

Andrew D. Grant

NORAMCO of Delaware,  
Wilmington, DE 19801

David E. Zacharias

The Institute for Cancer Research,  
Fox Chase, PA 19111

Linda M. Mascavage

Department of Chemistry, Beaver College,  
Glenside, PA 19038

George E. Kemmerer and David R. Dalton \* [1]

Department of Chemistry, Temple University,  
Philadelphia, PA 19122

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A single *N*-chloromethylcodinium iodide has been isolated from the reaction of chloriodomethane with codeine. Complete proton and carbon nmr and X-ray analyses dictate that this stable material bears the chloromethyl group axial. It is identical (except for the anion) to one of the salts obtained on long term storage of codeine in dichloromethane.

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It has been recognized for years that some amines react with dichloromethane to yield salts [2]. More recently, some of the adventitiously obtained products from the reaction of dichloromethane (used as a solvent) with some *secondary* amines have been elucidated [3] and, in at least one case, dichloromethane has been utilized specifically as a reactant [4].

Since caution in wrenching alkaloids out of their cellular matrices (largely to avoid artifacts of isolation) is al-

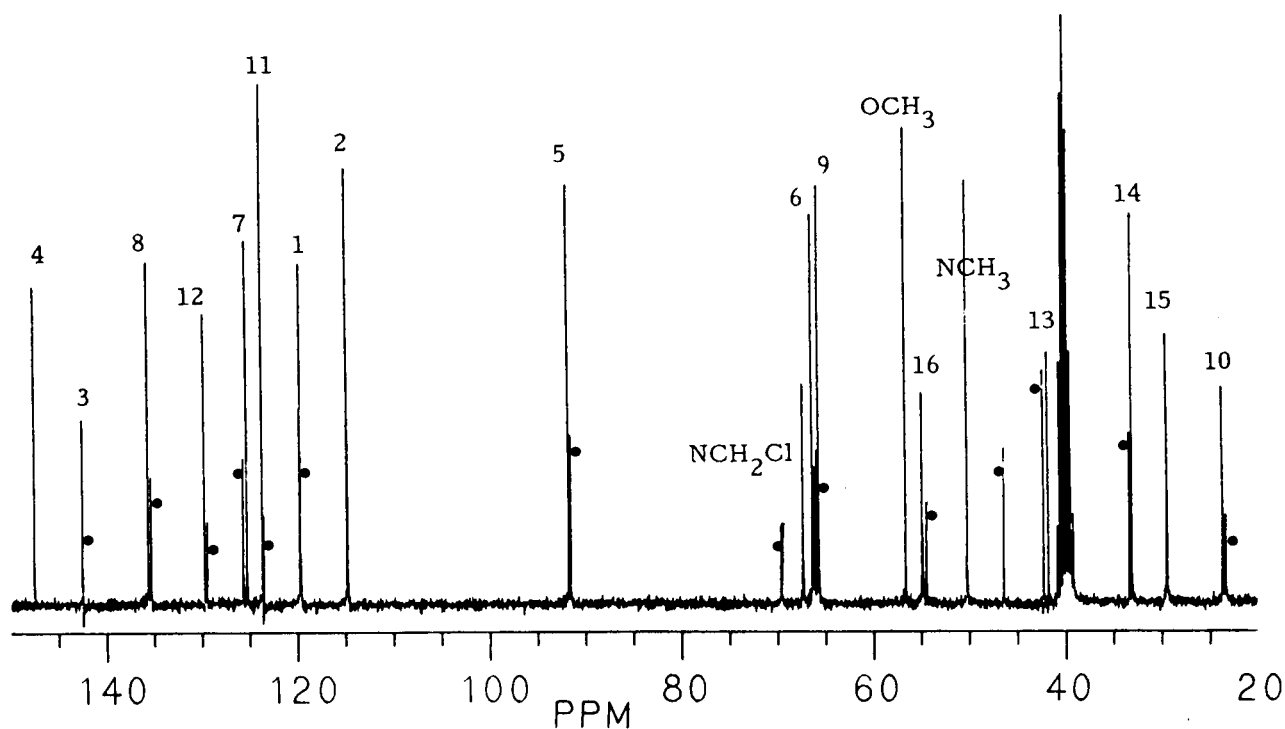
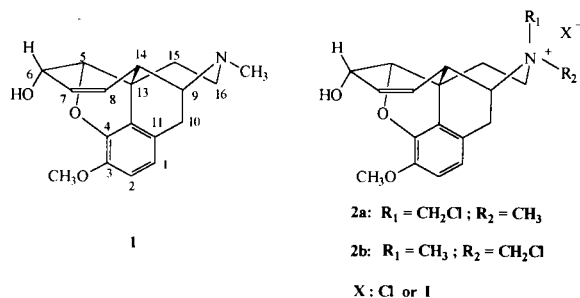


