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# The Structure of Lasiocarpine: a Pyrrolizidine Alkaloid

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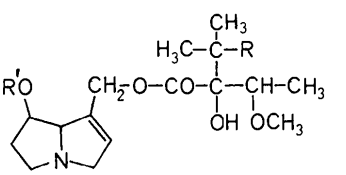
## Abstract

Orthorhombic crystals of the hepatotoxic pyrrolizidine alkaloid, lasiocarpine ($C_{21}H_{33}NO_7$, $M_r$ = 411·5), crystallize in the space group $P2_12_12_1$, with $a$ = 10·066 (2), $b$ = 13·023 (2), $c$ = 17·479 (3) Å, $U$ = 2291·3 (5) Å$^3$ and $Z$ = 4; $D_c$ = 1·19 Mg m$^{-3}$, $F(000)$ = 888, $\mu$(Cu $K\alpha$) = 0·74 mm$^{-1}$. The structure was solved by direct methods with diffractometer data measured with Cu $K\alpha$ radiation, and full-matrix least-squares refinement converged at $R$ = 0·067 for 1396 observed reflections. Lasiocarpine is a di-ester which does not form a covalent macro-ring, and the relative configuration at the asymmetric centres in the molecule is the same as in the related alkaloid, heliotrine ($C_{16}H_{27}NO_5$). An intermolecular hydrogen bond involving one of the hydroxyl substituents and the N atom links the lasiocarpine molecules into helices extending along the $b$ axis.

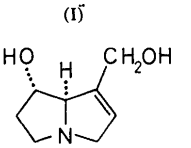
## Introduction

The hepatotoxic pyrrolizidine alkaloids are of increasing concern as possible causes of human poisoning. Apart from their presence in some traditional herbal medicines, they are low-level contaminants in certain foodstuffs, a circumstance which has to be considered in relation to the cumulative nature of their toxic effects, including carcinogenicity (*e.g.* Huxtable, 1979). Interest in these aspects has drawn attention to gaps in knowledge of the stereochemistry of some of the alkaloids now being investigated. To define the stereochemistry of the alkaloids in question, crystal structure analyses are being undertaken.

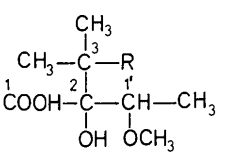
Lasiocarpine is one of the main toxic alkaloids of *Heliotropium lasiocarpum*, at one time the cause of human poisoning in the USSR (Khanin, 1956), and of *H. europaeum* which, in Australia, is a continuing source of chronic liver disease in sheep (Bull, Dick, Keast & Edgar, 1956). The chemical structure of lasiocarpine [I: $R$ = OH, $R'$ = $COC(CH_3)$=$CHCH_3$] and the absolute configuration of the aminoalcohol, (+)-heliotridine (II), have been known for many years (Culvenor, Drummond & Price, 1954: Warren, 1966). The relative configuration of the lasiocarpic acid moiety has not been determined, although the decomposition of lasiocarpic acid, 2,3-dihydroxy-2-(1′-methoxyethyl)-3-methylbutanoic acid (III: $R$ = OH), in hydrochloric acid to give (+)-2-methoxy-4-methyl-3-pentanone (IV) shows that lasiocarpic acid has the same absolute configuration at C(1′) as heliotric acid, 2-hydroxy-2-(1′-methoxyethyl)-3-methylbutanoic acid (III: $R$ = H) (Crowley & Culvenor, 1960). The absolute configuration of (−)-heliotric acid (Culvenor, Drummond & Price, 1954) has been established as (2*S*,1′*R*) by the chemical studies of Kochetkov, Likhosherstov & Kulakov (1969), and the relative configuration was confirmed from the X-ray crystal structure of heliotrine (I: $R$ = $R'$ = H) by Wodak (1975).



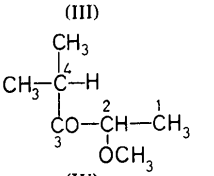
(I)



(II)



(III)



(IV)

This is the first reported crystal structure of a hepatotoxic pyrrolizidine alkaloid with two ester functions which are not linked in a covalent macro-ring.

