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Refinement of the Crystal Structure of Codeine Hydrobromide Dihydrate, and Establishment of the Absolute Configuration of the Codeine Molecule

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The structure of codeine hydrobromide dihydrate has been refined with the use of complete three-dimensional intensity data, and the absolute configuration of the codeine molecule has been established on the basis of the anomalous scattering of Cu $K\alpha$ radiation by the bromine atom.

Introduction

The stereochemical configuration of the codeine molecule was determined in this laboratory (Lindsey & Barnes, 1955) by a two-dimensional study of codeine hydrobromide dihydrate. Because of extensive overlap in two of the three centrosymmetrical projections ($P2_12_12_1$), however, no attempt was made to attain high accuracy in the measurements of bond lengths and bond angles, nor to establish the absolute configuration of the codeine molecule. The final R-factors were 0·19, 0·24, and 0·28 for the three axial projections, and the standard deviations of the various bond lengths and bond angles from those generally accepted were estimated as 0·06 Å and 6°, respectively. Greatly improved computational facilities since the earlier investigation have now prompted a three-dimensional refinement, and the opportunity to remeasure the intensities of a group of low-order reflections with the use of a very accurate counter spectrometer has made possible a direct determination of the absolute configuration of the codeine molecule.

Data collection

Three-dimensional data were collected by means of equi-inclination Weissenberg photographs of the $hk0$ to $hk6$ levels using Cu $K\alpha$ radiation. Precession photographs of the $h0l$, $h1l$, $0kl$, and $1kl$ levels were taken with Mo $K\alpha$ radiation in order to supplement these intensity data and to correlate the observed intensities of the various levels. Other precession photographs were obtained along non-conventional directions, such as [110] and [120], with both Cu $K\alpha$ and Cr $K\alpha$ radiation in a preliminary search for pairs of reflections which might show the effect of anomalous scattering. A total of 2023 non-equivalent reflections within the Cu $K\alpha$ sphere was observed, representing more than 90% of the possible number. Absorption corrections were not applied because the crystals were about 0·3 mm. in cross-section and the linear absorption coefficients are only 35 cm.$^{-1}$ and 25 cm.$^{-1}$ for Cu $K\alpha$ and Mo $K\alpha$ radiations, respectively. Lorentz and polarization corrections were obtained from suitable charts. The observed structure amplitudes were placed on an absolute scale by comparison with $|F_c(hk0)|$ for the best resolved projection, and the scale was adjusted later by comparison with $|F_c(hkl)|$.

The cell dimensions were remeasured with a counter spectrometer, equipped with a single-crystal orienter of the type described by Furnas (1957), Cu $K\alpha_1$ radiation ($\lambda = 1{\cdot}54050$ Å), and a crystal of dimensions $0{\cdot}4 \times 0{\cdot}04 \times 0{\cdot}03$ mm., mounted with the needle axis along the rotation axis of the goniometer head. The new values,

$$a = 13{\cdot}089 \pm 0{\cdot}010,\ b = 20{\cdot}825 \pm 0{\cdot}015,\ c = 6{\cdot}808 \pm 0{\cdot}005\ \text{Å},$$

are in very good agreement with those previously reported (Lindsey & Barnes, 1955).

The intensities of some low-angle reflections also were measured with this equipment because such reflections are the most useful for an investigation of possible violations of Friedel's law. Although Cr and Mo radiations are more powerful for this purpose, Cu radiation was employed because it was immediately available. Three observations of the counting rate at the peak position of each reflection, and of the background in its vicinity, were made and the difference of the means was accepted as representing the intensity of the reflection. Approximate absorption corrections, experimentally estimated as a function of φ, and appropriate Lorentz and polarization corrections, calculated on an IBM 650 computer for each reflection, were applied. The structure amplitudes of the observed reflections (hkl, $h\bar{k}\bar{l}$) were placed on an absolute scale by comparison with those calculated on the basis of the final parameters obtained from the three-dimensional refinement of the structure.

Structure refinement

During the collection of the three-dimensional data a preliminary refinement of the structure was carried out on the axial projections. As noted by Lindsey &

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Barnes (1955) the shape of the electron-density projection of the bromine atom on (001) indicated greater thermal vibration along the direction of x than along y. Separate temperature-factor constants, B_x and B_y, therefore, were evaluated by a least-squares refinement of the $hk0$ data, and were employed in calculations of the bromine contributions to be subtracted from the values of $F_o(hk0)$ in order to determine the contributions of the light atoms alone to the observed structure amplitudes. A single cycle of Fourier refinement of the x, y co-ordinates of the light atoms reduced R for this zone from 0·19 to $0{\cdot}14_5$, which corresponds to a reduction in R from 0·40 to 0·32 for the contributions of the light atoms alone. Further refinement by a differential synthesis reduced R to $0{\cdot}13_5$. The average shift in the x, y fractional co-ordinates was about 0·001.

Preliminary refinement of the z co-ordinates, which were the ones most difficult to establish accurately in the original investigation, was carried out by generalized projections utilizing the $1kl$ data, because the normal projections on (100) and (010) suffer heavily from overlap. The advantages of generalized projections have been pointed out by Dyer (1951); they were of particular interest in the present study because they appear to have been employed previously only in centrosymmetrical cases. Furthermore, the coordinates of the bromine atom not only were known with reasonable accuracy but the value of the x co-ordinate (0·14) ensured that Br would appear with appreciable weight in both the sine and the cosine projections. The phases of the 203 observed $1kl$ reflections were calculated from the x, y co-ordinates refined according to the preceding paragraph, and the z coordinates given by Lindsey & Barnes (1955). Many of the atoms which were not resolved in the original normal projection on (100) were well resolved either in the sine or in the cosine map. The average shift in the fractional z co-ordinates was 0·007.

