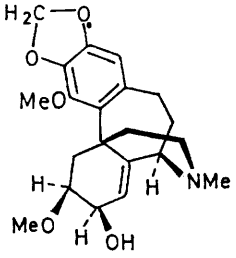
Molecular Structure and Absolute Stereochemistry of a 1-Phenylethylisoquinoline Alkaloid from *Colchicum cornigerum*: *X*-ray Analysis of a Methiodide Derivative

By **A. Forbes Cameron** * and **Christine Hannaway**, Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

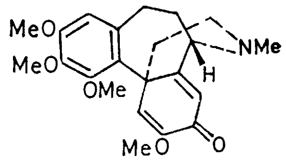
The alkaloid CC-2 (*Colchicum cornigerum* alkaloid number 2) has been shown to possess the molecular structure and absolute stereochemistry (I) by single-crystal *X*-ray analysis of a methiodide derivative. Crystals are orthorhombic, space group $P2_12_12_1$, with $Z = 4$ in a unit cell of dimensions $a = 7{\cdot}75(2)$, $b = 14{\cdot}57(2)$, $c = 21{\cdot}55(4)$ Å. The structure was solved by the heavy-atom method by use of 1739 visually estimated independent reflexions, and refined by block-diagonal least-squares calculations to R 0·13. The absolute configuration was determined by considering anomalous scattering effects.

THE rare alkaloids of the plant *Colchicum cornigerum* have proved to be of considerable biosynthetic interest. Although the main alkaloids from this source, such as colchicine, cornigerine, and demecolcine, have been shown to be tropolones,[1] the discovery[2] that (—)-*O*-methylandrocymbine (II) is the precursor of colchicine and related alkaloids, indicates that these tropolones should be classed as highly modified 1-phenylethylisoquinoline systems. More recently, Battersby and co-workers[3] have described a further eight alkaloids isolated from *C. cornigerum*, all of which belong to the new class of substances derived from 1-phenylethylisoquinoline. In particular, one alkaloid, autumnaline (III) is the first unmodified 1-phenylethylisoquinoline to be found in nature, and the remaining seven compounds could in principle be biosynthesised from (+)- or (—)-autumnaline by two alternative modes of phenol coupling.

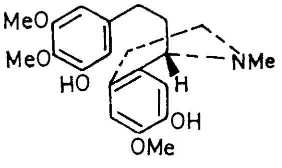
The structures and stereochemistries of seven of the eight alkaloids studied by Battersby and co-workers could be assigned unambiguously by a combination of



(I)



(II)



(III)

---

[1] M. Saleh, S. El-Gangihi, A. El-Hamidi, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1963, **28**, 3413; H. Potěšilová, J. Šantavý, A. El-Hamidi, and F. Šantavý, *ibid.*, 1969, **34**, 3540.

[2] A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *Chem. Comm.*, 1966, 603; A. R. Battersby, *Pure and Applied Chem.*, 1967, **14**, 117.

[3] A. R. Battersby, R. Ramage, A. F. Cameron, C. Hannaway, and F. Šantavý, *J. Chem. Soc.* (*C*), 1971, 3514.

spectroscopic techniques and chemical modification. However, for the eighth compound, code-named CC-2, it proved impossible to resolve the structure solely on the bases of spectroscopic and chemical evidence. We therefore undertook a single-crystal *X*-ray analysis of the methiodide of the *O*-acetyl derivative of CC-2, which proved that the structure and absolute stereochemistry of the alkaloid are described by the formula (I).

EXPERIMENTAL

Crystal Data.—$[C_{24}H_{32}O_6N]^+I^-$, $M = 558$. Orthorhombic, $a = 7{\cdot}75(2)$, $b = 14{\cdot}57(2)$, $c = 21{\cdot}55(4)$, $U = 2433$ Å^3, $D_m = 1{\cdot}51$ (by flotation), $Z = 4$, $D_c = 1{\cdot}52$, $F(000) = 1136$. Space group $P2_12_12_1$ (D_2^4, No. 19) from systematic absences. Cu-K_α radiation, $\lambda = 1{\cdot}5418$ Å; μ(Cu-K_α) $= 108{\cdot}6$ cm^{-1}. Crystal size *ca.* $0{\cdot}6 \times 0{\cdot}3 \times 0{\cdot}1$ mm.

