*al.*, 1984*c*). Comparison of the atomic charge densities calculated for the present molecule with those for the 4-phenylthiosemicarbazide (Nandi *et al.*, 1984*c*) indicates that the electron-releasing methoxy group also increases the accumulation of negative charge on N(3). Consequently an increase in the reductive capacity and donor ability of the compound over 4-phenylthiosemicarbazide has been observed (Ray, 1981). The similarity in the charge-density distribution and the antibacterial activity of the *para* chloro and *para* methoxy derivatives of 4-phenylthiosemicarbazide indicate that the electron-releasing effect of the methoxy group is responsible for the increased antibacterial activity of 4-(4-methoxyphenyl)thiosemicarbazide over the 4-phenylthiosemicarbazide.

We thank Mr S. Chaudhuri of Bose Institute, Calcutta for many useful discussions.

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# Structure of Codeine

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(*Received* 14 *February* 1983; *accepted* 17 *December* 1986)

**Abstract.** 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol, $C_{18}H_{21}NO_3$, $M_r = 299{\cdot}4$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}491$ (7), $b = 13{\cdot}697$ (12), $c = 14{\cdot}775$ (14) Å, $V = 1516$ (2) Å$^3$, $Z = 4$, $D_x = 1{\cdot}312$ g cm$^{-3}$, $\lambda$(Mo $K\alpha$) = 0·71069 Å, $\mu = 0{\cdot}83$ cm$^{-1}$, $F(000) = 640$, $T = 296$ K, $R = 0{\cdot}038$ for 1205 unique reflections with $F^2 > 2\sigma(F^2)$. The crystal structure of codeine is related to that of morphine hydrate, which belongs to the same group, has the same rigid molecular skeleton, and closely similar cell parameters. Unlike morphine hydrate, the codeine structure lacks hydrogen bonds. This produces a different molecular packing, characterized by a small, approximately 3 Å, shift in the molecular centers, and a rotation of the codeine molecules of approximately 40°.

**Introduction.** The crystal-structure determination of codeine (I) was undertaken to establish the atomic and thermal parameters for later use in the calculation of a standard X-ray diffraction pattern for use in forensic-science laboratories. The basic configuration of codeine was originally determined by the structural analysis of codeine hydrobromide dihydrate (Lindsey & Barnes,

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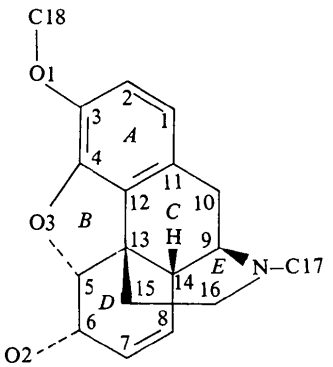
0108-2701/87/050977-03$01.50 

1955) and refined by Kartha, Ahmed & Barnes (1962). References were made in the codeine hydrobromide structure analysis (Kartha *et al.*, 1962) to possible hydrogen bonds; however, the H-atom positions were not refined.




(I)

**Experimental.** Recrystallization was from a solution of ether and petroleum ether. A crystal of size 0·15 × 0·45 × 0·50 mm was selected for data collection. The space group is orthorhombic, $P2_12_12_1$ based on systematic absences in $h00$, $0k0$, and $00l$ reflections for odd indices. Least-squares refinement of the cell dimensions was made with 15 reflections with $4 < 2\theta < 42°$, centered on a Syntex $P2_1$ diffractometer.

Intensities were collected for 1962 independent reflections with a maximum $h = 13$, $k = 23$ and $l = 25$ [one octant, $(\sin\theta)/\lambda \leq 0{\cdot}816$ Å$^{-1}$, Mo $K\alpha$] with the $\theta$–$2\theta$ technique; of these 1205 had $F^2 > 2\sigma(F^2)$ and were regarded as observed. No absorption correction was applied because the measured intensities for three reflections only varied with path length through the crystal by an average of 2% when the crystal was systematically rotated around the diffraction vector ($\psi$ scans).