Final refinement of the atomic co-ordinates was carried out by three cycles of differential syntheses with the use of all the observed three-dimensional data. The anisotropy in the thermal vibration of the bromine atom was represented in the structure-factor calculations by two isotropic half-atoms separated slightly along x (Kartha & Ahmed, 1960). Assuming the same temperature-factor constant $B = 2{\cdot}5$ Å^2 for all atoms, and the atomic co-ordinates obtained from the preliminary two-dimensional refinement, the R-factor for all the observed three-dimensional data was $0{\cdot}18_4$. The first set of observed and calculated differential syntheses indicated shifts of 0·018, 0·022, and 0·050 Å in the x, y, and z co-ordinates, respectively. Structure factors calculated with the revised coordinates and with separate isotropic temperature factors ($B = 2{\cdot}2$ to $4{\cdot}0$ Å^2) for each atom showed $R = 0{\cdot}15_9$. After the second set of differential syntheses the mean changes in the x, y, and z co-ordinates were 0·008, 0·008, and 0·007 Å, respectively, and the mean finite-summation error was approximately 0·02 Å. The observed shifts, corrected for finite summation, were multiplied by 1·4 to speed the refinement, and the temperature factors were modified according to

Table 1. *Refined fractional atomic co-ordinates and temperature-factor constants*

Atom	x	y	z	B (Å^2)
C_1	0·1194	0·4668	0·4593	2·4
C_2	0·2246	0·4576	0·4845	2·9
C_3	0·2699	0·4017	0·4229	2·9
C_4	0·2078	0·3537	0·3470	2·0
C_5	0·1512	0·2711	0·1520	1·8
C_6	0·1625	0·2837	−0·0663	2·0
C_7	0·1188	0·3484	−0·1323	2·4
C_8	0·0307	0·3687	−0·0598	2·0
C_9	−0·1018	0·3719	0·2131	2·0
C_{10}	−0·0530	0·4290	0·3218	2·4
C_{11}	0·0561	0·4199	0·3813	2·0
C_{12}	0·1042	0·3618	0·3356	1·8
C_{13}	0·0570	0·3037	0·2409	2·0
C_{14}	−0·0242	0·3305	0·0936	1·8
C_{15}	0·0021	0·2607	0·3905	2·4
C_{16}	−0·0859	0·2952	0·4941	2·9
CH_3'	0·4428	0·4350	0·5011	4·6
CH_3''	−0·2464	0·3534	0·4523	3·5
N	−0·1549	0·3249	0·3504	2·5
O_1	0·3740	0·3865	0·4273	3·2
O_2	0·2386	0·2973	0·2619	2·5
OH	0·2651	0·2758	−0·1329	3·2
H_2O'	0·4295	0·3292	0·0620	5·5
H_2O''	0·8566	0·4814	0·8079	5·5
Br	0·1403	0·0954	0·0489	—
$(\frac{1}{2}Br)_1$*	0·1333	0·0954	0·0489	3·1
$(\frac{1}{2}Br)_2$*	0·1473	0·0954	0·0489	3·1

* Positions of the half bromine atoms employed to represent the anisotropic vibration of the bromine atom for which

$$B_x = 3{\cdot}8 \text{ Å}^2, \quad B_y = B_z = 3{\cdot}1 \text{ Å}^2.$$

Table 2. *Observed and calculated electron densities* (e.Å^{-3}) *and mean curvatures* (e.Å^{-5})

	ϱ		Mean curvatures	
Atom	Obs.	Calc.	Obs.	Calc.
C_1	9·8	9·9	91	92
C_2	9·1	9·1	83	80
C_3	9·2	9·1	82	79
C_4	10·6	10·8	102	102
C_5	10·9	10·7	104	100
C_6	10·1	9·9	93	90
C_7	9·7	9·8	90	89
C_8	10·0	9·9	95	91
C_9	9·9	9·7	90	88
C_{10}	9·6	9·5	86	84
C_{11}	10·1	9·8	94	88
C_{12}	11·2	10·9	109	105
C_{13}	10·4	9·9	93	87
C_{14}	11·0	10·5	103	99
C_{15}	9·9	9·8	92	89
C_{16}	9·0	8·9	82	78
CH_3'	6·5	7·0	50	53
CH_3''	8·0	8·1	68	67
N	11·9	12·0	108	107
O_1	12·4	13·1	104	107
O_2	14·5	13·7	123	113
OH	12·9	13·2	109	112
H_2O'	8·0	9·3	54	66
H_2O''	8·5	9·6	63	72
Br	77·1	79·6	728	752

the peak heights and curvatures of the observed and calculated electron densities. Structure factors calculated on this basis gave $R=0{\cdot}14_3$. The third, and final, set of observed and calculated differential syntheses produced mean corrected shifts along x, y, and z of 0·004, 0·005, and 0·006 Å, respectively. Structure factors calculated after application of the corrected shifts multiplied by 1·66, and after further modification of the temperature factors according to the observed and calculated peak heights and curvatures, gave $R=0{\cdot}13_1$. Replacement of $|F_o|$ for some of the low-angle reflections by more accurate values derived from the counter-spectrometer data reduced R to a final value of $0{\cdot}12_6$ for 2023 observed reflections. Throughout the refinement the two methyl groups were treated as freely rotating CH_3 groups (Cruickshank, 1955) but the contributions of the remaining hydrogen atoms were not included in the structure-factor calculations. Values of $|F_o|$ cover the range from 2 to 154. For the 219 unobserved reflections within the Cu $K\alpha$ sphere, $|F_c| < 10$ for 213, and $14 > |F_c| > 10$ for 6.

