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The Structure and Absolute Configuration of (+)-3-Methoxy-*N*-methylmorphinan (Dextromethorphan) Hydrobromide Monohydrate

BY L. GYLBERT AND D. CARLSTRÖM

Department of Medical Biophysics, Karolinska Institutet, S-104 01 *Stockholm* 60, *Sweden*

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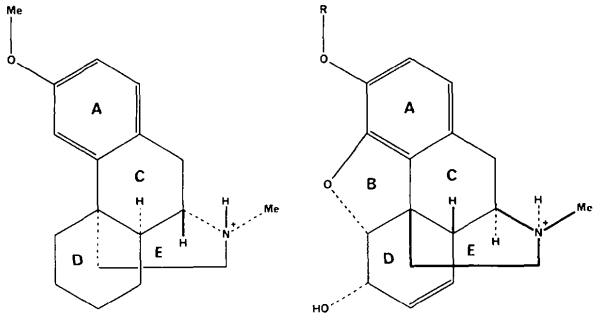
The drug dextromethorphan crystallizes as the hydrobromide monohydrate in the orthorhombic space group $P2_12_12_1$ with cell dimensions $a = 9{\cdot}217$, $b = 27{\cdot}398$, $c = 7{\cdot}063$ Å. The structure was determined by the heavy-atom technique with 2050 observed symmetry-independent reflexions collected by diffractometry. Full-matrix least-squares refinement yielded a final R value of 0·057. The absolute configuration of the cation, determined from the anomalous dispersion of Br^-, was found to be opposite to that of natural (−)-morphine. In the crystal the packing of the cations is determined by hydrogen bonds; the piperidine NH^+ acts as donor to the water molecule which in its turn forms two $OH\cdots Br^-$ bonds running in infinite zigzag chains parallel to **a**.

Introduction

Dextromethorphan (I) is a synthetic drug with a strong antitussive effect and it is in this respect similar to codeine (II), the methyl ether of morphine (III). However, dextromethorphan lacks the analgetic and narcotic properties of its (−)-enantiomorph and other laevorotatory morphine derivatives. The present study is part of an investigation on the molecular structures of morphine and related compounds.



(I) (II) R = Me (III) R = H

Experimental

By slow evaporation of an ethanol–water solution of dextromethorphan hydrobromide at +5 °C, orthorhombic colourless crystals were obtained. Preliminary unit-cell dimensions and systematic absences were determined from Weissenberg diagrams. An optically perfect crystal (0·5 × 0·5 × 0·4 mm), trimmed to an almost spherical shape, was mounted about **a** in a linear diffractometer (Pailred) for measurements of accurate unit-cell dimensions and integrated intensities.

Crystal data

Dextromethorphan [(+)-3-methoxy-*N*-methylmorphinan)] hydrobromide monohydrate, $C_{18}H_{25}O\text{-}N.HBr.H_2O$. $a = 9{\cdot}217$ (5), $b = 27{\cdot}398$ (10), $c = 7{\cdot}063$ (3) Å; $V = 1783{\cdot}6$ Å^3; FW 370·33; D_x ($Z = 4$) = 1·38 g cm^{-3}; μ(Mo $K\alpha$) = 23·47 cm^{-1}; $F(000) = 776$. Systematic extinctions ($h00$, h odd; $0k0$, k odd; $00l$, l odd) indicate unambiguously the space group $P2_12_12_1$.

Graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0{\cdot}7107$ Å) was used and all reflexions within $\sin\theta/\lambda \leq 0{\cdot}65$ were recorded for the layers $0kl$ through $12kl$. The mounting of the crystal was chosen so that hkl reflexions corresponded to a right-handed system of axes. Depending on its intensity, a reflexion was scanned from one to three times and the background was measured for 1 min on each side. At regular intervals standard reflexions were measured as a check on the stability of the crystal and the instrument. 2439 symmetry-independent reflexions were recorded, of which 389 were rejected either because of low intensity, $I_o < 2\sigma(I_o)$, or large background variations. In addition, 254 $1\bar{k}l$ reflexions were recorded for the determination of the absolute configuration. The net intensities of the reflexions were corrected for Lorentz and polarization factors and the structure amplitudes were put on an approximately absolute scale by Wilson statistics.

