295 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.