Figure 1. The  $^{13}\text{C}$  nmr (DMSO- $d_6$ ) spectrum of a mixture of the isomers **2a,b** (X = Cl). The minor isomer is represented with a •.

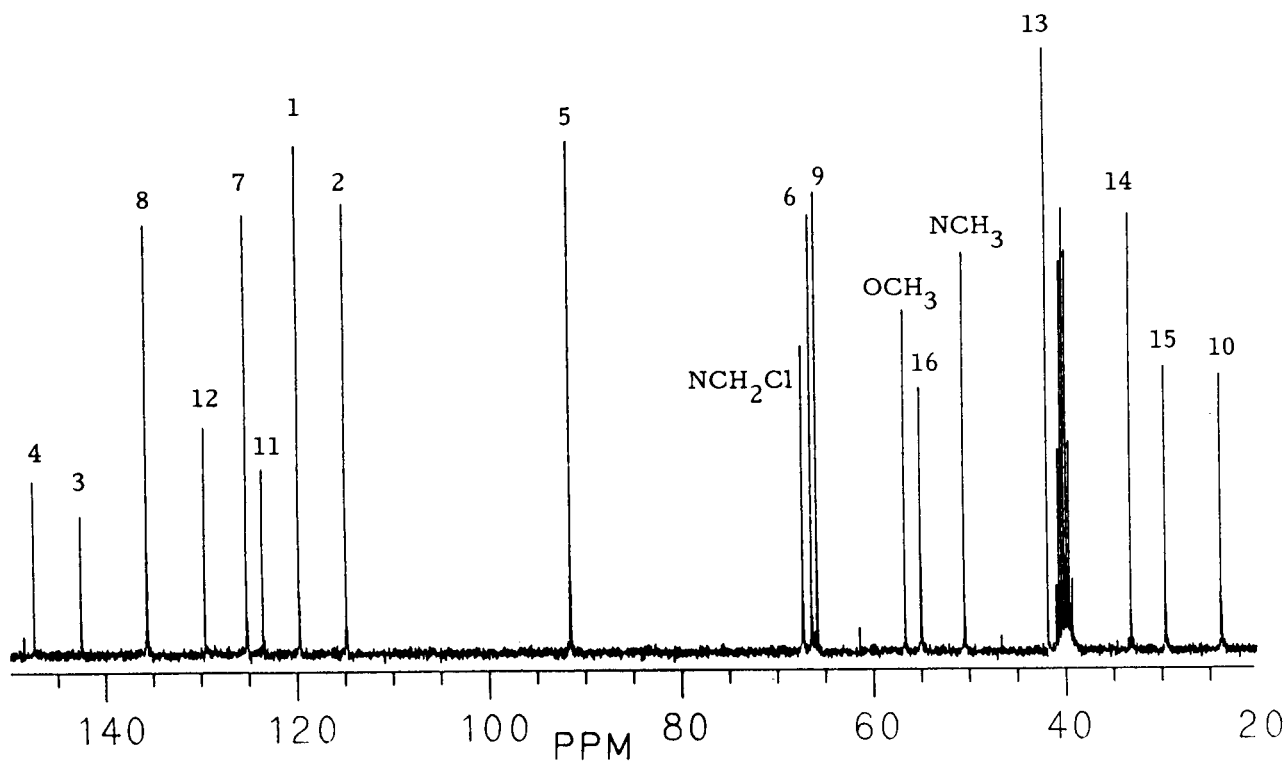


Figure 2. The  $^{13}\text{C}$  nmr ( $\text{DMSO-d}_6$ ) spectrum of **2a** (X = I).

