Analgesics. Part II.[1] Crystal Structure of Dihydrometacodeinone Hydrochloride

By **John Victor Tillack** and **Colin H. L. Kennard**,* Department of Chemistry, University of Queensland, Brisbane, Queensland 4067, Australia

The crystal structure of the title compound has been determined from three-dimensional diffractometer data by direct methods (tangent expansion formula). Crystals are orthorhombic, space group $P2_12_12_1$ with $Z = 4$ in a unit cell of dimensions: $a = 1147(1)$, $b = 1348(1)$, $c = 1053(1)$ pm. Least-squares refinement was halted at R 0·14 for 1559 observed reflections. The analysis has confirmed that the asymmetric carbon atoms C(5), C(13), and C(14) have the ααβ-configuration, with C(9) being unaltered during the transformation from thebaine to dihydrometacodeinone.

THE ' meta ' series of codeine derivatives[2] differ from codeine in having a five-membered *N*-heterocyclic ring. This results in three asymmetric carbon atoms, C(5), C(13), and C(14), with unknown stereochemistry, and gives rise to eight possible configurations for the molecule. The n.m.r. spectrum and Dreiding models indicate[3] that the ααβ-configuration is the most probable.

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[1] Part I, J. V. Tillack, R. C. Seccombe, C. H. L. Kennard, and P. W. T. Oh, *Rec. Trav. chim.*, in the press.

[2] C. Schöpf and H. Perrey, *Annalen*, 1930, **483**, 169.

[3] T. J. Batterham, K. H. Bell, and U. Weiss, *Austral. J. Chem.*, 1966, **19**, 321.

The stereochemistry of dihydrometacodeinone hydrochloride is of interest in considering the connection between molecular shape and analgesic activity of the compound.

DISCUSSION

The determination confirms the assignment[3] of the stereochemistries of the three asymmetric carbon atoms C(5), C(13), and C(14), as ααβ with respect to the relative orientations of the protons attached to C(5) and C(13) and of the C(14)–C(15) bond (Figure 1). The stereochemistry of C(9) remains unaltered during the transformation from thebaine to dihydrometacodeinone. As there are five fused rings in the molecule it is apparent that there will be considerable strain, and this must confer a high degree of rigidity. The angles between bonded atoms and aromatic ring (ring A in the conventional notation used with codeine congeners), deviate from 120° about the carbon atoms C(11), C(12), and C(4) shared with rings B and E, *e.g.* C(1)–C(11)–C(10) 131·1°. Atoms C(10), C(13), and O(2) are 19, 20, and 24 pm from the aromatic plane. Figure 2 shows that the major part of the molecule lies in the plane of the aromatic group, with the *N*-heterocyclic ring projecting from this plane, giving the molecule the overall T-shape common to morphine-type analgesics.

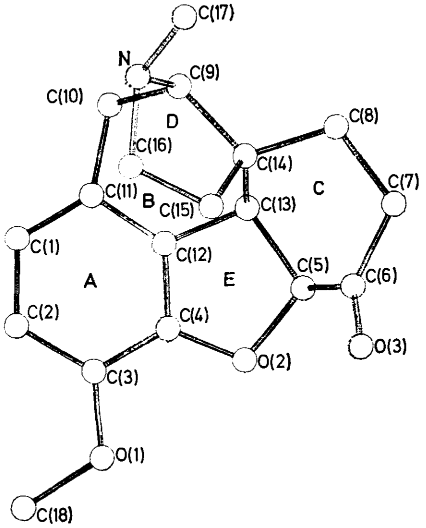

FIGURE 1 Projection normal to the benzene ring

Ring C is in the boat conformation, with the carbonyl group turned away from the bulk plane of the molecule in the direction of the *N*-heterocyclic ring.

The major structural differences from codeine, in terms of the bulk shape of the molecule, is the decreased shielding of the nitrogen atom. The *meta*-linkage causes the *N*-heterocyclic ring to swing further from the aromatic section of the molecule than in the codeine. The spatial relationships of the nitrogen atom and the benzene ring are considered important in the receptor site theory.[4] It is thought that the different analgesic activity of this compound is due in part to the difference in fit in the 'receptor site' as a result of the different stereochemistry about the cationic centre. The intrinsic activity of the drug may also be affected by greater availability of the lone pair of electrons of the nitrogen atom.

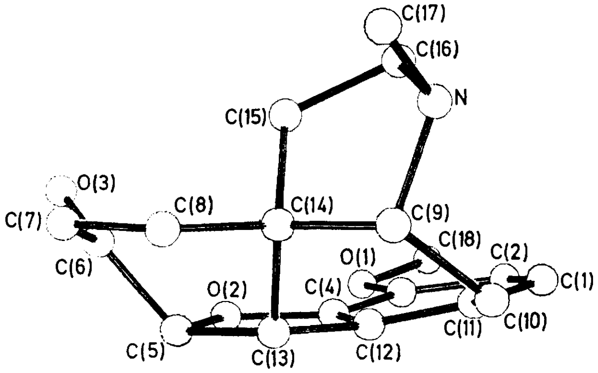

FIGURE 2 Another view of the dihydrometacodeinone molecule

The chlorine atoms lie in columns parallel to the *a* axis, giving chains of chlorine–nitrogen interactions (Cl · · · N 295 pm). The only other short intermolecular contacts are O(3) · · · C(17) (328 pm) and O(3) · · · C(8) (334 pm). As the hydrogen atom of the hydrochloride has not been located, interpretation of the crystal packing is difficult, however the packing of the molecules appears to be influenced by the Cl–N interactions (Figure 3).

