

## Conformations and Hydrogen Bonding in Codeine and Morphine Salts\*

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The conformations and hydrogen bonding in crystals of codeine and morphine salts, which are nearly isomorphous, are discussed. It is suggested that the chemical reactions which led to the original stereochemical assignments might well be reinterpreted, and a satisfactory alternative to the originally proposed (and unsatisfactory) hydrogen bonding scheme in codeine hydrobromide is formulated.

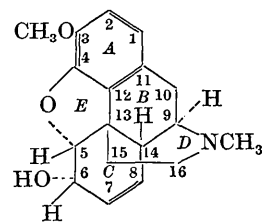
Because of increasing interest in conformational relationships and their effects on chemical reactivities, especially in molecules which contain ring systems, we have examined in detail the conformations in the codeine molecule in the crystal structure of codeine hydrobromide dihydrate (Kartha, Ahmed & Barnes, 1962). The structural results, as reported, consist in large part of the customary table of atomic coordinates from which it is troublesome to gain a clear picture of the spatial relationships among the atoms in the molecule. These relationships should make possible a more precise discussion of the chemistry of codeine and morphine derivatives. Such a discussion, especially of those reactions the interpretation (Bentley & Cardwell, 1955; Bose, 1954; Stork, 1952) of which led to the original stereochemical assignments on purely chemical grounds, seems necessary, since these interpretations have been a source of controversy. We have also examined the hydrogen-bonding scheme discussed by Kartha *et al.* (1962), have concluded that it is certainly incorrect, and suggest a satisfactory one. Finally, we wish to emphasize the point previously discussed briefly that, although the codeine molecule has a methoxy group where morphine has a hydroxyl group, the hydrohalides of the two compounds are very nearly isomorphous.

### Conformations in codeine

The conventional stereochemical representation of codeine (the free base) (I) happens also to be the

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(I)

correct absolute configuration (Kartha *et al.*, 1962). This formulation emphasizes the relationship of the compound to phenanthrene, but obscures the true steric relationships among the five rings. As has been pointed out (Kartha *et al.*, 1962; Lindsey & Barnes, 1955), the shape of the molecule actually approximates a **T**, as was also noted by Mackay & Hodgkin (1955) in their determination of the crystal structure of morphine hydrochloride dihydrate.

Two views of the codeine cation, prepared from the parameters of Kartha *et al.* (1962), are shown in Fig. 1, where it may be seen that the mean plane of rings *A*, *B* (except *C*(14)) and *E* are perpendicular to the mean plane of rings *C* and *D*.† The ring fusions are *B-C cis* and *C-E cis*. (As a consequence of the connectivity, if the *B-C* fusion is *cis* the *C-D* fusion must be *trans*, and *vice versa*.) This structure and its mirror image comprise one of three enantiomorphous pairs, of the eight formally possible arising from the asymmetry at *C*(5), *C*(13), *C*(14) and *C*(9), which can be constructed without unacceptably excessive strain. In the other two pairs, the ring fusions are *B-C trans* and *C-E cis* or *trans*. The conformation of ring *C* is half-boat in the correct structure and the conformations with minimum strain are half-boat and half-chair,

† In the preparation of this and other figures, the positions of the hydrogen atoms were assumed.