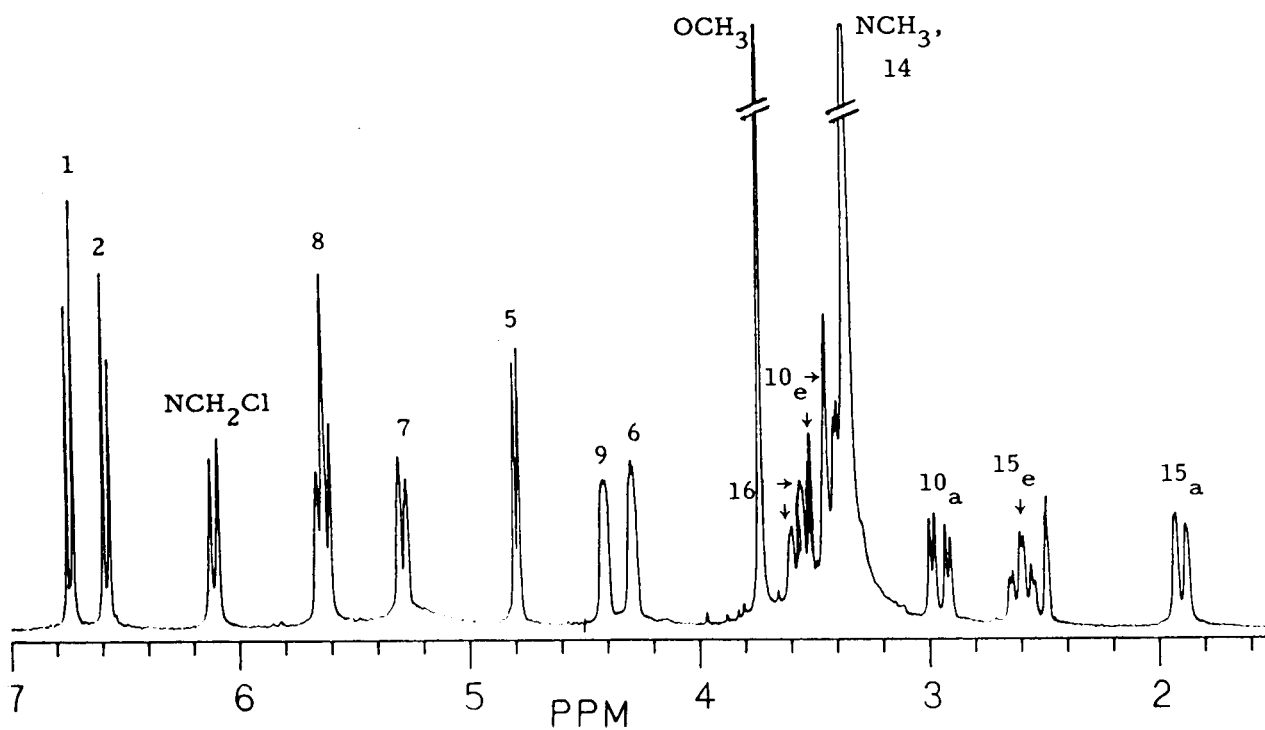


Figure 3. The  $^1\text{H}$  nmr ( $\text{DMSO-d}_6$ ) spectrum of **2a** (X = I).

ways advisable, the use of dichloromethane, the subsequent removal of which can be accomplished at low temperature, has been advocated despite its reactivity [5,6] and, indeed, the occasional isolation of product(s) from its reaction with those nitrogenous bases [7,8].