The final fractional atomic co-ordinates and temperature-factor constants are listed in Table 1 where the designations of the atoms are the same as those employed by Lindsey & Barnes (1955). The observed and calculated peak heights, and the mean curvatures

Table 3. *Observed and calculated structure amplitudes of the reflections examined for the effect of anomalous scattering by the bromine atoms*

hkl	$F_o(hkl)$	$F_o(h\bar{k}l)$	$F_c(hkl)$	$F_c(h\bar{k}l)$
111	68·7	67·2	64·2	65·7
121	93·6	92·3	99·2	95·8
131	41·7	43·4	43·4	42·5
141	154·5	153·5	173·1	174·0
151	36·0	39·4	32·4	28·9
161	70·8	69·8	72·7	73·4
171	50·2	51·8	50·6	49·0
181	55·1	54·3	53·1	56·5
191	22·3	23·9	23·4	20·4
1,10,1	14·3	15·5	12·4	12·1
1,11,1	61·8	60·7	64·4	66·7
211	30·5	28·2	28·4	29·9
221	15·7	13·8	13·0	16·2
231	73·0	75·9	73·3	71·1
241	88·8	91·1	94·6	93·1
251	120·2	118·2	125·8	128·2
261	123·3	125·5	126·4	124·4
271	52·3	52·9	53·7	52·2
2,10,1	90·6	94·1	90·4	90·1
311	89·5	87·4	84·3	84·6
321	53·6	52·7	51·2	54·6
331	26·4	29·2	25·2	22·9
341	76·4	76·4	78·7	78·7
351	79·3	78·0	70·9	73·5
361	31·0	30·4	33·8	35·6
371	22·0	24·4	23·1	20·7
381	47·5	47·4	47·2	47·2
411	63·4	61·3	55·4	57·6
421	32·4	34·1	34·6	31·8
431	87·3	86·2	78·8	79·5
441	40·6	42·7	34·7	33·9
451	28·4	29·0	32·3	31·8
461	28·4	26·6	19·7	23·1
471	78·0	81·1	68·6	67·0
491	43·1	44·2	43·8	43·8
511	35·5	37·3	30·4	28·3
521	95·0	90·9	86·6	89·4
531	42·6	42·4	37·5	37·8
541	48·8	52·3	48·5	45·7
551	41·0	45·1	39·3	36·5
561	63·8	64·4	58·4	58·6
571	48·9	49·2	45·7	46·2
611	52·2	52·9	46·0	45·1
621	50·7	48·1	43·0	46·1
631	85·5	85·1	82·6	80·2
641	49·0	51·6	52·1	51·6
651	23·1	22·0	20·7	22·0
112	34·7	28·4	25·1	31·1
122	104·3	101·9	104·6	104·5
132	76·1	79·4	78·3	74·8
142	43·5	47·8	45·5	42·1
152	34·2	38·2	36·7	35·7
162	38·2	35·6	29·5	33·2
172	57·0	57·5	61·0	60·7
182	41·0	45·4	45·8	42·5
192	46·9	47·8	47·3	48·1
212	29·3	32·4	35·3	30·8
222	90·9	89·5	89·3	91·5
232	110·2	106·2	107·3	111·4
242	27·0	28·4	28·7	26·2
252	53·4	52·8	50·4	48·8
262	51·5	50·8	50·4	50·3
272	48·1	44·8	50·3	51·7
282	16·5	18·1	20·4	17·8
312	39·8	34·6	32·9	37·3
322	84·0	88·8	87·3	85·1
332	46·1	49·1	45·6	43·6
342	44·9	41·0	38·5	43·6
352	55·5	58·3	55·2	52·2
362	72·7	72·7	69·9	69·2
372	111·9	109·2	108·8	109·2
412	68·9	68·8	71·4	70·1
422	21·1	22·7	23·9	21·4
442	35·5	39·6	39·4	35·8
452	32·1	32·4	38·0	39·2
462	62·4	62·9	66·9	66·6
472	31·4	32·3	25·6	25·6
512	48·0	48·3	46·6	46·9
522	45·7	43·5	42·1	44·0
532	23·0	21·7	16·6	18·8
542	18·7	20·6	18·5	16·1
552	110·3	112·3	106·7	107·0
612	45·7	44·3	39·4	40·7
622	15·5	18·6	19·7	16·0
113	24·1	27·5	21·9	19·2
123	41·9	39·2	43·6	45·6
133	97·8	91·8	104·4	103·6
143	37·5	35·2	35·0	39·3
163	51·0	48·5	48·3	51·5
213	69·3	65·5	75·4	77·2
223	32·5	32·5	35·6	34·6
233	50·4	50·5	55·9	55·0
243	56·8	53·1	54·6	57·4
253	48·0	49·2	52·6	48·5
263	56·5	56·2	59·0	55·3
313	71·7	71·0	75·5	74·4
323	42·1	44·4	45·8	44·2
333	37·2	34·9	36·9	40·2
343	37·1	39·1	41·6	40·0
353	47·3	48·1	43·0	43·2
413	30·6	30·7	28·5	27·5
423	47·7	45·7	46·0	46·3
433	42·6	44·3	40·4	37·7

of electron density at the atomic positions are given in Table 2.

Absolute configuration

In $P2_12_12_1$,

$$|F(hkl)| = |F(\bar{h}\bar{k}\bar{l})| = |F(\bar{h}kl)| = |F(h\bar{k}l)| = |F(hk\bar{l})|$$

when there is no violation of Friedel's law. Several types of pairs of reflections, therefore, may be selected for an investigation of the effects of anomalous scattering. Crystals of codeine hydrobromide dihydrate are elongated along z and, therefore, are most conveniently mounted with this direction along the φ-axis of the goniostat (Furnas, 1957), and possible absorption is least along x and y. All hkl and $h\bar{k}\bar{l}$ reflections for which $d > 1{\cdot}8$ Å (Cu $K\alpha_1$) were selected as the basis for the determination of the absolute configuration of the codeine molecule. Structure factors were calculated with the atomic co-ordinates of Table 1, and observed structure amplitudes were derived according to a right-handed system of axes from the accurate counter-spectrometer measurements of the intensities. Of 191 pairs of observed reflections, $|F_c(hkl)| = |F_c(h\bar{k}\bar{l})|$ for 88, regardless of any effect of anomalous scattering, because either the A part or the B part of the structure-factor expression ($P2_12_12_1$) is zero. The high degree of accuracy attained in the counter-spectrometer measurements is indicated by a discrepancy of only 1·5% between $|F_o(hkl)|$ and $|F_o(h\bar{k}\bar{l})|$ for these 88 pairs. Furthermore, for all 191 pairs, the R-factor calculated for $|F_o|$'s derived from the photographic data and $|F_c|$'s for the co-ordinates of Table 1 was 0·12, but it was only 0·07 when $|F_o|_{\text{mean}} = \frac{1}{2}|F_o(hkl)| + \frac{1}{2}|F_o(h\bar{k}\bar{l})|$ from the spectrometer measurements was substituted for $|F_o|$. Addition of the contributions of all the hydrogen atoms (assumed to be in their theoretical positions relative to the other atoms) to $|F_c|$ reduced R to $0{\cdot}06_3$.