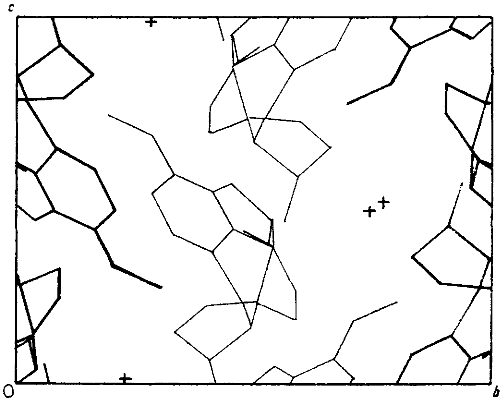

FIGURE 3 Packing of the molecules projected in the *bc* plane. + Marks location of a chlorine atom

EXPERIMENTAL

Crystal Data.—$C_{18}H_{22}ClNO_3$, M = 335·5. Orthorhombic, a = 1147(1), b = 1348(1), c = 1053(1) pm, U = 1·628 nm^3, D_m = 1·35 (flotation), Z = 4, D_c = 1·37, $F(000)$ = 712. Space group $P2_12_12_1$ (D_2^4, No. 19). Cu-K_α Radiation, λ = 154·18 pm.

Intensity data for the layers 0—8*hkl* and *h*0—12*l* were collected from two crystals by use of a PDP8/S controlled Supper equi-inclination diffractometer.[5] Intensities were

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[4] A. G. Beckett, 'Progress in Drug Research,' Birkhäuser, Basel, 1959, pp. 524—530.

[5] H. C. Freeman, J. M. Guss, C. E. Nockolds, R. Page, and A. Webster, *Acta. Cryst.*, 1970, *A*, **26**, 149.

measured by the ω scan method at a rate dependent on peak intensity to give constant counting statistics. After correcting for Lorentz and polarization factors, the two data sets were scaled together [6,7] to give 1711 independent reflections of which 1549 were considered observed having $I > 2{\cdot}5\sigma(I)$. No correction was made for absorption.

Structure Determination and Refinement.—The structure was determined by direct methods by application of the tangent expansion formula. Attempts to expand a starting set of three origin-defining reflections and one enantiomorph-defining reflection failed to reveal the structure. It was thought that triplet relationships involving the highly interactive reflection (3,5,3) gave incorrect phase assignment early in the sequence. In order to overcome this difficulty, three symbolic phases were included in the starting set and the tangent expansion formula applied using the program TANFIZ.[8] Symbolic phases were assigned starting values of 0, $\pi/2$, π, $3\pi/2$ giving, on interactive refinement, 64 solutions. The lowest R_K (0·25) was used to select one set. An E map based on these phases revealed the structure.

Three cycles of full-matrix least-squares refinement with isotropic temperature factors reduced the conventional R to 0·14 and R' to 0·12; (where $R' = [\Sigma w|F_o - F_c|^2/\Sigma|F_o|^2]^{\frac{1}{2}}$). Refinement was halted at this stage. A difference-Fourier showed peaks and troughs about the chlorine atom indicative of anisotropic thermal motion. There were no unassignable features. Table 1 lists atomic parameters, and Tables 2 and 3 interatomic distances and angles. Observed and calculated structure amplitudes ($\times 10$) are in Supplementary Publication No. SUP 20824 (5 pp.).*

TABLE 1

Atomic positions (fractional co-ordinates) and temperature factors, with estimated standard deviations in parentheses

Atom	x/a	y/b	z/c	B/Å^2
Cl	0·2880(3)	0·2269(2)	0·0029(3)	3·8(1)
C(1)	−0·2380(10)	0·6697(8)	0·9160(11)	3·0(2)
C(2)	−0·1870(10)	0·7121(8)	1·0259(11)	2·7(2)
C(3)	−0·0859(12)	0·6707(9)	1·0774(12)	3·4(2)
C(4)	−0·0441(10)	0·5857(8)	1·0253(11)	2·8(2)
C(5)	0·0785(10)	0·4584(8)	0·9602(11)	3·0(2)
C(6)	0·1883(10)	0·4688(8)	0·8863(12)	3·1(2)
C(7)	0·1944(11)	0·4091(8)	0·7633(12)	2·8(2)
C(8)	0·0816(10)	0·4087(7)	0·6806(10)	2·5(2)
C(9)	−0·1142(9)	0·5058(7)	0·6559(10)	2·2(2)
C(10)	−0·2261(11)	0·5289(8)	0·7408(12)	2·9(2)
C(11)	−0·1942(10)	0·5837(8)	0·8632(10)	2·5(2)
C(12)	−0·1007(10)	0·5423(8)	0·9249(11)	2·4(2)
C(13)	−0·0295(10)	0·4612(8)	0·8700(11)	2·6(2)
C(14)	0·0002(9)	0·4924(7)	0·7304(10)	1·7(2)
C(15)	0·0594(9)	0·5971(7)	0·7216(10)	1·9(2)
C(16)	−0·0245(9)	0·6626(7)	0·6459(10)	2·0(2)
C(17)	−0·0387(11)	0·5621(8)	0·4441(11)	2·9(2)
C(18)	−0·0644(13)	0·8039(9)	1·2338(14)	4·4(3)
N	−0·0963(8)	0·5920(6)	0·5695(8)	2·2(2)
O(1)	−0·0234(8)	0·7094(6)	1·1764(9)	4·3(2)
O(2)	0·0630(7)	0·5409(5)	1·0531(8)	3·3(2)
O(3)	0·2691(8)	0·5180(6)	0·9246(9)	4·4(2)