Crystallographic Measurements.—Unit-cell parameters were determined from oscillation and Weissenberg photographs taken with Cu-K_α radiation. A small crystal, rotating about *a*, was exposed to Cu-K_α radiation, and 1739 independent intensities from the reciprocal-lattice nets 0—6*kl* were recorded on Weissenberg photographs by use of the multiple-film technique. Intensities, estimated visually by comparison with a calibrated strip, were corrected for the appropriate Lorentz and polarisation factors, and were subsequently placed on an approximate absolute scale by making $k\Sigma|F_o| = \Sigma|F_c|$ for each layer. Absorption effects were not considered.

Structure Determination.—The position of the iodide ion was determined from the three-dimensional Patterson function, and the analysis thereafter proceeded directly on the basis of the phase-determining heavy-atom method. The complete alkaloid skeleton was revealed in the course of four successive structure-factor and electron-density calculations which also effected preliminary refinement, reducing *R* to 0·22. In these calculations, an overall isotropic thermal parameter, U_{iso} 0·06 Å^2, was assumed.

Structure Refinement.—The refinement of positional, vibrational, and scale parameters by block-diagonal three-dimensional least-squares calculations converged after 8 cycles when *R* was 0·134 and R' ($= \Sigma w\Delta^2/\Sigma w|F_o|^2$) was 0·029. After cycle 4 the data were put on an overall absolute scale by use of the refined values of the layer-scale factors, and in all subsequent cycles the overall scale factor was refined. Also after cycle 4, anisotropic thermal parameters for the iodide ion were refined, although all other atoms continued to be refined isotropically.

In all cycles, a weighting scheme of the form: $\sqrt{w} = (\{1 - \exp[-p_1(\sin\theta/\lambda)^2]\}/[1 + p_2|F_o| + p_3|F_o|^2])^{\frac{1}{2}}$ was applied to the data. Initially the *p* parameters were chosen to give unit weights to all reflexions, but they were varied in later cycles as indicated by an ($|F_o|$ and $\sin\theta/\lambda$) analysis of $w\Delta^2$. The final values are p_1 100, p_2 0·001, and p_3 0·0005.

On convergence of the least-squares refinement, structure factors were calculated and a difference synthesis and electron-density distribution were evaluated. Neither revealed any errors in the structure, and although the difference synthesis showed diffuse peaks in positions stereochemically acceptable for hydrogen atoms, it was impossible to determine their co-ordinates with any accuracy. Both the structure determination and refinement were therefore considered complete.

In all structure-factor calculations atomic scattering factors were taken from ref. 4. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 20662 (2 pp.).* Fractional co-ordinates, U_{iso} and U_{ij} values for all non-hydrogen atoms are in Table 1. Table 2 contains bond lengths, valency angles, intra- and inter-molecular non-bonded distances. Estimated standard deviations, derived from the inverse of the least-squares normal-equation matrix, are included in Tables 1 and 2, but are probably best regarded as underestimates. Table 3 gives details of best-plane calculations performed for various parts of the molecular framework.

TABLE 1

Fractional co-ordinates, and thermal parameters (Å^2) with estimated standard deviations in parentheses

	x/a	y/b	z/c	U_{iso}
I(1)	0·20782(28)	0·25804(11)	0·19354(10)	*
O(1)	0·6990(32)	−0·1634(14)	0·5289(09)	0·075(5)
O(2)	0·4272(26)	−0·1602(13)	0·4841(08)	0·061(5)
O(3)	0·3300(23)	−0·0374(11)	0·3869(07)	0·051(4)
O(4)	0·6206(30)	0·2157(14)	0·4507(09)	0·070(5)
O(5)	0·6943(32)	0·3736(13)	0·3880(09)	0·074(5)
O(6)	0·4571(31)	0·4543(14)	0·4018(09)	0·075(6)
N(1)	0·7768(31)	0·0650(13)	0·2241(09)	0·051(5)
C(1)	0·5332(38)	−0·0982(17)	0·4559(12)	0·050(6)
C(2)	0·7020(42)	−0·0978(17)	0·4815(12)	0·055(6)
C(3)	0·8128(48)	−0·0459(21)	0·4629(14)	0·072(8)
C(4)	0·7815(41)	0·0210(17)	0·4140(12)	0·057(7)
C(5)	0·6229(37)	0·0241(16)	0·3873(11)	0·046(6)
C(6)	0·4987(34)	−0·0365(16)	0·4094(11)	0·046(6)
C(7)	0·2596(45)	−0·1232(21)	0·3600(14)	0·070(8)
C(8)	0·9388(42)	0·0724(19)	0·3892(13)	0·063(7)
C(9)	0·9694(41)	0·0510(19)	0·3205(12)	0·058(7)
C(10)	0·8558(36)	0·1148(17)	0·2792(12)	0·049(6)
C(11)	0·7158(34)	0·1578(14)	0·3171(10)	0·040(5)
C(12)	0·5663(36)	0·0968(17)	0·3398(12)	0·050(6)
C(13)	0·4233(33)	0·1616(15)	0·3663(10)	0·042(6)
C(14)	0·4847(40)	0·2409(21)	0·4026(13)	0·065(7)
C(15)	0·5916(36)	0·3031(17)	0·3579(11)	0·050(6)
C(16)	0·7145(40)	0·2507(19)	0·3246(12)	0·067(7)
C(17)	0·4923(35)	0·0539(16)	0·2815(11)	0·046(6)
C(18)	0·6371(37)	0·0013(16)	0·2451(11)	0·048(6)
C(19)	0·7240(55)	0·1363(25)	0·1769(16)	0·089(11)
C(20)	0·9358(57)	0·0073(27)	0·1949(18)	0·096(11)
C(21)	0·6047(43)	0·4471(20)	0·4088(13)	0·063(7)
C(22)	0·7441(46)	0·5147(20)	0·4338(14)	0·070(8)
C(23)	0·5256(62)	0·1765(31)	0·5068(18)	0·104(13)
C(24)	0·5457(46)	−0·2157(22)	0·5202(15)	0·073(8)