Data reduction, structure-factor calculations, least-squares refinements, and Fourier synthesis were carried out using the *XRAY*76 system of programs (Stewart, 1976). Direct-phasing methods were employed using *MULTAN* (Germain, Main & Woolfson, 1971). The scattering factors of C, N and O used were those of Cromer & Mann (1968) and for H those of Stewart, Davidson & Simpson (1965).

The positions of 22 atoms were determined from an $E$ map computed from 272 normalized structure factors phased by *MULTAN* and weighted according to the estimate of the probability of the correctness of the phase ($E \geq 1{\cdot}35$). The H atoms bonded to atoms C1, C2, C7, C8, C15 and C16 were placed at their idealized positions, and the remaining H atoms were found by difference synthesis.

The positional and anisotropic thermal parameters for all non-H atoms were refined on $F$ by full-matrix least squares to $R = 0{\cdot}038$. All H-atom positions were then refined except those connected to C1, C2, C8, C10, C15 and C16. The H atoms were assigned isotropic temperature factors equivalent to those of the atoms to which they were attached. The maximum shift = 0·274$\sigma$, average shift = 0·047$\sigma$ with the final $wR = 0{\cdot}031$ for all atoms and $w = 1/\sigma^2(F)$. A final difference synthesis with all data showed no peaks greater than 0·12 e Å$^{-3}$.

Table 1. *Final non-H-atom positional parameters* ($\times 10^4$) *and* $B_{eq}$ *for codeine*

| | $x$ | $y$ | $z$ | $B_{eq}$*(Å$^2$) |
|---|---|---|---|---|
| C1 | 7617 (8) | 11336 (3) | 7559 (4) | 3·8 (3) |
| C2 | 6595 (7) | 11673 (3) | 8271 (3) | 3·5 (3) |
| C3 | 6604 (8) | 11224 (3) | 9118 (3) | 3·5 (3) |
| C4 | 7769 (8) | 10445 (3) | 9212 (3) | 3·1 (2) |
| C5 | 8818 (7) | 8949 (3) | 9645 (3) | 3·5 (3) |
| C6 | 7450 (8) | 8148 (3) | 9451 (4) | 4·2 (3) |
| C7 | 6861 (8) | 8091 (4) | 8490 (4) | 4·8 (3) |
| C8 | 7987 (8) | 8250 (4) | 7809 (3) | 4·4 (3) |
| C9 | 10778 (8) | 9106 (4) | 7197 (3) | 3·9 (3) |
| C10 | 9760 (7) | 10042 (4) | 6902 (3) | 4·4 (3) |
| C11 | 8780 (8) | 10548 (3) | 7663 (3) | 3·5 (3) |
| C12 | 8875 (7) | 10160 (3) | 8533 (3) | 2·8 (2) |
| C13 | 9912 (7) | 9272 (4) | 8810 (3) | 2·8 (2) |
| C14 | 9870 (8) | 8569 (3) | 8001 (3) | 3·4 (2) |
| C15 | 11850 (8) | 9483 (3) | 9043 (3) | 3·6 (3) |
| C16 | 12861 (7) | 9889 (4) | 8258 (4) | 4·5 (3) |
| C17 | 13767 (8) | 9604 (4) | 6692 (4) | 5·3 (3) |
| C18 | 4246 (9) | 12189 (4) | 9733 (4) | 6·5 (4) |
| N | 12664 (6) | 9253 (3) | 7455 (3) | 4·1 (2) |
| O1 | 5553 (5) | 11449 (2) | 9844 (2) | 4·8 (2) |
| O2 | 5981 (5) | 8204 (3) | 10063 (3) | 5·8 (2) |
| O3 | 7853 (5) | 9834 (2) | 9959 (2) | 3·4 (2) |

* $B_{eq} = 8\pi^2(U_{11} + U_{22} + U_{33})/3$.