When codeine (**1**) is allowed to stand at room temperature for lengthy periods in dichloromethane, a small quantity of white crystalline material is deposited. Although the  $^1\text{H}$  nmr spectrum was quite complicated,  $^{13}\text{C}$  nmr (Figure 1) analysis provided the data presented in Table 1 and dictated that this crystalline mass was a mixture of the isomers **2a,b**:  $\text{X} = \text{Cl}$ . However, as their separation could not be effected and as the yield was low, the dichloromethane was replaced with chloriodomethane so that the Menshutkin reaction [9] might be better realized [10].

Table 1

 $^{13}\text{C}$  and  $^1\text{H}$  NMR Data for *N*-Chloromethylcodinium Salts **2** [a]

Carbon [b]	$^{13}\text{C}$ Shift <b>2a</b>	$^{13}\text{C}$ Shift <b>2b</b>	$^1\text{H}$ Shift <b>2a</b>
1	119.64	119.57	6.74, d, $J_{1,2} = 8.1$
2	114.76	114.70	6.58, d, $J_{2,1} = 8.1$
3	142.47	142.43	
4	147.44	147.51	
5	91.70	91.43	4.84, d, $J_{5,6} = 6.0$
6	66.29	66.04	4.32, d, $J_{6,5} = 6.0$
7	125.11	125.60	5.29, d, $J_{7,8} = 9.9$
8	135.52	135.23	5.67, d, $J_{8,7} = 9.9$
9	65.69	65.80	4.44, s (b)
10	23.63	23.25	ax 2.97, dd, $J_{\text{gem}} = 20.4$ eq 3.49, d
11	123.57	123.45	
12	129.65	129.49	
13	41.65	41.20	
14	33.02	33.26	3.65, s (b)
15	29.41	29.37	ax 1.92, dd, $J = 14.5, 3.3$ eq 2.63, dd, $J = 14.5, 4.5$
16	54.89	54.34	ax 3.61, d (b) eq 3.66, d (b)
O-CH <sub>3</sub>	56.55	56.53	3.77, s
N-CH <sub>3</sub>	50.35	46.32	3.39, s (b)
N-CH <sub>2</sub> Cl	67.19	69.52	diastereotopic, 5.68 and 6.04, d, $J_{\text{gem}} = 9.9$

[a] Chemical shifts are in ppm ( $\delta$ ) from TMS. Coupling constants are in Hz. Spectra were taken in sealed, degassed DMSO- $d_6$ . The  $^{13}\text{C}$  spectra were taken at 75.46 MHz and  $^1\text{H}$  spectra at 300.1 MHz. [b] Numbering as given on structure **1**.

In the event, in refluxing toluene (or, with greater facility, in refluxing ethanol), reaction of codeine (**1**) with the more labile alkylating agent readily produced a *single* isomer, identified as **2a**:  $\text{X} = \text{I}$  by  $^1\text{H}$  (Figure 2),  $^{13}\text{C}$  nmr (Figure 3), and single crystal X-ray analysis [11,12] (Figure 4). The nmr data are summarized in Table 1 and selected crystal data in Table 2.