* Anisotropic thermal parameters U_{ij} ($10^4 \times$ Å^2) with estimated standard deviations

	U_{11}	U_{22}	U_{33}	$2U_{23}$	$2U_{31}$	$2U_{12}$
I(1)	641(12)	475(7)	911(12)	260(19)	−112(22)	−194(19)

The anisotropic thermal parameter is in the form:

$$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{32}lkc^*b^* + 2U_{31}lhc^*a^* + 2U_{12}kha^*b^*)].$$

The atomic numbering is shown in Figure 1, and the molecular packing viewed down *a* is shown in Figure 2.

Determination of Absolute Stereochemistry.—Marked differences were observed in the intensities of 45 Bijvoet pairs of reflexions arising from the anomalous scatter of Cu-K_α radiation, principally by the iodide ion.[5] Including complex terms, structure amplitudes corresponding to these 45 pairs of reflexions were calculated for both enantiomorphic

---

* See Notice to Authors No. 7 in *J.C.S. Dalton*, 1972, index issue.

[4] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962.

[5] J. M. Bijvoet, *Proc. Acad. Sci. Amsterdam*, 1949, **52**, 313.

TABLE 2

Interatomic distances and angles with estimated standard deviations in parentheses

(*a*) Bond distances (Å)

C(1)–C(2)	1·42(4)	C(11)–C(16)	1·36(4)
C(1)–C(6)	1·37(4)	C(12)–C(17)	1·51(3)
C(1)–O(2)	1·36(3)	C(12)–C(13)	1·54(4)
C(2)–C(3)	1·21(3)	C(13)–C(14)	1·47(4)
C(2)–O(1)	1·40(3)	C(14)–C(15)	1·56(3)
C(3)–C(4)	1·46(4)	C(14)–O(4)	1·52(3)
C(4)–C(5)	1·36(4)	C(15)–C(16)	1·42(4)
C(4)–C(8)	1·53(4)	C(15)–O(5)	1·45(3)
C(5)–C(6)	1·39(3)	C(17)–C(18)	1·57(3)
C(5)–C(12)	1·54(4)	C(18)–N(1)	1·50(4)
C(6)–O(3)	1·39(3)	C(19)–N(1)	1·51(4)
C(7)–O(3)	1·48(3)	C(20)–N(1)	1·62(4)
C(8)–C(9)	1·53(4)	C(21)–C(22)	1·56(3)
C(9)–C(10)	1·56(3)	C(21)–O(5)	1·35(3)
C(10)–C(11)	1·50(4)	C(21)–O(6)	1·16(3)
C(10)–N(1)	1·52(4)	C(23)–O(4)	1·53(3)
C(11)–C(12)	1·54(3)	C(24)–O(1)	1·42(3)
		C(24)–O(2)	1·45(3)

(*b*) Valency angles (°)