For the 103 pairs of reflections which might be expected to show the effect of anomalous scattering by the bromine atom, the A_c and B_c parts of the structure factors, after inclusion of the hydrogen contributions, were modified by replacing $(f_{\text{O}})_{\text{Br}}$ with $(f_{\text{O}} + \Delta f' + i\Delta f'')_{\text{Br}}$, where $\Delta f' = -0{\cdot}9$ and $\Delta f'' = +1{\cdot}5$ (Dauben & Templeton, 1955), and allowance was made for the anisotropic thermal motion of Br in the manner already described. The agreement between individual values of $|F_c|$, corrected in this way, and $|F_o|$ is best for $|F_o(hkl)|$ and $|F_c(h\bar{k}\bar{l})|$, and for $|F_o(h\bar{k}\bar{l})|$ and $|F_c(hkl)|$, for 87% of these pairs of reflections as can be seen by an examination of Table 3. The effect of the anomalous scattering is most significant for eight pairs, each of which shows a discrepancy $> 10\%$ between $|F_o(hkl)|$ and $|F_o(h\bar{k}\bar{l})|$. For each of these pairs, $|F_o(hkl)|/|F_o(h\bar{k}\bar{l})|$ is virtually equal to $|F_c(h\bar{k}\bar{l})|/|F_c(hkl)|$ as demonstrated in Table 4. These results show that the absolute configuration of the codeine molecule corresponds to the mirror image of that represented by the atomic co-ordinates of Table 1. In an absolute sense, therefore, the co-ordinates of Table 1 represent those appropriate to a left-handed system of axes. The corresponding co-ordinates, defining the codeine molecule in its true configuration, and referred to a right-handed system of axes, may be obtained by changing the signs of all values of x, or of y, or of z in Table 1 (i.e., by reversing the direction of any one of the axes in the left-handed set).

Table 4. *Ratios of observed, and of calculated, structure amplitudes of reflections which show the effect of anomalous scattering most significantly*

hkl	$\|F_o(hkl)\|/\|F_o(h\bar{k}\bar{l})\|$	$\|F_c(h\bar{k}\bar{l})\|/\|F_c(hkl)\|$
551	0·91	0·93
112	1·22	1·24
152	0·90	0·97
182	0·90	0·93
212	0·90	0·87
312	1·15	1·13
442	0·90	0·91
622	0·83	0·81

Discussion

Interatomic distances and bond angles are listed in Tables 5 and 6, respectively, where the intramolecular values in parentheses have been recalculated with an IBM 650 computer for the unit-cell dimensions and atomic parameters of Lindsey & Barnes (1955). Close intramolecular contacts of 2·803 and 2·747 Å also occur between O_2 and O_1, and between O_2 and OH, respectively; in the latter case, $\angle$ C_6–OH–O_2 = 63·4° and $\angle$ O_2–OH–H_2O' = 64·1°, and there is no reason to consider the possibility of a hydrogen-bond bridge from OH to O_2. The codeine molecule in its absolute configuration is represented in Fig. 1, for the preparation of which the z co-ordinates of Table 1 were replaced by $1-z$.

Table 5. *Interatomic distances* (Å)

Intramolecular

CH_3'–O_1	1·443	(1·58)	C_{14}–C_8	1·497	(1·48)
O_1–C_3	1·399	(1·49)	C_8–C_7	1·324	(1·31)
C_3–C_2	1·372	(1·45)	C_7–C_6	1·531	(1·49)
C_2–C_1	1·401	(1·34)	C_6–C_5	1·516	(1·59)
C_1–C_{11}	1·387	(1·30)	C_6–OH	1·427	(1·46)
C_{11}–C_{12}	1·399	(1·40)	C_{14}–C_9	1·561	(1·59)
C_{12}–C_4	1·369	(1·32)	C_9–C_{10}	1·539	(1·63)
C_4–C_3	1·388	(1·37)	C_{10}–C_{11}	1·496	(1·52)
C_4–O_2	1·370	(1·45)	C_{13}–C_{15}	1·535	(1·47)
O_2–C_5	1·472	(1·40)	C_{15}–C_{16}	1·530	(1·46)
C_5–C_{13}	1·532	(1·62)	C_{16}–N	1·468	(1·52)
C_{13}–C_{12}	1·504	(1·54)	N–C_9	1·521	(1·50)
C_{13}–C_{14}	1·564	(1·58)	N–CH_3''	1·506	(1·56)

Intermolecular

C_1–C_7	3·716	C_9–OH	3·577	C_{16}–O_2	3·427
C_2–C_7	3·728	C_{10}–H_2O''	3·680	CH_3 –H_2O''	3·414
C_3–H_2O'	3·561	C_{11}–C_7	3·722	CH_3''–OH	3·463
C_4–H_2O'	3·528	C_{12}–C_7	3·638	N–C_6	3·817
C_5–Br	3·728	C_{13}–H_2O'	3·834	O_1–C_{15}	3·708
C_6–N	3·817	C_{14}–H_2O'	3·543	O_2–H_2O'	2·922
C_7–C_{12}	3·638	C_{15}–OH	3·644	OH–CH_3''	3·463
C_8–H_2O''	3·393				

Table 6. *Bond angles* (°)