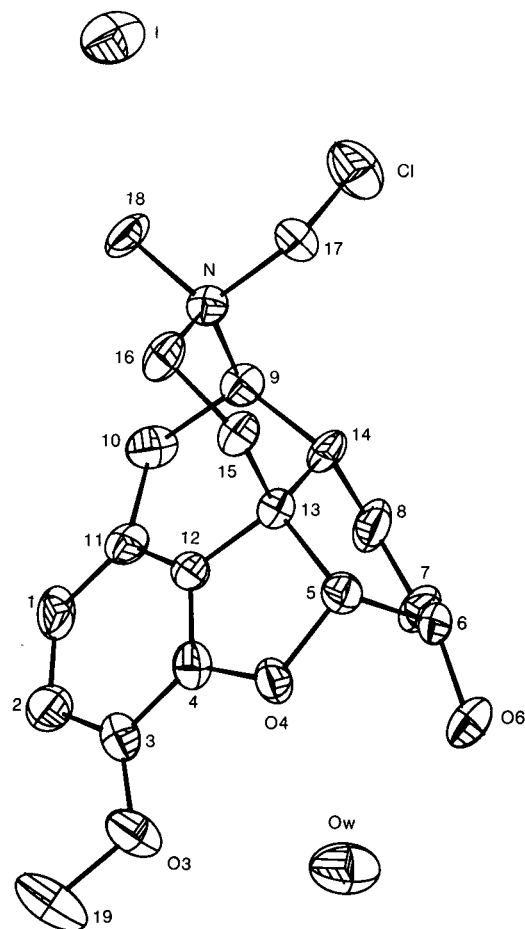


Figure 4. ORTEP illustration of the X-ray data for **2a** ( $\text{X} = \text{I}$ ) showing the atomic numbering used.

The isolation of a single isomer from the reaction of codeine (**1**) with chloriodomethane (and the recovery of unreacted starting material, see Experimental) argues for sluggish inversion through nitrogen [13] and sufficient steric encumbrance to the (presumed) bimolecular substitution reaction from the equatorial direction to preclude formation of the other isomer under these conditions. Interestingly, a significant steric interaction must be arising because of the *leaving group* (**I** versus **Cl**) in the Menshutkin reaction as both isomers **2a,b**:  $\text{X} = \text{Cl}$  (chloromethyl axial and chloromethyl equatorial, respectively) are found when the alkylation is effected using dichloromethane (albeit with the equatorial isomer present in lesser yield, ca. 2:1).

Reaction of codeine (**1**) with *meta*-chloroperoxybenzoic acid producing a single *N*-oxide to which (by nmr) is assigned the analogous structure (*i.e.*, methyl equatorial and oxygen axial) has also been reported [14]. Interestingly, in this case it also appears that an oxidizing agent with a smaller steric demand (hydrogen peroxide) produces both *N*-oxides, again with the axial isomer predominating [14].

**Table 2**  
Selected Bond Lengths and Angles of  
*N*-Chloromethylcodeinium Iodide Monohydrate

Distances (Å)			
Cl-C(17)	1.7623(7)	O(3)-C(19)	1.42(1)
O(4)-C(5)	1.446(9)	N-C(9)	1.552(9)
N-C(17)	1.53(1)	C(1)-C(2)	1.40(1)
C(2)-C(3)	1.39(1)	C(4)-C(12)	1.35(1)
C(5)-C(13)	1.54(1)	C(7)-C(8)	1.35(1)
C(9)-C(10)	1.53(1)	C(10)-C(11)	1.51(1)
C(12)-C(13)	1.52(1)	C(13)-C(15)	1.51(1)
O(3)-C(3)	1.39(1)	O(4)-C(4)	1.383(7)
O(6)-C(6)	1.41(1)	N-C(16)	1.51(1)
N-C(18)	1.508(9)	C(1)-C(11)	1.37(1)
C(3)-C(4)	1.38(1)	C(5)-C(6)	1.55(1)
C(6)-C(7)	1.48(1)	C(8)-C(14)	1.53(1)
C(9)-C(14)	1.54(1)	C(11)-C(12)	1.37(1)
C(13)-C(14)	1.53(1)	C(15)-C(16)	1.50(1)
Angles (degrees)			
C(3)-O(3)-C(19)	117.9(8)	C(6)-C(7)-C(8)	122.1(8)
C(9)-N-C(17)	111.6(6)	N-C(9)-C(14)	108.1(6)
C(16)-N-C(18)	111.3(7)	C(1)-C(11)-C(10)	125.3(8)
C(1)-C(2)-C(3)	120.8(8)	C(4)-C(12)-C(11)	123.1(6)
C(2)-C(3)-C(4)	116.9(8)	C(5)-C(13)-C(14)	116.2(6)
C(3)-C(4)-C(12)	120.9(6)	C(14)-C(13)-C(15)	109.9(6)
C(6)-C(5)-C(13)	113.6(6)	C(9)-C(14)-C(14)	107.7(6)
C(5)-C(6)-C(7)	113.3(6)	C(9)-N-C(16)	110.9(5)
N-C(9)-C(10)	112.0(7)	C(16)-N-C(17)	105.8(6)
C(9)-C(10)-C(11)	116.6(7)	C(2)-C(1)-C(11)	120.9(7)
C(10)-C(11)-C(12)	117.4(6)	O(3)-C(3)-C(4)	115.8(7)
C(5)-C(13)-C(12)	94.4(6)	O(4)-C(4)-C(12)	113.1(7)
C(12)-C(13)-C(15)	111.6(6)	O(4)-C(5)-C(13)	107.1(6)
C(8)-C(14)-C(13)	110.4(7)	O(6)-C(6)-C(7)	113.3(7)
N-C(16)-C(15)	112.5(6)	C(7)-C(8)-C(14)	117.9(6)
C(4)-O(4)-C(5)	105.8(6)	C(10)-C(9)-C(14)	112.8(6)
C(9)-N-C(18)	109.7(6)	C(1)-C(11)-C(12)	116.8(7)
C(17)-N-C(18)	107.4(6)	C(11)-C(12)-C(13)	126.5(6)
O(3)-C(3)-C(2)	126.8(7)	C(12)-C(13)-C(14)	106.3(6)
O(4)-C(4)-C(3)	126.0(7)	C(8)-C(14)-C(9)	111.6(6)
O(4)-C(5)-C(6)	109.8(6)	C(13)-C(15)-C(16)	113.7(6)
O(6)-C(6)-C(5)	111.7(6)		