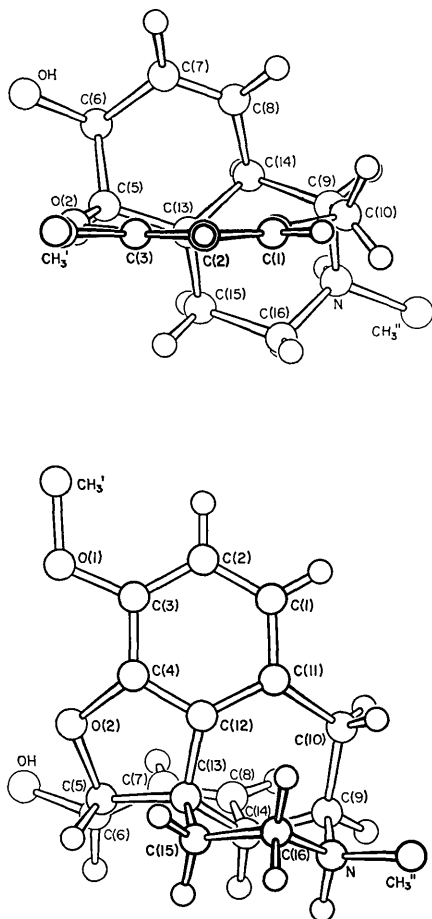


Fig. 1. The codeine cation. (Top) A view parallel to rings *A*, *B*, and *E* and looking down the line joining atoms *C*(2) and *C*(12). (Bottom) A view perpendicular to rings *A*, *B*, and *E* approximately parallel to rings *C* and *D*.

respectively, in the other two pairs. The relative configurations at two other asymmetric atoms, *C*(6) and *N* (which is quaternary in the salt) cannot be deduced from the chemical structure alone.

Of the five rings, only *D* is saturated. The conformations about its six single bonds are shown in Fig. 2; all are seen to be staggered, and the ring assumes the chair form. Evidently the strain produced by the ring fusions is distributed through the molecule such that very little occurs in ring *D*.

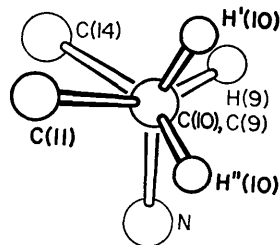


Fig. 3. Conformations about the single bond *C*(10)–*C*(9) in ring *B*.

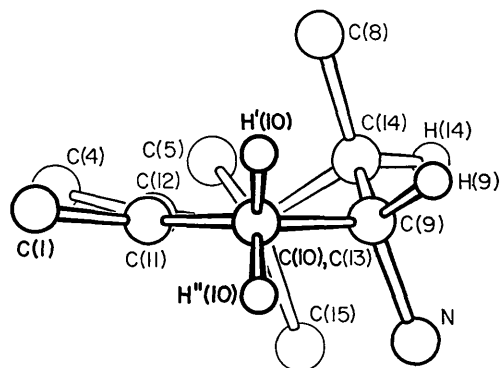


Fig. 4. Ring *B*, viewed along the line *C*(10)⋯*C*(13).

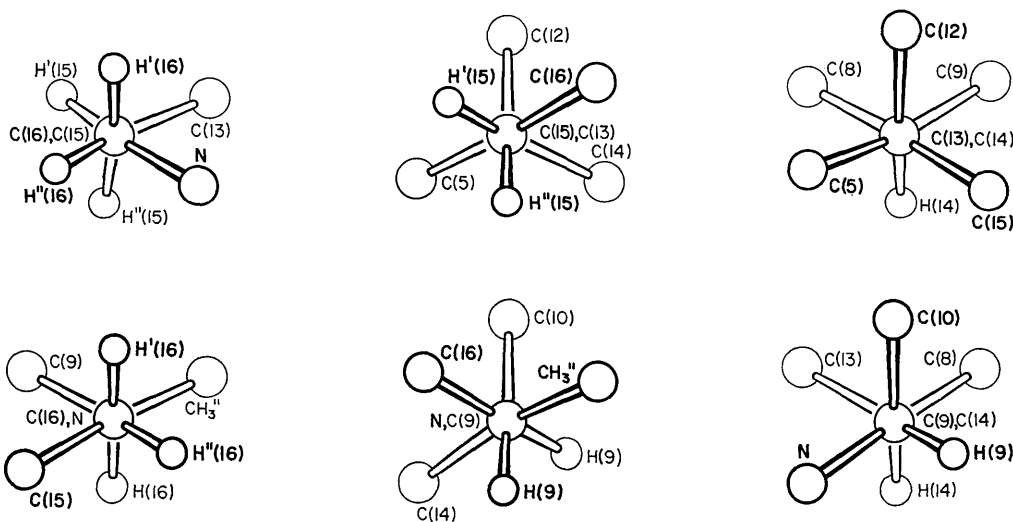


Fig. 2. Conformations about the six single bonds of ring *D*.