$CH_3'–O_1–C_3$	117·2	(112)	$C_{12}–C_{13}–C_{14}$	105·5	(105)
$O_1–C_3–C_4$	114·5	(111)	$C_{15}–C_{13}–C_{14}$	108·4	(107)
$O_1–C_3–C_2$	127·3	(129)	$C_5–C_{13}–C_{14}$	116·9	(108)
$C_4–C_3–C_2$	118·2	(119)	$C_{12}–C_{13}–C_{15}$	112·2	(120)
$C_3–C_2–C_1$	120·2	(115)	$C_{13}–C_{14}–C_8$	108·1	(112)
$C_2–C_1–C_{11}$	122·5	(129)	$C_{13}–C_{14}–C_9$	107·8	(108)
$C_1–C_{11}–C_{12}$	115·2	(113)	$C_8–C_{14}–C_9$	112·5	(112)
$C_{10}–C_{11}–C_1$	125·8	(129)	$C_{13}–C_{15}–C_{16}$	112·6	(112)
$C_{10}–C_{11}–C_{12}$	118·6	(118)	$C_{15}–C_{16}–N$	110·7	(105)
$C_{11}–C_{12}–C_4$	122·7	(125)	$C_{16}–N–C_9$	113·6	(116)
$C_{13}–C_{12}–C_{11}$	127·3	(126)	$C_{16}–N–CH_3''$	110·4	(109)
$C_{13}–C_{12}–C_4$	109·4	(109)	$C_9–N–CH_3''$	113·1	(108)
$C_{12}–C_4–C_3$	120·8	(118)	$N–C_9–C_{14}$	105·2	(102)
$C_{12}–C_4–O_2$	111·9	(115)	$N–C_9–C_{10}$	113·0	(111)
$C_3–C_4–O_2$	127·0	(126)	$C_{14}–C_9–C_{10}$	114·0	(109)
$C_4–O_2–C_5$	107·7	(102)	$C_9–C_{10}–C_{11}$	115·4	(119)
$O_2–C_5–C_{13}$	105·1	(108)	$C_5–C_6–OH$	112·5	(104)
$C_6–C_5–C_{13}$	112·8	(118)	$C_7–C_6–OH$	111·2	(107)
$C_6–C_5–O_2$	111·0	(119)	$C_5–C_6–C_7$	113·9	(100)
$C_5–C_{13}–C_{12}$	101·3	(96)	$C_6–C_7–C_8$	119·8	(123)
$C_5–C_{13}–C_{15}$	112·4	(119)	$C_7–C_8–C_{14}$	120·6	(118)

The e.s.d.'s of the refined atomic co-ordinates, assuming $\sigma(F)=|\Delta F|$ and including a factor of 1·66 to allow for errors in the phases of the *hkl* reflections, have r.m.s. values of 0·015 Å for C, N, O, and 0·002 Å for Br. On the average, therefore, the e.s.d. of a bond length is 0·021 Å. The e.s.d. of the bond angles is of the order of 1·1° to 1·3°. The means of the differences between the old and the new data are 0·002, 0·002, and 0·008 in the x, y, and z fractional atomic co-ordinates (corresponding to 0·026, 0·042, and 0·054 Å), respectively, 0·05 Å in the interatomic distances, and 3° in the bond angles, with maximum deviations not exceeding three times the mean in any case. The effect of the refinement on individual bond lengths and angles is apparent from the data given in Tables 5 and 6.

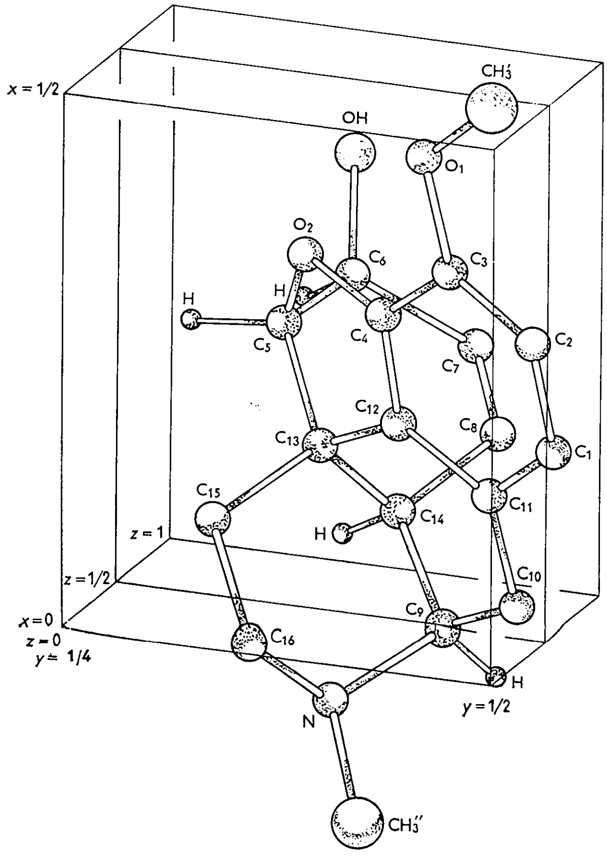

Fig. 1. Model showing the absolute configuration of the codeine molecule (only those H's on C_5, C_6, C_9, C_{14} are shown).

As a result of refinement the benzene ring has become more regular although it now appears not to be exactly planar. The best mean plane through C_1, C_2, C_3, C_4, C_{12}, and C_{11}, based on the co-ordinates of Table 1, with z replaced by $-z$ and referred to a right-handed system of axes, is given by the equation

$$0·1408X+0·3696Y+0·9186Z-0·9264=0\ ,$$

where X, Y, and Z are in Å. All atoms are within $\pm 0·02$ Å of this plane with the exception of C_{12} (common to the benzene ring, the O-ring, and one of the carbocyclic rings) which is 0·048 Å from it. Furthermore, O_1, CH_3', the O-ring, and one of the carbocyclic rings (the latter two fused to the benzene ring and to each other) are very nearly in the same plane as that of the benzene ring, with the exception of C_5 and C_9. On the other hand the piperidine ring and the other carbocyclic ring extend outwards from this plane on opposite sides to form the arms of a T-shaped molecule as established previously for codeine (Lindsey & Barnes, 1955) and for morphine (Mackay & Hodgkin, 1955). The five-ring system, therefore, may be considered in terms of two planes, one, through C_1, C_2, C_3, C_4, C_{11}, C_{12}, C_{10}, O_2, defined, in the present case, by the equation

$$0·1933X+0·4253Y+0·8842Z-1·6352=0\ , \quad (1)$$

and the second, through C_5, C_6, C_7, C_8, C_{13}, C_{14}, C_9, N, C_{16}, C_{15}, defined by the equation

$$0·4680X+0·7369Y-0·4878Z-5·5118=0\ , \quad (2)$$

where X, Y, and Z are in Å and refer to a right-handed system of axes and the atomic co-ordinates of Table 1 with z replaced by $-z$. The angle between the two planes is 88·4°. The distances of individual atoms from the mean planes (1) and (2) are shown in Fig. 2, and it may be noted that they indicate a boat form for the carbocyclic ring which contains $C_7=C_8$, and a chair form for the piperidine ring.