C(2)–C(1)–C(6)	117(3)	C(14)–C(15)–C(16)	111(3)
C(2)–C(1)–O(2)	113(2)	C(14)–C(15)–O(5)	115(3)
C(6)–C(1)–O(2)	130(2)	C(16)–C(15)–O(5)	104(3)
C(1)–C(2)–C(3)	122(3)	C(15)–C(16)–C(11)	127(3)
C(1)–C(2)–O(1)	105(2)	C(12)–C(17)–C(18)	110(2)
C(3)–C(2)–O(1)	134(3)	C(17)–C(18)–N(1)	111(2)
C(2)–C(3)–C(4)	123(3)	C(22)–C(21)–O(5)	105(2)
C(3)–C(4)–C(5)	119(3)	C(22)–C(21)–O(6)	132(3)
C(3)–C(4)–C(8)	117(2)	O(5)–C(21)–O(6)	122(2)
C(5)–C(4)–C(8)	124(3)	O(1)–C(24)–O(2)	107(2)
C(4)–C(5)–C(6)	118(2)	C(2)–O(1)–C(24)	106(2)
C(4)–C(5)–C(12)	124(2)	C(1)–O(2)–C(24)	103(2)
C(6)–C(5)–C(12)	118(3)	C(6)–O(3)–C(7)	119(3)
C(5)–C(6)–C(1)	122(2)	C(14)–O(4)–C(23)	107(2)
C(5)–C(6)–O(3)	122(3)	C(15)–O(5)–C(21)	115(2)
C(1)–C(6)–O(3)	116(3)	C(10)–C(11)–C(12)	119(3)
C(4)–C(8)–C(9)	111(3)	C(12)–C(11)–C(16)	122(3)
C(8)–C(9)–C(10)	110(3)	C(5)–C(12)–C(11)	113(2)
C(9)–C(10)–C(11)	110(2)	C(5)–C(12)–C(13)	112(2)
C(9)–C(10)–N(1)	113(2)	C(5)–C(12)–C(17)	112(3)
C(11)–C(10)–N(1)	110(3)	C(11)–C(12)–C(13)	107(2)
C(11)–C(12)–C(17)	105(2)	C(10)–N(1)–C(19)	104(3)
C(13)–C(12)–C(17)	106(3)	C(10)–N(1)–C(20)	109(2)
C(12)–C(13)–C(14)	116(3)	C(18)–N(1)–C(19)	112(2)
C(14)–C(14)–C(15)	107(2)	C(18)–N(1)–C(20)	116(3)
C(13)–C(14)–O(4)	113(2)	C(19)–N(1)–C(20)	108(2)
C(15)–C(14)–O(4)	101(3)		

(*c*) Some intramolecular non-bonded distances (Å)

O(1) ··· O(2)	2·32	O(4) ··· C(5)	3·11
O(2) ··· O(3)	2·86	O(4) ··· C(16)	2·86
O(2) ··· C(7)	3·02	O(6) ··· C(14)	3·12
O(3) ··· C(13)	3·02	C(4) ··· C(10)	3·26
O(3) ··· C(17)	2·92	C(4) ··· C(11)	2·93
O(4) ··· C(4)	3·20	C(5) ··· C(18)	3·09

(*d*) Some intermolecular contacts <4·0 Å

I(1) ··· C(10$^{\mathrm{I}}$)	3·90	O(6) ··· C(20$^{\mathrm{II}}$)	3·77
I(1) ··· C(18$^{\mathrm{II}}$)	3·97	O(6) ··· C(2$^{\mathrm{VI}}$)	3·82
O(1) ··· O(2$^{\mathrm{III}}$)	3·13	C(1) ··· C(2$^{\mathrm{VI}}$)	3·49
O(1) ··· C(19$^{\mathrm{IV}}$)	3·27	C(2) ··· C(24$^{\mathrm{III}}$)	3·81
O(1) ··· C(24$^{\mathrm{III}}$)	3·38	C(3) ··· C(21$^{\mathrm{V}}$)	3·85
O(1) ··· O(6$^{\mathrm{V}}$)	3·94	C(3) ··· C(24$^{\mathrm{III}}$)	3·93
O(1) ··· C(7$^{\mathrm{III}}$)	3·95	C(6) ··· C(22$^{\mathrm{VI}}$)	3·93
O(2) ··· C(22$^{\mathrm{VI}}$)	3·11	C(7) ··· C(8$^{\mathrm{I}}$)	3·83
O(2) ··· C(24$^{\mathrm{VII}}$)	3·47	C(7) ··· C(9$^{\mathrm{I}}$)	3·50
O(3) ··· C(9$^{\mathrm{I}}$)	3·39	C(7) ··· C(19$^{\mathrm{VIII}}$)	3·60
O(3) ··· C(8$^{\mathrm{I}}$)	3·43	C(7) ··· C(24$^{\mathrm{VII}}$)	3·86
O(3) ··· C(22$^{\mathrm{VI}}$)	3·94	C(9) ··· C(13$^{\mathrm{IX}}$)	3·99
O(4) ··· C(23$^{\mathrm{V}}$)	3·63	C(14) ··· C(21$^{\mathrm{VIII}}$)	3·89
O(5) ··· C(23$^{\mathrm{V}}$)	3·50	C(19) ··· C(24$^{\mathrm{X}}$)	3·99
O(6) ··· C(18$^{\mathrm{II}}$)	3·32	C(20) ··· C(22$^{\mathrm{XI}}$)	3·72
O(6) ··· C(3$^{\mathrm{VI}}$)	3·40	C(22) ··· C(23$^{\mathrm{V}}$)	3·76
O(6) ··· C(19$^{\mathrm{II}}$)	3·45	C(22) ··· C(24$^{\mathrm{V}}$)	3·88
O(6) ··· N(1$^{\mathrm{II}}$)	3·64		