Determination and refinement of the structure

The position of the Br^- ion was obtained from a three-dimensional Patterson function. Four electron-density syntheses, the first phased by the bromide ion alone followed by successively more complete structures, gave the coordinates of all the non-hydrogen atoms of

the molecule as well as one atom corresponding to water of crystallization. The structure was refined by full-matrix least squares. After three cycles of refinement, the first with isotropic and the remainder with anisotropic thermal parameters, the R index ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$) had dropped from an initial value of 0·177 to 0·078. At this stage the weighting scheme $w = 1/(a + |F_o| + c|F_o|^2)$, with $a = 30$ and $c = 0{\cdot}01$, was applied. Since no H atoms could be found in a difference synthesis, positional parameters were calculated from stereochemical considerations for H atoms bonded to non-methyl C atoms and N. These 26 H atoms were given a fixed B value of 3·0 Å^2 and, although not refined, were included in the subsequent calculations. The absolute configuration of dextromethorphan was established by calculating the structure amplitudes for $1kl$ and $1\bar{k}l$ for the refined structure for comparison with the observed F values of selected Bijvoet pairs. Once the absolute configuration had been determined the refinement was continued with corrections for the real and imaginary parts of the anomalous dispersion for Br^- until the shifts of the coordinates were appreciably smaller than their e.s.d.'s. The final cycle of refinement of the non-hydrogen atoms yielded an R value of 0·057 for 2050 observed reflexions. The final positional parameters are given in Table 1.* The scattering factors for H, C, O and Br^- were those given in *International Tables for X-ray Crystallography* (1962) while that for N^+ was interpolated from the values for O^+ and B^+. The corrections for the real and imaginary parts of the anomalous dispersion of Br^- were taken from *International Tables for X-ray Crystallography* (1974). The computations were carried out on an IBM 360/75 computer with our program system (Bergin, 1971). The stereoscopic drawing, however, was produced by the plotting program *ORTEP* (Johnson, 1965).

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32582 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Final positional parameters*

Standard deviations are in parentheses. All values are multiplied by 10^4.

	x	y	z
C(1)	3680 (7)	918 (2)	8009 (8)
C(2)	3329 (6)	425 (2)	7972 (8)
C(3)	4199 (5)	112 (2)	6884 (7)
C(4)	5372 (5)	294 (2)	5890 (7)
C(5)	8223 (6)	630 (2)	4486 (9)
C(6)	9007 (6)	517 (2)	6310 (12)
C(7)	9583 (8)	983 (3)	7242 (12)
C(8)	8355 (7)	1354 (2)	7529 (9)
C(9)	6375 (6)	1830 (2)	5869 (7)
C(10)	5167 (7)	1641 (2)	7166 (9)
C(11)	4859 (6)	1104 (2)	7019 (8)
C(12)	5721 (5)	790 (2)	5933 (7)
C(13)	6976 (5)	988 (2)	4745 (7)
C(14)	7568 (6)	1460 (2)	5670 (8)
C(15)	6360 (7)	1129 (2)	2777 (8)
C(16)	5235 (7)	1527 (2)	2875 (9)
C(17)	4815 (8)	2391 (2)	3929 (12)
C(18)	2802 (7)	−586 (2)	7771 (10)
N	5838 (5)	1959 (2)	3919 (6)
O	3964 (4)	−376 (1)	6699 (5)
O(W)	2951 (6)	2685 (2)	8322 (8)
Br	1319 (1)	1970 (0)	1267 (1)

Description and discussion of the molecule

Geometry of the molecule

The numbering system of the atoms of the dextromethorphan molecule (Fig. 1) is that commonly accepted for the morphine and morphinan skeletons. To make comparisons easier the lettering of the four rings is the same as that usually used for morphine and its derivatives.