In the piperidine ring, each of the two sets of atoms, N, C_9, C_{13}, C_{15}, and, N, C_{16}, C_{13}, C_{14}, is more nearly planar than C_{15}, C_{16}, C_9, C_{14}; in the first, N is $-0·027$ Å, C_9 is $+0·027$ Å, C_{13} is $-0·026$ Å, and C_{15} is $+0·025$ Å from their mean plane, whereas C_{14} is $-0·787$ Å and C_{16} is $+0·634$ Å from this plane, thus again demonstrating the chair form of this ring. The bond lengths and angles have magnitudes similar to those of the

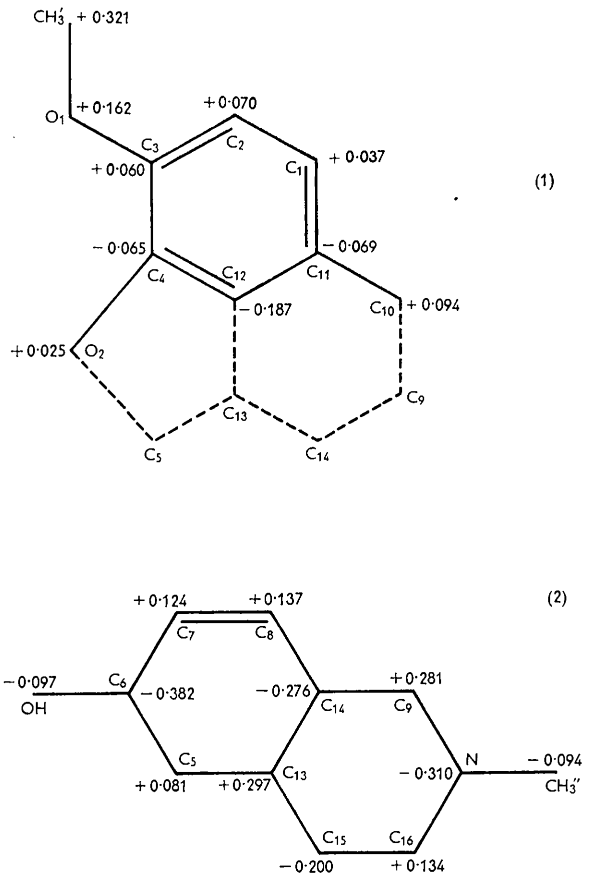

Fig. 2. Distances of atoms from mean planes (1) and (2); see text.

piperidine ring in the molecule of alphaprodine (Kartha, Ahmed & Barnes, 1960).

The high degree of packing efficiency within the structure is indicated by the interatomic distances listed in the lower section of Table 5, where the numerical values represent the shortest intermolecular distances, exclusive of those involved in possible H-bonds, from each of the atoms of one codeine molecule (neglecting hydrogen atoms) to atoms of neighbouring molecules of codeine, H_2O, or HBr. Most of the atoms also make other contacts which are almost as close.

Although no direct determination of the positions of the hydrogen atoms was attempted because of the presence of the heavy bromine atom, N is only 2·772 Å away from the OH on C_6 of an adjacent codeine molecule, which strongly suggests the presence of a hydrogen bond, O–H · · · N. Other close contacts, indicative of possible H-bonding, exist between O_1 and H_2O, OH and H_2O', H_2O' and Br, H_2O'' and Br (two). That O_2–H_2O' = 2·922 Å represents only a close van der Waals contact, and not a very long H-bond, is supported by the values of 57·7° and 58·1° for the angles O_2–H_2O'–OH and O_2–H_2O'–O_1, respectively.

In strychnine hydrobromide dihydrate (Robertson & Beevers, 1951), D(−)-isoleucine hydrobromide monohydrate (Trommel & Bijvoet, 1954), and 11-amino-undecanoic acid hydrobromide hemihydrate (Sim, 1955), Br is not only H-bonded to water molecules at distances of 3·15, 3·30, and 3·41 Å in the first, 3·30 and 3·35 Å in the second (also with a 3·29 Å bond from Br to OH), and 3·38 Å in the third but there are H-bonds between Br and N of 3·17, 3·35, and 3·38 Å, respectively, in the three crystal structures. In codeine hydrobromide dihydrate, however, the closest approach of Br (at $x-\frac{1}{2}, \frac{1}{2}-y, \bar{z}$) to N (at x, y, z) is 4·163 Å so that HBr is in close contact only with the water molecules. This is also true of HI in the structure of morphine hydriodide dihydrate (Mackay & Hodgkin, 1955).

The interatomic distances and angles suggestive of H-bonding are collected in Table 7. It is of interest to note that the addition of a H-bonded OH to the N of the piperidine ring completes an approximately tetrahedral co-ordination around N, and that there are almost planar distributions of the three H-bonds around OH, H_2O', and HBr. The bond angles involving OH are not far from the tetrahedral value for H_2O'–OH–N (two hydrogen bonds), and approach 120° for H_2O'–OH–C_6 and for C_6–OH–N. Although H_2O'

Table 7. *Interatomic distances and angles involving possible hydrogen bonds* (· · ·)