Final positional parameters are given in Table 1 for non-H atoms. Calculated torsion angles, bond distances and angles within rings *A*, *B*, *C*, *D* and *E* are shown in Table 2.*

**Discussion.** The codeine molecule has the characteristic *T* conformation (Fig. 1) reported for morphine in morphine hydrate (Bye, 1976) and morphine derivatives. The morphine molecule differs from codeine in that an H replaces the C18 methyl group. The bond lengths and angles (Table 2) are the same as those reported for morphine (Bye, 1976), within experimental error. However, there are some differences between these and those reported for codeine hydrobromide dihydrate (Kartha *et al.*, 1962) and other morphine derivatives. The different bond distances for C9–N (1·521 Å) and C16–N (1·468 Å) reported for codeine hydrobromide dihydrate (Kartha *et al.*, 1962) were not found to be different in codeine, where they were 1·477 (7) and 1·479 (7) Å respectively. There is no apparent chemical reason for these two bonds to be

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters and bond distances have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43658 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond distances* (Å), *angles* (°) *and endocyclic torsion angles* (°) *for codeine*

| | | | |
|---|---|---|---|
| C1–C2 | 1·380 (8) | C14–C9 | 1·554 (7) |
| C2–C3 | 1·394 (7) | C9–C10 | 1·555 (7) |
| C3–C4 | 1·385 (7) | C10–C11 | 1·511 (7) |
| C4–C12 | 1·359 (7) | C14–C8 | 1·504 (8) |
| C12–C11 | 1·392 (6) | C8–C7 | 1·332 (8) |
| C11–C1 | 1·396 (7) | C7–C6 | 1·489 (8) |
| C3–O1 | 1·367 (6) | C6–C5 | 1·528 (7) |
| O1–C18 | 1·418 (7) | C6–O2 | 1·427 (7) |
| C12–C13 | 1·500 (7) | C9–N | 1·477 (7) |
| C13–C5 | 1·547 (7) | N–C16 | 1·479 (7) |
| C5–O3 | 1·486 (6) | C16–C15 | 1·492 (7) |
| O3–C4 | 1·386 (5) | C15–C13 | 1·520 (8) |
| C13–C14 | 1·536 (7) | N–C17 | 1·478 (7) |

| | | | |
|---|---|---|---|
| C1–C2–C3 | 122·3 (4) | C9–C10–C11 | 114·1 (4) |
| C2–C3–C4 | 115·7 (5) | C10–C11–C12 | 119·2 (4) |
| C3–C4–C12 | 122·1 (4) | C5–C13–C14 | 115·5 (4) |
| C4–C12–C11 | 122·7 (4) | C13–C14–C8 | 110·4 (4) |
| C12–C11–C1 | 115·4 (4) | C14–C8–C7 | 119·9 (5) |
| C11–C1–C2 | 121·4 (5) | C8–C7–C6 | 121·6 (5) |
| C3–O1–C18 | 117·9 (4) | C7–C6–C5 | 114·6 (4) |
| C4–C12–C13 | 110·3 (4) | C6–C5–C13 | 114·2 (4) |
| C12–C13–C5 | 100·1 (4) | C14–C9–N | 106·6 (4) |
| C13–C5–O3 | 105·8 (4) | C9–N–C16 | 112·5 (4) |
| C5–O3–C4 | 105·4 (3) | N–C16–C15 | 110·7 (4) |
| O3–C4–C12 | 112·8 (4) | C16–C15–C13 | 112·3 (4) |
| C11–C12–C13 | 126·0 (4) | C15–C13–C14 | 108·4 (4) |
| C12–C13–C14 | 106·6 (4) | C9–N–C17 | 112·5 (4) |
| C13–C14–C9 | 106·8 (4) | C16–N–C17 | 111·4 (4) |
| C14–C9–C10 | 113·0 (4) | | |

| Ring *A* | | Ring *B* | |
|---|---|---|---|
| C1–C2–C3–C4 | 2·9 (8) | O3–C5–C13–C12 | −22·3 (5) |
| C2–C3–C4–C12 | 2·2 (8) | C5–C13–C12–C4 | 15·1 (5) |
| C3–C4–C12–C11 | −7·8 (8) | C13–C12–C4–O3 | −1·7 (6) |
| C4–C12–C11–C1 | 7·5 (7) | C12–C4–O3–C5 | −13·4 (6) |
| C12–C11–C1–C2 | −2·3 (8) | C4–O3–C5–C13 | 22·5 (5) |
| C11–C1–C2–C3 | −2·9 (8) | | |