Ring *B* contains only one bond between tetrahedral carbon atoms (C(9)–C(10)) which is not also part of ring *D*. A view along this bond (Fig. 3) shows that the conformation is intermediate between staggered and eclipsed, the ring itself (Fig. 4) being neither half-chair nor half-boat. There is a rather close similarity between the conformation of ring *B* and that of ring *B* in aureomycin hydrochloride (Donohue, Dunitz, Trueblood & Webster, 1963), the latter also being fused to a benzene ring but not part of a bridge across a third ring.

Ring *C* contains three bonds between tetrahedral

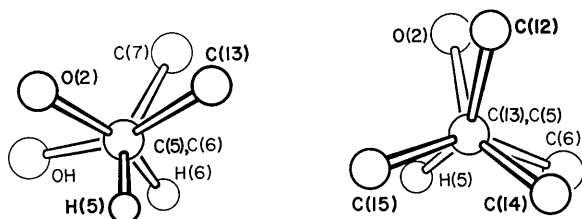


Fig. 5. Conformations about the single bonds C(5)–C(6) and C(13)–C(5) in ring *C*.

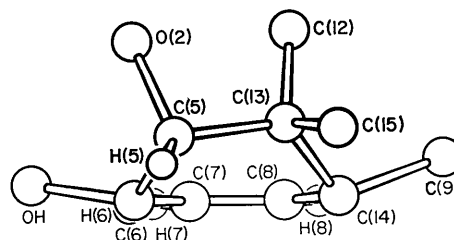


Fig. 6. Ring *C*, viewed along the line perpendicular to the double bond C(7)–C(8) and in the plane of atoms C(6), C(7), C(8), and C(14).

carbon atoms. One of these (C(13)–C(14)) is also part of ring *D* (Fig. 2) and views along the other two are shown in Fig. 5. Ring *C* approximates the half-boat, as shown in Fig. 6. This conformation, which is unstable by 2.7 kcal.mole<sup>-1</sup> relative to the half-chair (Beckett, Freeman & Pitzer, 1948), is a result of the *cis* fusion of rings *C* and *E* which forces the bonds C(5)–O and C(13)–C(12) to be very nearly eclipsed, as seen in Fig. 5. However, for ring *C* the torsion angle relating the bonds C(6)–(OH)(6) and C(5)–O is less