O–H · · · N	2·772 Å	H_2O' · · · H–Br	3·262 Å
H–O′–H · · · O–H	2·762	H–Br · · · H–O″–H	3·395
H–O′–H · · · O_1	2·852	H–Br · · · H–O″–H	3·397
OH · · · N–C_{16}	105·6°	O_1 · · · H_2O' · · · OH	112·9°
OH · · · N–C_9	109·3	O_1 · · · H_2O' · · · HBr	102·5
OH · · · N–CH_3''	104·1	OH · · · H_2O' · · · HBr	137·8
(C_{16}–N–C_9	113·6)	Σ	353·2°
(C_{16}–N–CH_3''	110·4)		
(C_9–N–CH_3''	113·1)	H_2O' · · · HBr · · · H_2O''	176·6°
Mean	109·3°	H_2O' · · · HBr · · · H_2O''	100·4
		H_2O'' · · · HBr · · · H_2O''	82·3
H_2O' · · · OH · · · N	105·5°	Σ	359·3°
H_2O' · · · OH–C_6	122·3		
C_6–OH · · · N	127·8	HBr · · · H_2O'' · · · HBr	123·0°
Σ	355·6°		

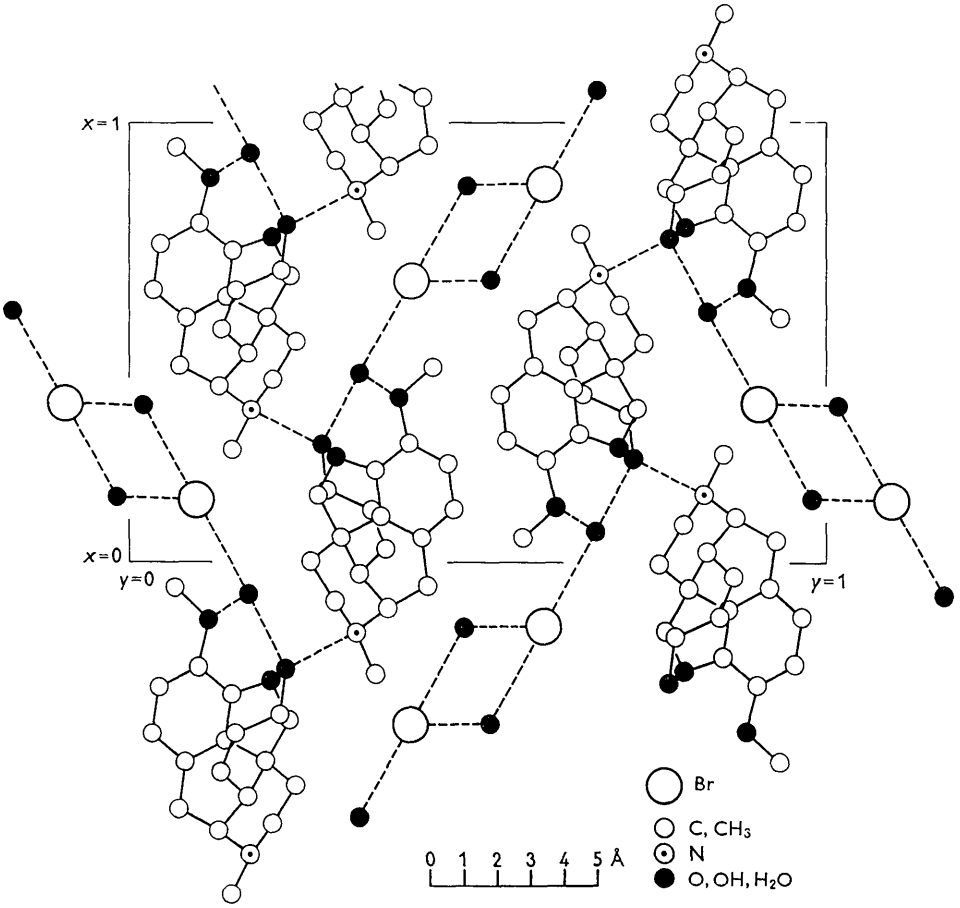

Fig. 3. Projection on (001) showing possible H-bonds (broken lines): right-handed axes ($+z$ directed away from observer).

and H_2O'' are represented as H-bonded to HBr it is, of course, possible that the degree of ionization may be such that the contacts should be expressed in terms of oxonium ions, H_3O^+, and bromide ions, Br^-. In any case, H_2O' leads into an $-HBr-H_2O''-HBr-H_2O''-$ spiral, around 2_1 along the direction of z, through HBr to H_2O'' in almost a straight line, with a second H_2O'' nearly at right angles which itself leads in almost a straight line out of the spiral through an HBr at a translation of $c/2$ after a half turn. The size of the bromide ions, and their mutual Coulombic repulsion, may account for the increase of the $HBr-H_2O''-HBr$ angle to 123·0°.

The system of possible H-bonds is represented by the broken lines in Fig. 3. Adjacent codeine molecules at x, y, z, and $x-\frac{1}{2}, \frac{1}{2}-y, \bar{z}$, and at $\bar{x}, \frac{1}{2}+y, \frac{1}{2}-z$, and $\frac{1}{2}-x, 1-y, \frac{1}{2}+z$, are joined into zigzag chains along the direction of x by H-bonds between the OH of one molecule of each pair and the N of the other ($O-H\cdots N$), while the O_1 and OH of each molecule are H-bonded to H_2O' ($-O_1\cdots H-O'-H\cdots O-H\cdots$). The zigzag chains are linked into a three-dimensional network by H-bonds involving H_2O', HBr, and H_2O''; chains of $\cdots Br\cdots H-O''-H\cdots Br\cdots H-O''-H\cdots$ spiral around the 2_1 axes along z with $Br-H\cdots O'$ laterals joining HBr's alternately to H_2O' at x, y, z and at $\frac{3}{2}-x, 1-y, \frac{1}{2}+z$ along one spiral (around $\frac{3}{4}, \frac{1}{2}, z$) and to H_2O' at $x-\frac{1}{2}, \frac{1}{2}-y, \bar{z}$ and at $1-x, y-\frac{1}{2}, \frac{1}{2}-z$ along the other (around $\frac{1}{4}, 0, z$).