The ring system of morphinans is closely related to that of morphine but differs by the loss of the ether bridge connecting C(4) and C(5) (ring B in morphine) and by hydrogenation of the C(7),C(8) double bond. Although dextromethorphan and natural (−)-morphine have opposite absolute configurations (see below) they

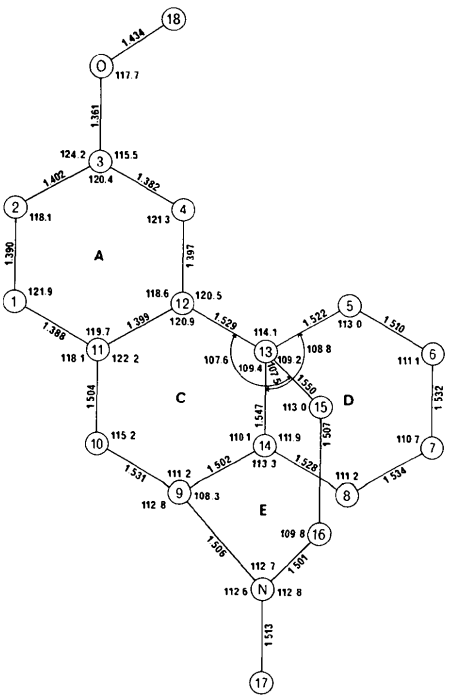


Fig. 1. Atomic numbering with bond lengths (Å) and bond angles (°) for (+)-3-methoxy-*N*-methylmorphinan (dextromethorphan). The e.s.d.'s are around 0·008 Å for C–C bonds and 0·5° for bond angles.

have a very similar architecture. The well established T-shape common to morphine, codeine and 7,8-dihydromorphines is also found in dextromethorphan. The angle between the least-squares planes through the atoms of the rings *A*, *C* and *D*, *E* respectively (planes II and III in Table 2) is 81·9°, *i.e.* close to the angle 82·6° found in naloxone (Karle, 1974) and not too far from 90·9° in morphine hydrochloride trihydrate (Gylbert, 1973), 86·6° in morphine free base (Bye, 1976) and 88·4° in codeine hydrobromide dihydrate (Kartha, Ahmed & Barnes, 1962).

In morphine and naloxone, both containing the ether bridge, the aromatic ring *A* is not perfectly planar [largest deviation in C(12) ≃ 0·03 Å]. This is, according to Bye (1976), caused by strain in the molecular skeleton. The disappearance of the 4,5-ether bridge seems to release the strain as ring *A* in dextromethorphan is strictly planar (plane I in Table 2). Another difference between morphine and codeine is that the carbocyclic ring *D* in dextromethorphan has a chair instead of a boat conformation. When investigating a 7,8-dihydromorphine derivative, Sasvári, Simon, Bognár & Makleit (1974) found that the *D* ring had a chair conformation and they concluded that the boat form of this ring in morphine and codeine is probably caused by the 7,8-double bond. However, in one of the four structure determinations of 7,8-dihydromorphines published, namely nalbufin (Sime, Dobler & Sime, 1976) the *D* ring obviously has a boat form in spite of having a saturated 7,8-bond. In dextromethorphan, which is devoid of both the ether bridge and the double bond, it is natural that the *D* ring assumes a chair form. A *D* ring in chair form has also been found in the only structure determination of a morphinan published so far, (−)-3-hydroxy-*N*-allylmorphinan (Blount, Mohacsi, Vane & Mannering, 1973). The piperidine ring (*E*) has the chair conformation found in all morphines, dihydromorphines, morphinanes and benzomorphanes so far investigated.

