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Dextromethorphan, an antitussive agent

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Key indicators

Single-crystal X-ray study
T = 273 K
Mean σ(C–C) = 0.002 Å
R factor = 0.038
wR factor = 0.102
Data-to-parameter ratio = 11.3

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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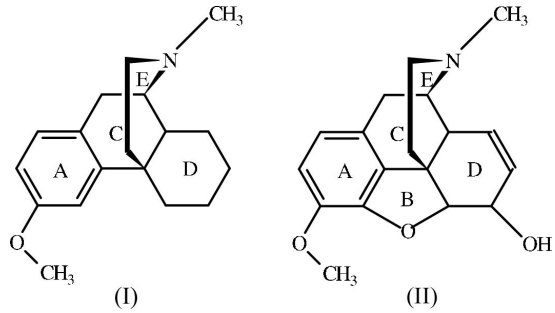
The title compound, 4-methoxy-12-methyl-12-azatetracyclo[9.3^{1,10}.0^{2,7}]heptadeca-2(7),3,5-triene, $C_{18}H_{25}NO$, has a T-shaped configuration, with the benzene ring (*A*) and the fused carbocyclic ring (*C*) forming the upright stock; the other carbocyclic ring (*D*) and the piperidine ring (*E*) are in the arm positions. Rings *C*, *D* and *E* have sofa, chair and chair conformations, respectively. In the crystal packing, the molecules are joined through C—H···O hydrogen bonding into chains running along the *c* axis.

Comment

Dextromethorphan (DTM), (I), is a synthetic drug with a strong antitussive effect. It belongs to the morphine group of alkaloids, which are derivatives of hydrophenanthrene containing a $–CH_2CH_2N(–CH_3)–$ bridge between positions 9 and 13. In this respect, it is similar to codeine, (II). In order to understand the title molecule better from a pharmacological point of view, we have determined the crystal structure of dextromethorphan, (I), which we report here.



Similar to what has been observed for codeine and morphine (Kartha *et al.*, 1962; Gylbert, 1973), the DTM molecule possesses asymmetric centres at positions C9, C13 and C14 (Fig. 1). The DTM ring system is closely related to that of morphine but differs in the loss of the ether bridge connecting atoms C4 and C5. The molecule has a T-shaped configuration (Gylbert & Carlstrom, 1977; Sasvári *et al.*, 1974; Kartha *et al.*, 1962). The stock of the T is composed of the benzene ring (ring *A*, atoms C1–C4/C11/C12) and the fused carbocyclic ring (ring *C*, atoms C9–C14). The angle between rings *A* and *C* is 4.2 (2)°. The two arms of the T are the carboxylic ring (ring *D*, atoms C5–C8/C13/C14) and the piperidine ring (ring *E*, atoms N1/C9/C13–C16). The angle between the least-squares planes of *P*1 (rings *A* and *C*) and *P*2 (rings *D* and *E*) is 81.8 (2)°. Rings *D* and *E* are nearly coplanar, the angle between them being 8.5 (4)°.

It has been reported (Bye, 1976) that the presence of a 4,5-ether bridge gives rise to some distortions in the planarity of

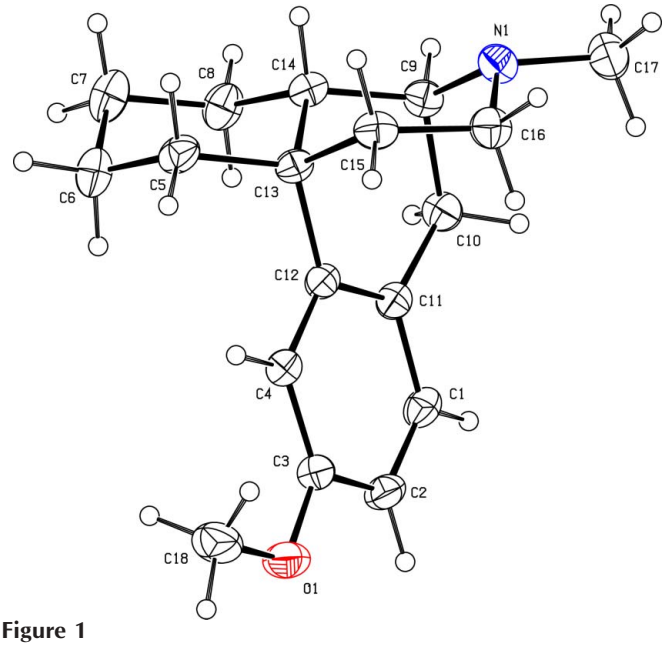


Figure 1
A view of (I), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

ring *A*. It is clear from the literature (Karle, 1974; Bye, 1976) that the planarity of the aromatic ring is influenced by the presence of the ether bridge at the 4,5-position. In the present structure, the absence of the ether bridge seems to release the strain, as ring *A* is almost planar (largest deviation from the mean plane is 0.014 Å). Ring *C* has a sofa conformation (ΔC_2[C_{11},C_{12}] = 15.54; Duax & Norton, 1975).