## Experimental

The specific rotation of the compound is $[\alpha]_D^{16°C}$ = −3·5° ($c$ = 20·0 g dm$^{-3}$ in ethanol) (Culvenor, Drummond & Price, 1954). Weissenberg photographs

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showed that prismatic crystals grown from light petroleum (b.p. 313–333 K) are orthorhombic and systematic absences indicated the space group $P2_12_12_1$. Cell parameters were determined by least squares from $2\theta$ values measured for 25 strong reflections with Cu $K\alpha$ radiation ($\bar{\lambda} = 1{\cdot}5418$ Å) on a diffractometer.

Integrated intensities were measured on a Rigaku-*AFC* four-circle diffractometer at 291 K with Cu $K\alpha$ radiation (graphite-crystal monochromator, $\bar{\lambda} = 1{\cdot}5418$ Å). The intensities were recorded by an $\omega$–$2\theta$ scan, $2\theta$ scan rate 2° min$^{-1}$, scan range ($\Delta\omega$) 1·2° + 0·5° tan $\theta$ and 10 s stationary background counts from a crystal *ca* 0·43 × 0·40 × 0·12 mm, aligned with the longest crystal axis, *a*, approximately parallel to the diffractometer $\varphi$ axis. Of the 1836 non-equivalent terms measured to a $2\theta$ maximum of 130°, the 1396 for which $|F_o| > 3\sigma|F_o|$ were used for the structure refinement. The intensities were corrected for Lorentz and polarization effects but not for absorption or extinction. The scattering factors for O, N and C were from Cromer & Mann (1968), that for H from Stewart, Davidson & Simpson (1965). Anomalous-dispersion corrections were made for the non-hydrogen atoms (Cromer & Liberman, 1970).

The structure was solved by direct methods, the $|E|$ terms being derived from a modified *K* curve (Karle, Hauptman & Christ, 1958). An *E* map calculated with 346 phased terms, with $|E|$ greater than 1·20, revealed the sites of the non-hydrogen atoms apart from those of three methyl C atoms; the latter were located on the subsequent difference map. After full-matrix least-squares refinement with isotropic temperature factors the conventional *R* value for the 1396 observed terms was 0·19. Further refinement with anisotropic temperature factors reduced *R* to 0·11. Although the subsequent difference map had maxima at the expected H-atom sites, not all were clearly resolved. The non-hydroxyl H atoms were therefore included at idealized positions; only one H atom of the hydroxyl substituents, *i.e.* that at O(17) – see Fig. 1 – was located by difference. The H-atom coordinates were not varied; H(26) to H(29) were given a common isotropic temperature factor which refined to a value $U = 0{\cdot}19$ Å$^2$, and all others were given a refined value, $U = 0{\cdot}13$ Å$^2$. The refinement converged at $R = 0{\cdot}067$ and $R_w = (\sum w||F_o| - |F_c||^2/\sum w|F_o|^2)^{1/2} = 0{\cdot}075$.

The direct-method calculations and least-squares refinements were made with *SHELX*76 (Sheldrick, 1976). In the latter, the function minimized was $\sum w(|F_o| - |F_c|)^2$ with the terms weighted according to $w = (\sigma^2|F_o| + 0{\cdot}0005|F_o|^2)^{-1}$. The mean parameter-shift to error ratio at convergence was 0·04:1 for all variables and 0·10:1 for parameters of atoms C(26) to C(29) whose temperature factors refined to unusually large values (see Table 1). The final difference map showed minima and maxima ranging from −0·19 to +0·34 e Å$^{-3}$, the latter lying in the near vicinity of atoms C(26), C(27) and C(28). Final atomic coordinates are given in Tables 1 and 2;* Fig. 1 which contains the atom numbering and Fig. 2 have been prepared from the output of *ORTEP* (Johnson, 1965).

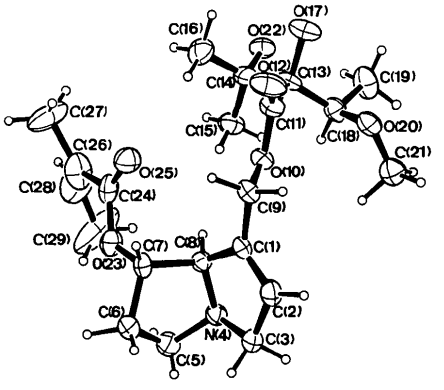


Fig. 1. A perspective view of the molecule with thermal ellipsoids scaled to 20% probability.