The bond lengths and angles in dextromethorphan (Fig. 1) are not far from expected values and are generally close to those reported for comparable parts of morphine and dihydromorphines. It is, however, evident that some of the tetrahedral angles are quite large. This is especially true for the C(9)–C(10)–C(11) angle (115·2°) but this angle is about equally large (113·8–115·4°) in morphines and dihydromorphines. Strain in the morphinan skeleton may explain why certain angles deviate from normal values but the strain is certainly less pronounced than in the morphine skeleton. This is also evident from the bond angles around the atoms C(11) and C(12) which in morphine, codeine and 7,8-dihydromorphines are heavily distorted [C(11)–C(12)–C(13) ≃ 127; C(4)–C(12)–C(13) ≃ 109°], whereas in dextromethorphan and in 6,7-benzomorphanes (Karle, Gilardi, Fratini & Karle, 1969; Fedeli, Giacomello, Cerrini & Vaciago, 1970; Cochran & Abola, 1975), all of which lack the ether bridge, these angles are close to normal trigonal values. The O atom of the methoxy group of dextromethorphan is nearly coplanar with the aromatic ring but deviates towards C(4) so that the C(4)–C(3)–O angle is only 115·5°. Such a deviation from a strictly trigonal arrangement is also observed for the methoxy group in codeine (Kartha, Ahmed & Barnes, 1962) where the corresponding angle is 114·5°.

Table 2. *Least-squares planes and deviations in* Å *of individual atoms*

Atoms marked with asterisks do not define the planes. Each plane is described by the equation $aX + bY + cZ = d$ where X, Y, Z are the coordinates in orthogonal ångström space.

Plane of benzene ring (I)

$a = 0·5887$	$b = -0·1587$	$c = 0·7926$	$d = 6·0837$ Å
C(1)	−0·002	C(12)	−0·002
C(2)	0·001	O*	−0·019
C(3)	0·000	C(10)*	0·018
C(4)	0·001	C(13)*	−0·072
C(11)	0·003	C(18)*	0·042

Plane involving the *A*, *C* rings (II)

$a = 0·5530$	$b = -0·1643$	$c = 0·8168$	$d = 6·0426$ Å	
C(1)	0·040	C(9)	−0·231	C(13)	−0·194
C(2)	0·062	C(10)	−0·013	C(14)	0·429
C(3)	0·018	C(11)	−0·013	C(18)*	0·133
C(4)	−0·039	C(12)	−0·060	O*	0·012

Plane involving the *E*, *D* rings (III)

$a = -0·7109$	$b = -0·4119$	$c = 0·5701$	$d = -4·1432$ Å
C(5)	−0·149	C(13)	0·368
C(6)	0·200	C(14)	−0·180
C(7)	−0·329	C(15)	−0·179
C(8)	0·172	C(16)	0·148
C(9)	0·265	N	−0·315

Angle between planes II and III = 81·9°.

Absolute configuration

From the calculated $F(hkl)$ and $F(h\bar{k}l)$, nine Bijvoet pairs exhibiting the greatest effect of anomalous scattering by the Br^- ion were selected. For each of these pairs $|F_c(hkl)|/|F_c(h\bar{k}l)|$ is virtually equal to $|F_o(hkl)|/|F_o(h\bar{k}l)|$ as is evident from Table 3. This

Table 3. *Ratios of calculated and observed structure factors of reflexions for which the effect of anomalous dispersion is most marked*

hkl	$\lvert F_c(hkl)\rvert/\lvert F_c(h\bar{k}l)\rvert$	$\lvert F_o(hkl)\rvert/\lvert F_o(h\bar{k}l)\rvert$
143	1·20	1·23
154	1·25	1·25
164	1·13	1·16
172	0·93	0·91
1,11,1	1·13	1·12
1,18,1	1·11	1·10
1,18,5	0·86	0·81
1,19,5	1·19	1·16
1,20,1	0·81	0·82