TABLE 2 (*Continued*)

Roman numeral superscripts refer to the following equivalent positions:

I $x - 1, y, z$
II $1 - x, \frac{1}{2} + x, \frac{1}{2} - z$
III $\frac{1}{2} + x, -\frac{1}{2} - y, 1 - z$
IV $\frac{3}{2} - x, -y, \frac{1}{2} + z$
V $\frac{1}{2} + x, \frac{1}{2} - y, 1 - z$
VI $-\frac{1}{2} + x, \frac{1}{2} - y, 1 - z$
VII $-\frac{1}{2} + x, -\frac{1}{2} - y, 1 - z$
VIII $1 - x, -\frac{1}{2} + y, \frac{1}{2} - z$
IX $1 + x, y, z$
X $\frac{3}{2} - x, -y, -\frac{1}{2} + z$
XI $2 - x, -\frac{1}{2} + y, \frac{1}{2} - z$

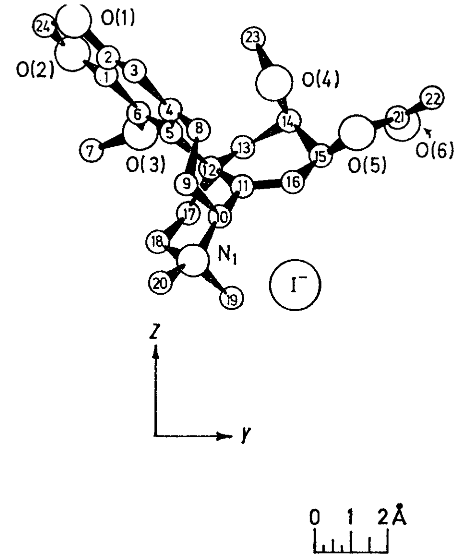


FIGURE 1 A view of the molecule of the alkaloid CC-2 showing the atomic numbering system used in the analysis

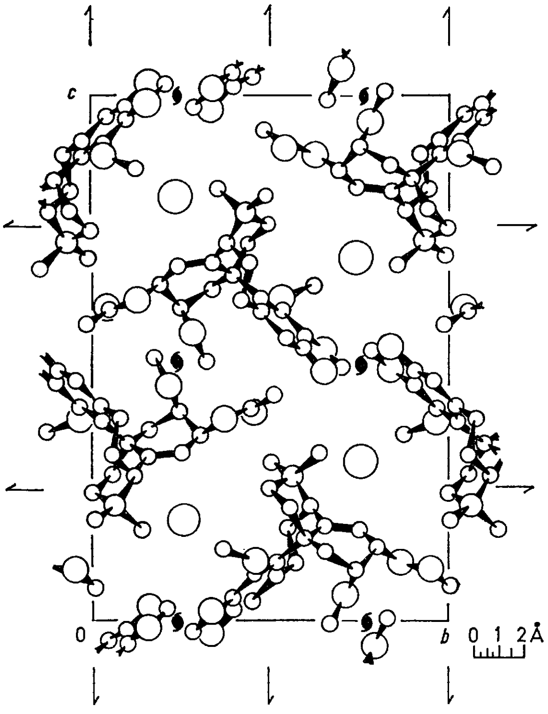


FIGURE 2 The molecular packing viewed down *a*

structural possibilities. One set of calculated structure amplitudes (Table 4) showed differences which were in the same sense in every case as the differences observed in the intensities, and the enantiomorph on which this set was based was chosen as being correct. This absolute stereochemistry is shown in all drawings and representations of the molecule.