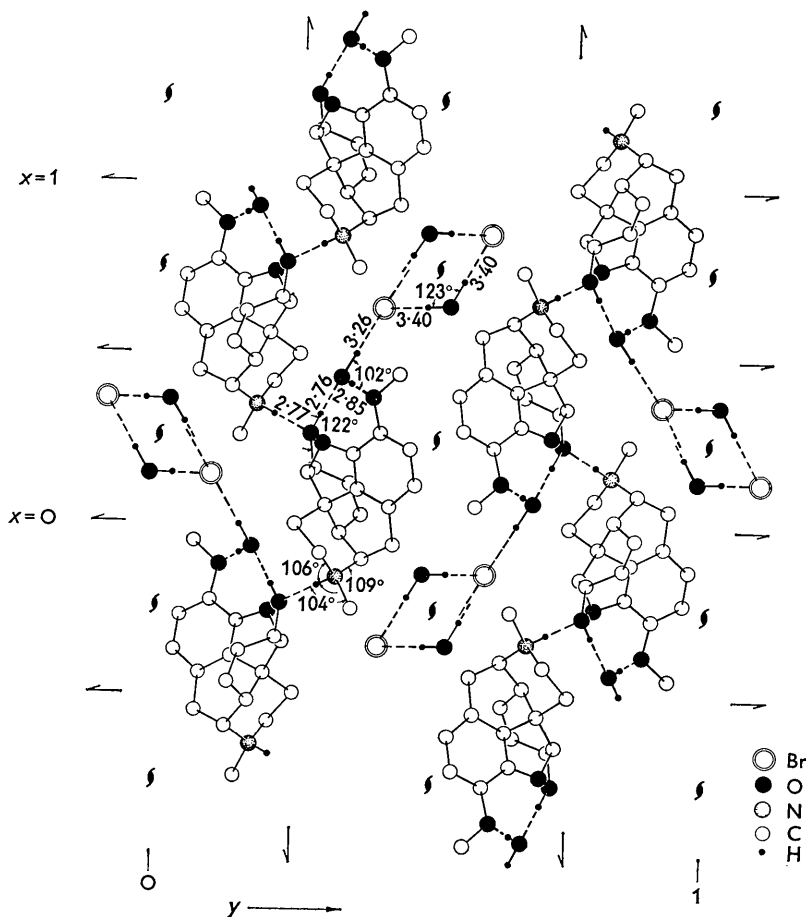


Fig. 7. The crystal structure of codeine hydrobromide dihydrate viewed down the *c* axis.

than  $60^\circ$  and (OH)(6) is more nearly equatorial than axial with respect to ring C.

With the determination of the molecular structures of codeine and morphine, and the precise geometrical relationships between the bonds as set forth in part above, a reinterpretation of the various reactions which led to the original stereochemical assignments is probably much to be desired, since in several cases the results have been either conflicting or ambiguous. Such considerations are beyond the scope of the present paper, and we may remark that the geometry of molecules is generally determined by crystal structure analysts who are often unaware of some of the implications of their results to organic chemists who, on the other hand, may not always realize that pertinent details of molecular structures can be won from the extensive and sometimes forbidding tables of published structural data.

### Hydrogen bonding in codeine hydrobromide dihydrate

The hydrogen-bonding scheme proposed by Kartha *et al.* (1962) makes use of the hydrogen atom of (OH)(6) of the codeine molecule, the four hydrogen atoms of the two water molecules, and a hydrogen atom of an HBr molecule; an alternate possibility that one of the  $H_2O$  molecules is  $H_3O^+$  by transfer of a proton from HBr was also considered. This second possibility requires a hydrogen-bond angle of  $138^\circ$ ; and even though the first possibility has acceptable geometry, neither is tenable in view of the well-known facts that codeine is a strong base and HBr a strong acid. Any scheme involving either HBr molecules or  $H_3O^+$  ions must accordingly be rejected in favor of one involving codeine ions protonated at the nitrogen atom.

The only satisfactory mode of hydrogen bonding,

Table 1. *Interatomic distances and angles involving hydrogen bonds*

Distances		Angles	
N <sup>+</sup> H...O	2.77 Å	C(16)-N <sup>+</sup> H...O	106°
		C(9)-N <sup>+</sup> H...O	109
		CH(3'')-N <sup>+</sup> H...O	104
OH...O'H <sub>2</sub>	2.76	C(6)-OH...O'H <sub>2</sub>	122
HO'H...O(1)	2.85	O(1)...HO'H...Br <sup>-</sup>	102
HO'H...Br <sup>-</sup>	3.26		
HO''H...Br <sup>-</sup>	3.40	Br <sup>-</sup> ...HO''H...Br <sup>-</sup>	123
HO'H...Br <sup>-</sup>	3.40		

Table 2. *Crystallographic data for morphine and codeine hydrohalides*

	a	b	c	Space group	Z	References
Morphine.HBr.2H <sub>2</sub> O	12.75	20.07	6.94	$P2_12_12_1$	4	Mackay & Hodgkin (1955)
Morphine.HI.2H <sub>2</sub> O	13.02	20.32	6.84	$P2_12_12_1$	4	Mackay & Hodgkin (1955)
Codeine.HBr.2H <sub>2</sub> O	13.09	20.82	6.81	$P2_12_12_1$	4	Kartha, Ahmed & Barnes (1962)
Codeine.HI.2H <sub>2</sub> O	13.44	21.38	6.83	$P2_12_12_1$	4	Lindsey & Barnes (1955)

then, uses the four hydrogen atoms of the two water molecules, the hydrogen atom of (OH)(6), and the hydrogen atom of the quaternary nitrogen atom. The resulting scheme and its relevant distances and angles are shown in Fig. 7 and listed in Table 1. All of the angles are quite satisfactory. The N-H...O and O-H...O distances are normal (Donohue, 1952; Fuller, 1959); data on O-H...Br<sup>-</sup> distances are rather meagre, but the observed values of 3.26, 3.40, and 3.40 Å are entirely reasonable.