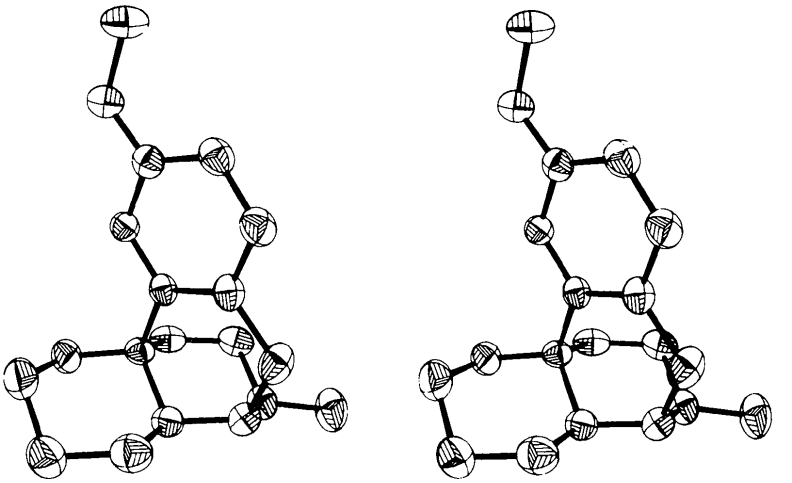


Fig. 2. Stereoscopic pair showing the (+)-3-methoxy-*N*-methylmorphinan (dextromethorphan) molecule in its absolute configuration. Thermal ellipsoids are scaled to 50% probability.

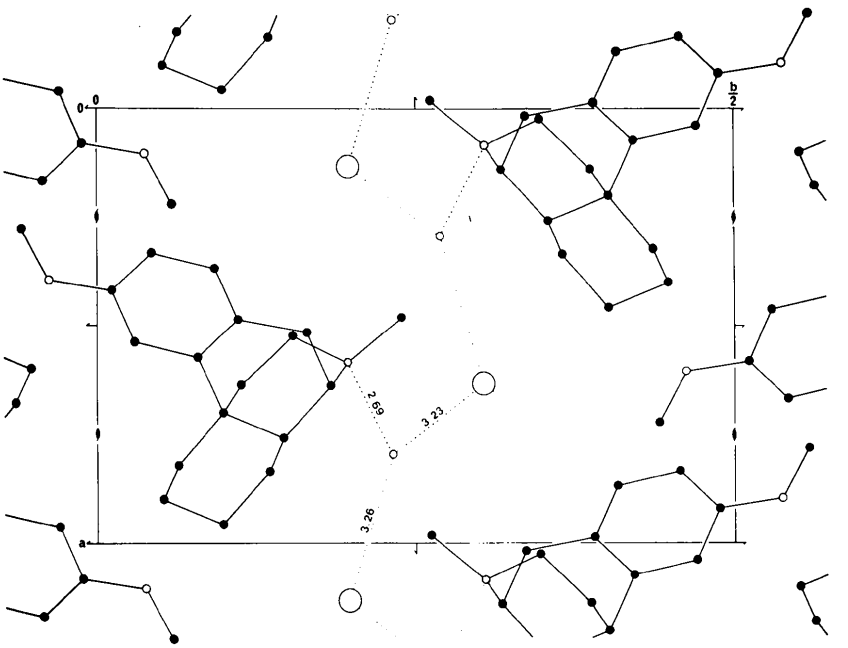


Fig. 3. Projection along **c** of the dextromethorphan hydrobromide monohydrate structure showing the packing and the hydrogen-bond scheme. Filled, open and stippled small circles represent C, O and N atoms respectively. The Br^- ions are represented by large circles. Distances are in Å.

shows that the absolute configuration of the dextromethorphan molecule corresponds to the atomic coordinates given in Table 1 and to the stereoscopic drawing in Fig. 2. While codeine and morphine possess asymmetric C atoms at positions 5, 6, 9, 13 and 14 the positions 5 and 6 in dextromethorphan are not asymmetric. Apart from smaller differences already mentioned, the dextromethorphan molecule is the mirror image of (–)-codeine (Kartha, Ahmed & Barnes, 1962) and hence also of (–)-morphine. The present determination of the absolute configuration of dextromethorphan confirms the results from chemical and physical data by Corrodi, Hellerbach, Züst, Hardegger & Schnider (1959). It is also in agreement with its pharmacological properties; the compound with opposite chirality is a morphine agonist.