## EXPERIMENTAL

### General.

Infrared (ir) spectra were taken on a Digilab FTS 40 spectrometer at either 0.5 or 2 cm<sup>-1</sup> resolution. The nmr (proton) spectra were taken at 300 and 500 MHz on General Electric QE-300 and/or Omega GN-500 systems - as a function of availability - while the <sup>13</sup>C spectra were routinely obtained at 75.46 MHz on the former. The hplc was effected on a Waters Delta Prep using reverse phase columns (C-18) and water-acetonitrile-acetic acid-ammonium acetate buffered solvents. A uv detector set at 254 nm was routinely used. Analyses were performed by Galbraith Laboratories Inc., Knoxville, TN.

### Chloromethylcodinium Chlorides **2a,b** (X = Cl).

Anhydrous codeine, **1**, was permitted to stand in dry methylene chloride for several months. A small quantity of white crystalline

solid was deposited. Filtration and recrystallization from methanol yielded a white solid, mp 180° dec. The <sup>13</sup>C nmr spectrum (DMSO-d<sub>6</sub>) of this material is presented Figure 1.

Anal. Calcd. for C<sub>19</sub>H<sub>23</sub>O<sub>3</sub>NCl<sub>2</sub>·2.5H<sub>2</sub>O: C, 53.11; H, 6.52. Found: C, 53.25; H, 6.56.

### Chloromethylcodinium Iodide (**2a**, X = I).

With stirring, under argon, a solution of anhydrous codeine (**1**) (1.00 g, 3.34 mmoles) in dry toluene (5 ml) was treated with chloriodomethane (0.50 ml, 1.21 g, 6.86 mmoles) added as one portion. The reaction mixture was stirred, with heating at 70-80° for 5 hours. On cooling, the tan residue (209.5 mg) was removed by filtration and the solvent evaporated from the light yellow filtrate at reduced pressure. The residue remaining after solvent removal was redissolved in anhydrous ethanol (15 ml) and a fresh portion of chloriodomethane (0.5 ml) added. This mixture was allowed to reflux, overnight, under an argon atmosphere. On cooling, an additional 476.2 mg of solid deposited. The two batches of identical (ir, potassium bromide) crystalline material were combined and recrystallized from ethanol to yield 529.4 mg (33%), mp 180° dec. The nmr spectra of this material are shown in Figure 2 and 3. The X-ray crystal structure is shown in Figure 4. By tlc (silica gel, hexane:acetone:methanol:ammonium hydroxide [60:40:20:1.5]) and hplc (*vide supra*), the combined mother liquors contained only unreacted codeine (**1**) and uncrystallized chloromethylcodinium iodide (**2a**).