### Hydrogen bonding in morphine hydriodide dihydrate

It might be expected that the hydrohalides of morphine, which have one more available hydrogen bonding atom than codeine, would have crystal structures differing considerably from those of the corresponding codeine salts. However, the crystallographic data (Table 2) reported for certain morphine and codeine salts strongly suggest close isomorphism. The remarkable similarity between the morphine and codeine salts, which was discussed by Kartha *et al.* (1962), is clearly shown in Figs. 7 and 8. The presence of the hydroxyl group at C(3) in morphine requires the formation of one more hydrogen bond, and this is accomplished merely by a change in orientation of the  $H_2O \cdots X^-$  system together with a small shift of the alkaloid ions along the *a* axis. It may be noted that the sense of the  $H_2O \cdots I^-$  helices in morphine hydriodide is different from that of the  $H_2O \cdots Br^-$  helices in codeine hydrobromide. This feature, together with the rather short  $H_2O \cdots I^-$  distance of 3.36 Å, could be improved by a relatively small adjustment in the *z* coordinate of the water molecule. This coordinate was estimated by Mackay & Hodgkin (1955) from an unresolved peak containing two other atoms in the (010) electron density projection, and may therefore be in error by the amount required to bring the two structures into even closer correspondence.

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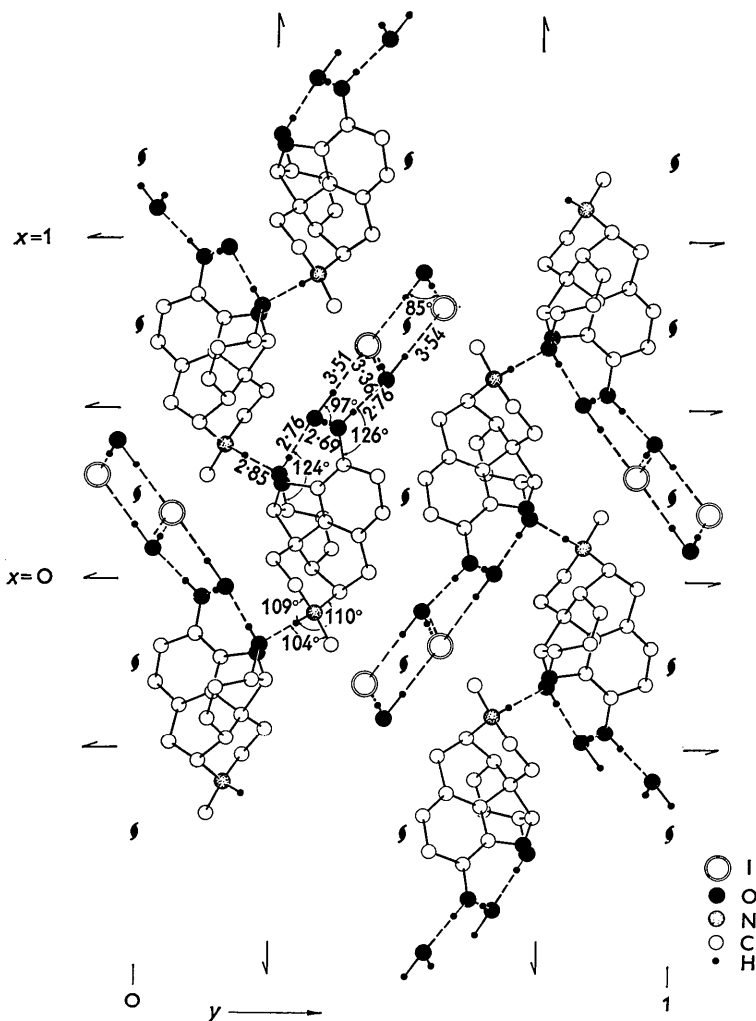


Fig. 8. The crystal structure of morphine hydriodide dihydrate viewed down the *c* axis.

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