Molecular packing and hydrogen bonds

The packing of the molecules and the hydrogen-bonding system are seen in Fig. 3. Although the positions of the H atoms could not be determined it is most probable that the short $N^+\cdots O(W)$ contact (2·69 Å) as well as the two short $O(W)\cdots Br^-$ contacts (3·23 and 3·26 Å) really represent hydrogen bonds. These contact distances agree well with generally accepted average values for the two types of bonds. The angles $C(9)-N^+\cdots O(W)$, $C(16)-N^+\cdots O(W)$ and $C(17)-N^+\cdots O(W)$ are all nearly tetrahedral showing that the proton on N^+ is directed towards the water O. Likewise, the $Br^-\cdots O(W)\cdots Br^-$ angle (124°) is favourable for hydrogen-bond formation. The water O atom deviates 0·18 Å from a plane through the two Br acceptor atoms and the N atom. The sum of the angles between the hydrogen bonds meeting at $O(W)$ is 359·02° and the hydrogen-bonding geometry is thus roughly plane-trigonal. This is a situation frequently found for water molecules in organic structures (Donohue, 1968). Accepting the above arrangement, in which all possible hydrogen bonds are present, a continuous $\cdots H-O-H\cdots Br^-$ chain is formed running in a zigzag fashion in the **a** direction. The dextromethorphan cations are linked by $N^+-H\cdots O(W)$ bonds to this chain. There are no other short intermolecular contacts in the structure violating ordinary packing requirements.

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References

BERGIN, R. (1971). Internal Report I/71. Department of Medical Physics, Karolinska Institutet, Stockholm.

BLOUNT, J. F., MOHACSI, E., VANE, F. M. & MANNERING, G. J. (1973). *J. Med. Chem.* **16**, 352–355.

BYE, E. (1976). *Acta Chem. Scand.* B**30**, 549–554.

COCHRAN, T. G. & ABOLA, J. E. (1975). *Acta Cryst.* B**31**, 919–921.

CORRODI, H., HELLERBACH, J., ZÜST, A., HARDEGGER, E. & SCHNIDER, O. (1959). *Helv. Chim. Acta*, **42**, 212–217.

DONOHUE, J. (1968). *Structural Chemistry and Molecular Biology*, edited by A. RICH & N. DAVIDSON, pp. 444–446. San Francisco: Freeman.

FEDELI, W., GIACOMELLO, G., CERRINI, S. & VACIAGO, A. (1970). *J. Chem. Soc.* (*B*), pp. 1190–1195.

GYLBERT, L. (1973). *Acta Cryst.* B**29**, 1630–1635.

International Tables for X-ray Crystallography (1962). Vol. III, p. 202. Birmingham: Kynoch Press.

International Tables for X-ray Crystallography (1974). Vol. IV, p. 149. Birmingham: Kynoch Press.

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee.

KARLE, I. L. (1974). *Acta Cryst.* B**30**, 1682–1686.

KARLE, I. L., GILARDI, R. D., FRATINI, A. V. & KARLE, J. (1969). *Acta Cryst.* B**25**, 1469–1479.

KARTHA, G., AHMED, F. R. & BARNES, W. H. (1962). *Acta Cryst.* **15**, 326–333.

SASVÁRI, K., SIMON, K., BOGNÁR, R. & MAKLEIT, S. (1974). *Acta Cryst.* B**30**, 634–641.

SIME, R. J., DOBLER, M. & SIME, R. L. (1976). *Acta Cryst.* B**32**, 809–812.