TABLE 3

Equations of best least-squares planes in the form $lX + mY + nZ = p$, where X, Y, and Z are co-ordinates in Å referred to the axes a, b, and c. Distances (Å) of atoms from the planes are given in square brackets

Plane (1):	l	m	n	p
C(1)—(6)	0·287	−0·675	−0·680	4·530
[C(1) 0·001, C(2) −0·004, C(3) 0·006, C(4) −0·005, C(5) 0·003, C(6) −0·001, C(8) 0·204, C(12) −0·141, O(1) −0·060, O(2) −0·039, O(3) −0·037, C(24) 0·320]				
Plane (2):				
C(4), C(5), C(8), C(11), C(12)	0·199	−0·670	−0·716	5·307
[C(4) −0·079, C(5) 0·058, C(12) −0·005, C(11) −0·020, C(8) 0·046, C(9) 1·362, C(10) 1·201]				
Plane (3):				
C(8)—(11)	−0·609	−0·793	0·025	5·428
[C(8) 0·052, C(9) 0·089, C(10) −0·090, C(11) 0·053]				
Plane (4):				
C(11)—C(13), C(16)	0·435	−0·142	0·889	8·165
[C(11) −0·003, C(12) 0·054, C(13) −0·055, C(15) 0·059, C(16) −0·055, C(14) 0·683]				
Plane (5):				
C(12), C(10), C(17), N(1)	−0·287	0·891	−0·353	2·561
[C(12) −0·026, C(10) 0·025, C(17) 0·026, N(1) −0·026, C(11) 0·606, C(18) −0·702, C(19) 1·376, C(20) −0·908)]				

DISCUSSION

Molecular Geometry.—For the most part, the molecular dimensions correspond to literature values for similar bond types. Slight discrepancies may possibly be attributed both to the dominating effect of the iodide ion resulting in an analysis of limited accuracy, and also to relatively poor diffraction data arising from severe decomposition of the crystals on exposure to X-rays. (Since a very limited quantity of material was available, it did not prove possible to collect data from several crystals.) For these reasons we limit our discussion of the molecular geometry to a brief mention of the salient features of the conformation.

Within the limits of the experimental accuracy, both the benzene ring and the directly bonded substituents O(1), O(2), O(3), and C(12), lie in one plane, although C(8) is significantly distant from this plane by 0·20 Å. C(24) is also removed by 0·32 Å from the benzenoid plane. The displacements of C(8) and C(24) from this plane may probably be attributed to a reduction of angular strain throughout the aromatic system.

The cycloheptene ring adopts an ‘envelope-like’ conformation in which atoms C(4), C(5), C(8), C(11), and C(12) are experimentally planar, this plane being inclined at an angle of 65° to the best-plane calculated through atoms C(8)—(11). This conformation is clearly seen in Figure 1. That the latter group of four atoms is strictly non-planar is evidenced by the torsion angle of 16° about the C(9)–C(10) bond, such that there is a slight staggering of substituents on C(9) and C(10).

The cyclohexene ring adopts neither the ‘half-chair’ nor ‘half-boat’ conformations commonly found for such rings, in which four of the atoms (of the double-bond system) are planar, and the other two atoms are found either above and below this plane (half-chair), or on the same side of the plane (half-boat). In this instance, C(13) lies very close to the plane of atoms C(11), C(13), C(15), and C(16) of the double-bond system, while C(14) is displaced 0·68 Å from this plane. An examination of this arrangement reveals that there results a lessening of the steric and torsional interactions between the methoxy and carboxylate substituents on C(14) and C(15) respectively. The other six-membered ring system, the bridging piperidinium group, is found to adopt a chair conformation in which C(11) and C(18) are respectively displaced 0·61 and 0·70 Å above and below the plane of atoms C(10), C(12), C(17), and N(1).

There are several O · · · C intermolecular distances $<3·40$ Å; in particular, C(22) and O(2) of neighbouring molecules are separated by 3·11 Å. The closest contacts of the iodide ion to the alkaloid molecules are represented by the distances of 3·90 and 3·97 Å respectively from C(10) and C(18) of different molecules. Other intermolecular separations are greater than or equal to van der Waals' distances.

We thank Professor A. R. Battersby and Dr. R. Ramage for suggesting this problem, and for supplying crystals. Calculations were performed on the Glasgow University KDF9 computer with local programs. We also thank the Anderson Trust for a postgraduate award (to C. H.).

[2/1416 *Received*, 19*th June*, 1972]