Atomic scattering factors for carbon, nitrogen, oxygen, and chlorine were taken from ref. 9. No corrections were applied for anomalous dispersion. All computations were made by use of local versions of standard programs [10] on a CDC 3600 computer at the Division of Computing Research, C.S.I.R.O., Canberra.

TABLE 2

Bond lengths (pm), with estimated standard deviations in parentheses

C(1)–C(2)	142(3)	C(9)–C(10)	159(3)
C(2)–C(3)	140(3)	C(10)–C(11)	153(3)
C(3)–C(4)	136(3)	C(11)–C(1)	138(3)
C(3)–O(1)	137(3)	C(11)–C(12)	137(3)
O(1)–C(18)	149(2)	C(12)–C(4)	137(3)
C(4)–O(2)	140(2)	C(12)–C(13)	148(3)
O(2)–C(5)	149(2)	C(13)–C(5)	156(3)
C(5)–C(6)	149(3)	C(13)–C(14)	157(3)
C(6)–O(3)	121(2)	C(14)–C(15)	157(3)
C(6)–C(7)	153(3)	C(15)–C(16)	153(3)
C(7)–C(8)	156(3)	C(16)–N	149(3)
C(8)–C(14)	155(3)	N–C(9)	149(3)
C(14)–C(9)	154(3)	N–C(17)	153(3)

TABLE 3

Bond angles (deg.); estimated standard deviations 1°

C(2)–C(1)–C(11)	121·1	C(1)–C(11)–C(12)	115·8
C(1)–C(2)–C(3)	119·9	C(10)–C(11)–C(12)	112·9
C(2)–C(3)–O(1)	125·3	C(4)–C(12)–C(11)	124·1
C(4)–C(3)–O(1)	116·4	C(4)–C(12)–C(13)	110·8
C(4)–C(3)–C(2)	118·3	C(11)–C(12)–C(13)	123·1
C(3)–C(4)–O(2)	126·1	C(5)–C(13)–C(12)	102·6
C(3)–C(4)–C(12)	120·3	C(5)–C(13)–C(14)	113·8
C(12)–C(4)–O(2)	113·1	C(12)–C(13)–C(14)	106·7
C(6)–C(5)–O(2)	111·9	C(8)–C(14)–C(9)	115·1
C(6)–C(5)–C(13)	110·6	C(8)–C(14)–C(13)	104·6
C(13)–C(5)–O(2)	106·6	C(8)–C(14)–C(15)	111·9
C(5)–C(6)–C(7)	115·7	C(9)–C(14)–C(13)	108·9
C(5)–C(6)–O(3)	121·8	C(9)–C(14)–C(15)	103·5
C(7)–C(6)–O(3)	122·5	C(13)–C(14)–C(15)	113·0
C(6)–C(7)–C(8)	115·9	C(14)–C(15)–C(16)	106·1
C(7)–C(8)–C(14)	107·9	C(15)–C(16)–N	105·0
C(10)–C(9)–C(14)	115·0	C(9)–N–C(16)	104·2
C(10)–C(9)–N	107·5	C(9)–N–C(17)	112·4
C(14)–C(9)–N	106·5	C(16)–N–C(17)	113·2
C(9)–C(10)–C(11)	111·9	C(3)–O(1)–C(18)	118·1
C(1)–C(11)–C(10)	131·1	C(4)–O(2)–C(5)	106·8

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* For details see Notice to Authors No. 7 in *J.C.S. Dalton*, 1972, Index issue.

[6] A. D. Rae, *Acta Cryst.*, 1965, **19**, 683.

[7] A. D. Rae and A. B. Blake, *Acta Cryst.*, 1966, **20**, 586.

[8] TANFIZ, Tangent expansion program, by S. Motherwell and E. Larson, modified locally by J. V. Tillack, 1971.

[9] 'International Tables for X-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962, pp. 201—227.

[10] PREDAP, Structure factor program, by K. G. Shields, 1971; FORDAP, Fourier program, by A. Zalkin and R. J. Dellaca, modified by K. G. Shields, 1971; ORFLS, full-matrix least-squares program, by W. R. Busing, K. O. Martin, and H. A. Levy, 1964.