| Ring *C* | | Ring *D* | |
|---|---|---|---|
| C12–C13–C14–C9 | 60·8 (5) | C5–C6–C7–C8 | 37·0 (7) |
| C13–C14–C9–C10 | −62·9 (5) | C6–C7–C8–C14 | −4·7 (8) |
| C14–C9–C10–C11 | 30·6 (6) | C7–C8–C14–C13 | −37·2 (6) |
| C9–C10–C11–C12 | 0·6 (7) | C8–C14–C13–C5 | 46·7 (6) |
| C10–C11–C12–C13 | 1·3 (8) | C14–C13–C5–C6 | −16·8 (6) |
| C11–C12–C13–C14 | −33·3 (7) | C13–C5–C6–C7 | −23·6 (6) |

| Ring *E* | |
|---|---|
| C15–C13–C14–C9 | −62·0 (5) |
| C13–C14–C9–N | 64·9 (5) |
| C14–C9–N–C16 | −63·1 (5) |
| C9–N–C16–C15 | 57·0 (5) |
| N–C16–C15–C13 | −52·8 (5) |
| C16–C15–C13–C14 | 56·8 (5) |

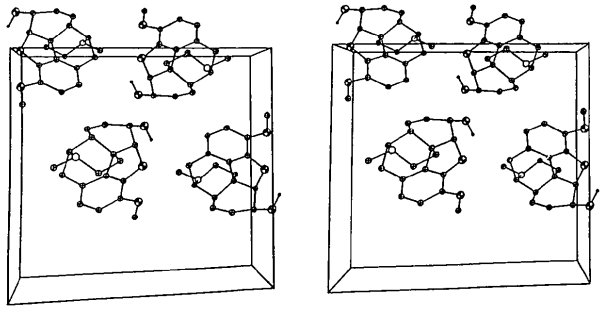


Fig. 1. Stereoscopic view (*ORTEP*, Johnson, 1965) of codeine showing the arrangement of the molecules in the unit cell (● O, ⊕ C and ○ N). From an origin in the lower left corner, **c** is to the right, **b** is vertical and **a** is into the page.

substantially different, and no differences were found in the morphine structure (Bye, 1976) which has these bond distances equal to 1·476 (5) and 1·475 (5) Å respectively, essentially the same as those in this work.

It is interesting to note the short C3–O1 bond length of 1·367 (6) Å found in codeine and also reported in the morphine structure (Bye, 1976), where it is 1·359 Å. The O1 atom is connected to an H atom in morphine and a methyl group in codeine. It was reasoned by Bye (1976) that this short bond distance resulted from a 'strong O–H···N hydrogen bond'. However, this short distance is also present in codeine, without the effect of hydrogen bonding.

Ring *A* shows some deviation from planarity (Table 2) which would be expected with a substituted benzene ring such as this. The endocyclic torsion angles of ring *B* are consistent with an envelope conformation. Atoms C9–C10–C11–C12–C13 of ring *C* are nearly coplanar. Ring *D*, which is distorted by the C5–O3–C4 ether bond, takes on a distorted boat conformation. Ring *E* is in a characteristic chair form.

The unit cell of codeine is strikingly similar to that of morphine hydrate: space group $P2_12_12_1$, $a = 7{\cdot}438$ (1), $b = 13{\cdot}751$ (3), $c = 14{\cdot}901$ (3) Å (Bye, 1976), with no lattice parameter differing from its codeine counterpart by more than 0·8%. This suggested a comparison of the two structures.

By appropriate space-group symmetry operations, it can be shown that a molecule-to-molecule correspondence exists between the two structures, with the steric centers of corresponding molecules differing by only 3 Å from each other. While the molecular packing in morphine hydrate is governed by a network of intermolecular hydrogen bonds, there are no hydrogen bonds in the codeine structure. As a result, the codeine molecules assume orientations which differ by about 40° from their morphine counterparts. Thus, the loss of hydrogen bonding brings about a repacking of the molecules, which is primarily rotational. Clearly, the two crystals cannot be regarded as 'isostructural', and the very close similarity in lattice parameters is not an obvious consequence of the relationship that does exist between the structures.

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