The effect on the crystal structure of replacing OH (on C_3) in morphine by OCH_3 in codeine is apparent from a comparison of Fig. 4 of Mackay & Hodgkin (1955) with the present Fig. 3, bearing in mind that I has been replaced by Br in the latter. The tilt of the alkaloid molecule relative to the crystallographic axes has not been affected to any appreciable extent, but the molecules related by the 2_1 axes parallel to z have been displaced by about 1·8 Å relative to one another along the direction of x in Fig. 3 (y in Mackay & Hodgkin, 1955, Fig. 4). In morphine hydriodide dihydrate $O_1-H_2O''=2·76$ Å, $O_1-H_2O'=2·69$ Å, and $OH-H_2O'=2·75$ Å, all representative of probable H-bonds. The corresponding distances in codeine hydrobromide dihydrate are 4·55, 2·85, and 2·76 Å, respectively. The introduction of CH_3', therefore, has greatly increased the distance between O_1 and H_2O'' with the elimination of a H-bond, but has had no significant effect on the distance between OH and

H_2O'. The distance between O_1 and H_2O' has been increased to a value which is not much greater than the average for possible H-bonding, and the angle O_1–H_2O'–OH is not far from the tetrahedral value (see Table 5). It is possible, therefore, that the H-bond ($O_1 \cdots$ H–O′–H $\cdots$ O–H) between O_1 and H_2O' in morphine hydriodide dihydrate has merely been weakened, and not eliminated, in codeine hydrobromide dihydrate; this possibility has been recognized by the broken line between O_1 and H_2O' in the present Fig. 3.

The initial crystal structure investigation of morphine hydriodide dihydrate (Mackay & Hodgkin, 1955) and of codeine hydrobromide dihydrate (Lindsey & Barnes, 1955) independently confirmed the stereochemical configuration of morphine and codeine derived by Stork (1952) and by Rapoport & Lavigne (1953). At the same time Bentley & Cardwell (1955) and Kalvoda, Buchschacher & Jeger (1955) deduced an absolute configuration for morphine and related alkaloids from chemical and physical data which corresponds with that now found by direct crystal-structure analysis. In Fig. 1 of the present paper, if the carbocyclic ring containing $C_7=C_8$ is imagined to be rotated about a line through C_5 and C_{14} until it forms an extension of the oxide ring, the benzene ring and the other carbocyclic ring, a formal diagram is obtained which corresponds in all particulars with formula XII of Bentley & Cardwell (1955) when $R=CH_3$, and with formula XXVI of Kalvoda, Buchschacher & Jeger (1955) when the OH on C_3 is replaced by OCH_3. The hydrogen atoms on C_5, C_6, C_{14} (all in axial positions) and the ethanamine bridge are all *trans* to O_2, the hydrogen atom on C_9 and the OH on C_6 are both in equatorial positions, and the three-dimensional configuration is that of the present Fig. 1 and not the mirror image.

Although no attempts were made in the earlier stereochemical investigations to establish the absolute configuration, it is of interest to note that in Mackay & Hodgkin (1955) the co-ordinates of their Table 1 (referred to a right-handed system of axes) as well as the model shown in their Fig. 3, and the model implicit in the representation of overlapping atoms in the projection shown in Fig. 5 of Lindsey & Barnes (1955), all correspond with the true configuration. In the last case this arose fortuitously from considering the *z* co-ordinates (Lindsey & Barnes, 1955, Table 2) according to a left-handed system of axes for direct comparison with the conventional diagram as presented in Fig. 1 of the same paper. Finally, diagram I(*b*) of Rapoport & Lavigne (1953), in which the C_{15}–C_{16} bond should appear as though crossing in front of the C_{14}–C_{18} bond, and their model I(*a*), in which the piperidine ring should be in the chair (and not the boat) form, also represent the absolute configuration, while the formal diagram CCXLVII ($R=CH_3$) of Stork (1952) corresponds with its mirror image.

Data for the more accurate redetermination of the unit cell dimensions, and the intensities of the reflections which served to establish the absolute configuration, were collected by one of us (G. K.) at the Protein Structure Project, Brooklyn, N.Y. and at the Department of Biophysics, Roswell Park Memorial Institute, Buffalo, N.Y.; we wish to express our sincere gratitude to Dr David Harker for permission to use his elegant counter spectrometer equipment for this purpose. Grateful acknowledgment also is made to Army Pay Ledger Unit No. 1 in Ottawa, and to the Mathematics Department of the University of Ottawa, for the use of IBM 650 computers and for the co-operation of their respective staffs, and to Mrs M. E. Pippy of this laboratory for much assistance with the computations.

References

Bentley, K. W. & Cardwell, H. M. E. (1955). *J. Chem. Soc.*, p. 3252.

Cruickshank, D. W. J. (1955). Private communication.

Cruickshank, D. W. J. & Robertson, A. P. (1953). *Acta Cryst.* **6**, 698.

Dauben, C. H. & Templeton, D. H. (1955). *Acta Cryst.* **8**, 841.

Dyer, H. B. (1951). *Acta Cryst.* **4**, 42.

Furnas, T. C. (1957). *Single Crystal Orienter Instruction Manual.* Milwaukee: General Electric Co.

Kalvoda, J., Buchschacher, P. & Jeger, O. (1955). *Helv. Chim. Acta* **38**, 1847.

Kartha, G. & Ahmed, F. R. (1960). *Acta Cryst.* **13**, 532.

Kartha, G., Ahmed, F. R. & Barnes, W. H. (1960). *Acta Cryst.* **13**, 525.

Lindsey, J. M. & Barnes, W. H. (1955). *Acta Cryst.* **8**, 227.

Mackay, M. & Hodgkin, D. C. (1955). *J. Chem. Soc.*, p. 3261.

Rapoport, H. & Lavigne, J. B. (1953). *J. Amer. Chem. Soc.* **75**, 5329.

Robertson, J. H. & Beevers, C. A. (1951). *Acta Cryst.* **4**, 270.

Sim, G. A. (1955). *Acta Cryst.* **8**, 833.

Stork, G. in Manske, R. H. F. & Holmes, H. L. (1952). *The Alkaloids*, vol. II, p. 176. New York: Academic Press.

Trommel, J. & Bijvoet, J. M. (1954). *Acta Cryst.* **7**, 703.