### Acknowledgement.

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- [11] Crystals of *N*-chloromethylcodeinium iodide monohydrate, C<sub>19</sub>H<sub>23</sub>ClINO<sub>3</sub>·H<sub>2</sub>O are orthorhombic, space group *p* 2<sub>1</sub>2<sub>1</sub>, with *a* = 14.622(4), *b* = 19.897(3), *c* = 6.890(1) Å, *v* = 2004.6(8) Å<sup>3</sup>, *z* = 4, *d*<sub>calc</sub> = 1.64 g cm<sup>-3</sup>, *μ* = 17.36 cm<sup>-1</sup>, *F*(000) = 992, *T* = 293 K. Three-dimensional X-ray diffraction data were collected on a crystal 0.22 x 0.10 x 0.35 mm in size with a Siemens-Nicolet P3m diffractometer using variable *ω*-scans (rate range 4.19 - 58.6 deg.min<sup>-1</sup>, depending on reflection intensity) and monochromatized MoK $\alpha$  X-radiation, ( $\lambda$  = 0.71069 Å), in the 2 $\theta$ -range 0 to 52°. A total of 2274 Bragg reflections was surveyed and reduced to structure amplitudes by correction for geometric factors and X-ray absorption and placed on an absolute scale. In this way, 1582 unique data having *I*  $\geq$  2.50  $\sigma$ (*I*) were obtained for use in further calcula-

tions. Values for  $\alpha(F)$  were obtained from the relation  $\alpha(F) = (F/2)[\sigma^2(I)/I^2 + \delta^2]^{1/2}$ , where  $I$  is the integrated reflection intensity observed,  $\alpha(I)$  is derived from counting statistics and  $\delta (=0.023)$  is an instrumental uncertainty determined from the variation in the intensities of 4 reference reflections periodically monitored during the data collection. The structure was solved using Patterson and Fourier methods. The position and thermal parameters were refined on  $F$  with isotropic and then anisotropic thermal parameters using a full-matrix least-squares procedure (H. L. Carrell, H.-S. Shieh and F. Takusagawa, Institute for Cancer Research, Fox Chase Cancer Center). Before anisotropic refinement, the absolute configuration of the molecule was determined from the anomalous X-ray scattering of the iodine, chlorine and oxygen atoms by the R-factor ratio test [12a,b]. All hydrogen atoms were found from successive difference Fourier maps and included in the final refinement with isotropic thermal factors equivalents to those of the atoms to which they are bonded. Only those hydrogens attached to the water oxygen and O(6) were refined. The final residuals are  $R_{obs} = 0.050$ ,  $wR_{obs} = 0.056$ ,  $R_{all} = 0.082$ ,  $wR_{all} = 0.066$  for 238 variables refined. The final difference Fourier map had  $\rho_{max} = 0.67$ ,  $\rho_{min} = -0.52$  e/Å<sup>3</sup>. The quantity minimized during the refinement was  $\Sigma(w | | F_{obs} | - | F_{calc} | | )^2$ , with

the weight,  $w = (\sigma^2(F))^{-1}$  for each reflection.

The complete set of atomic coordinates for this structure will be available in due course from the Cambridge Crystallographic Data Centre. They may be obtained, on request, from The Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK or directly from D.E.Z. The ORTEP representation was produced according to C. K. Johnson, ORTEP: A Fortran Thermal-ellipsoid Plot Program for Crystal Structure Illustrations. Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN (1965).

[12] The *absolute* configuration is that shown (Figure 4) and was determined from the anomalous X-ray scattering of the iodide. It is in accord with that for codeine hydrobromide dihydrate. See [a] W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965); [b] G. Dartha, F. R. Ahmed and W. H. Barnes, *ibid.*, **15**, 326 (1962).

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