In contrast with what has been observed in codeine (Kartha *et al.*, 1962; Gylbert, 1973), the C7—C8 bond (Table 1) is saturated in the DTM molecule. Furthermore, the molecule does not have an ether bridge and consequently ring *D* changes its conformation from boat to chair (ΔC_2[C_5,C_6] = 0.76). However, in one of the four structures of 7,8-dihydromorphines (Sime *et al.*, 1976), ring *D* obviously has a boat form in spite of having a saturated 7,8-bond. Ring *E* has the chair conformation (ΔC_2[C_9,C_{14}] = 0.82) found in all morphines and related structures.

The bond lengths and angles of DTM are generally comparable with those in similar structures. However, some of the tetrahedral angles are quite high, especially for the angle C9—C10—C11 [114.4 (2)°]. This type of distortion has been observed in morphines and dihydromorphines (113.8–115.4°). This could be attributed to the strain in the DTM skeleton, which is certainly less pronounced than in the morphine skeleton. This is further evident from the bond angles around some of the atoms (C4, C11 and C12), which in azidomorphine and codeine are heavily distorted (Sasvári *et al.*, 1974; Kartha *et al.*, 1962), whereas these angles are close to normal trigonal values in those structures [including (I); Table 1] which lack the ether bridge.

The O atom of the methoxy group of DTM is 0.094 (1) Å out of plane of the aromatic ring. Furthermore, it deviates away from atom C4, so that the C4—C3—O angle is 124.0 (1)°.

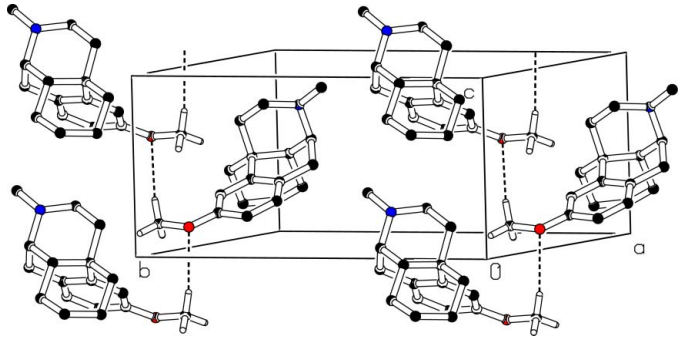


Figure 2
A partial packing diagram for (I), showing the C—H···O hydrogen-bonded (dashed lines) molecules forming chains along the *c* axis. H atoms not involved in hydrogen bonding have been omitted.

This type of deviation was observed in similar structures (Bjornevåg *et al.*, 1983).

In the crystal structure, the molecules of (I) are packed *via* C—H···O hydrogen bonds (Table 2), forming chains of type *C*3 (Bernstein *et al.*, 1995) along the *c* axis.

Experimental

The title compound was obtained from Natco Research Centre, Hyderabad, and recrystallized from methanol.

Crystal data

$C_{18}H_{25}NO$
M_r = 271.39
Orthorhombic, $P2_12_12_1$
a = 14.0356 (12) Å
b = 15.0658 (13) Å
c = 7.1354 (6) Å
V = 1508.8 (2) Å^3
Z = 4
D_x = 1.195 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 6946 reflections
θ = 2.7–27.8°
μ = 0.07 mm^{-1}
T = 273 (2) K
Block, colourless
0.22 × 0.18 × 0.16 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
Absorption correction: none
13046 measured reflections
2066 independent reflections
1963 reflections with $I > 2\sigma(I)$
R_{int} = 0.021
θ_{max} = 28.0°
h = −18 → 18
k = −19 → 19
l = −9 → 9

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.102
S = 1.08
2066 reflections
183 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0624P)^2 + 0.1352P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C3—O1	1.371 (2)	C16—N1	1.467 (2)
C7—C8	1.529 (3)	C17—N1	1.454 (2)
C9—N1	1.468 (2)	C18—O1	1.418 (2)
C11—C12—C4	119.17 (14)	C4—C12—C13	119.94 (14)
C11—C12—C13	120.66 (14)		

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C18—H18B···O1^{i}	0.96	2.60	3.480 (3)	153

Symmetry code: (i) $-x+\frac{5}{2}, -y, z+\frac{1}{2}$.

All H atoms were placed in geometrically idealized positions and allowed to ride on their parent atoms, with C—H distances in the range 0.93–0.98 Å, and with U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms and 1.2U_{eq}(C) for other H atoms. In the absence of significant anomalous scattering effects, the absolute configuration could not be established in this analysis. Therefore, it was arbitrarily assigned and the Friedel pairs were merged.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP3* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PARST* (Nardelli, 1995).

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