* Lists of structure factors, anisotropic thermal parameters, and hydrogen coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36254 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final atomic coordinates of the non-hydrogen atoms* (×10$^4$) *with e.s.d.'s in parentheses and equivalent isotropic temperature factors*

The $B_{eq}$ were calculated from the refined anisotropic thermal parameters as $B_{eq} = 8\pi^2 U_{eq}$.

| | *x* | *y* | *z* | $B_{eq}$ (Å$^2$) |
|---|---|---|---|---|
| C(1) | 8398 (6) | 3429 (5) | 3383 (3) | 4·8 (3) |
| C(2) | 8968 (7) | 4061 (6) | 3881 (4) | 6·2 (4) |
| C(3) | 9468 (8) | 5009 (5) | 3505 (4) | 6·4 (4) |
| N(4) | 8926 (6) | 4943 (4) | 2721 (3) | 5·7 (2) |
| C(5) | 9914 (9) | 5154 (5) | 2131 (4) | 7·2 (4) |
| C(6) | 10684 (9) | 4136 (6) | 2022 (4) | 7·4 (4) |
| C(7) | 9567 (7) | 3348 (6) | 2073 (3) | 5·9 (3) |
| C(8) | 8493 (7) | 3867 (4) | 2591 (3) | 5·1 (3) |
| C(9) | 7818 (7) | 2407 (5) | 3559 (4) | 5·2 (3) |
| O(10) | 6435 (5) | 2453 (3) | 3329 (2) | 5·2 (2) |
| C(11) | 5720 (9) | 1590 (6) | 3467 (4) | 6·5 (4) |
| O(12) | 6208 (6) | 837 (4) | 3735 (4) | 7·5 (3) |
| C(13) | 4257 (8) | 1734 (5) | 3271 (4) | 5·7 (4) |
| C(14) | 4002 (10) | 1780 (6) | 2387 (4) | 7·0 (5) |
| C(15) | 4475 (9) | 2783 (6) | 2036 (4) | 7·7 (5) |
| C(16) | 4705 (11) | 862 (6) | 2024 (5) | 9·6 (6) |
| O(17) | 3615 (6) | 821 (4) | 3548 (3) | 8·3 (4) |
| C(18) | 3759 (8) | 2656 (7) | 3729 (4) | 6·8 (4) |
| C(19) | 2269 (9) | 2705 (9) | 3845 (6) | 9·8 (6) |
| O(20) | 4368 (5) | 2614 (4) | 4466 (3) | 7·5 (3) |
| C(21) | 4726 (10) | 3573 (7) | 4750 (5) | 9·6 (5) |
| O(22) | 2606 (5) | 1746 (4) | 2259 (3) | 7·2 (4) |
| O(23) | 9072 (6) | 3232 (4) | 1303 (2) | 7·2 (5) |
| C(24) | 8264 (10) | 2397 (9) | 1185 (4) | 7·1 (5) |
| O(25) | 8030 (6) | 1767 (5) | 1669 (4) | 8·7 (4) |
| C(26) | 7785 (12) | 2317 (14) | 392 (6) | 10·8 (9) |
| C(27) | 7542 (19) | 1118 (8) | 110 (6) | 12·7 (14) |
| C(28) | 7442 (18) | 2905 (12) | −6 (8) | 13·5 (10) |
| C(29) | 7635 (25) | 4069 (10) | 98 (7) | 13·5 (19) |

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

| | | | |
|---|---|---|---|
| C(1)–C(2) | 1·328 (9) | C(13)–C(14) | 1·567 (10) |
| C(1)–C(8) | 1·500 (8) | C(13)–O(17) | 1·437 (9) |
| C(1)–C(9) | 1·486 (9) | C(13)–C(18) | 1·528 (11) |
| C(2)–C(3) | 1·486 (10) | C(14)–C(15) | 1·520 (11) |
| C(3)–N(4) | 1·477 (9) | C(14)–C(16) | 1·527 (12) |
| N(4)–C(5) | 1·459 (10) | C(14)–O(22) | 1·424 (11) |
| N(4)–C(8) | 1·485 (8) | C(18)–C(19) | 1·515 (12) |
| C(5)–C(6) | 1·547 (11) | C(18)–O(20) | 1·428 (9) |
| C(6)–C(7) | 1·525 (11) | O(20)–C(21) | 1·391 (11) |
| C(7)–C(8) | 1·564 (9) | O(23)–C(24) | 1·374 (12) |
| C(7)–O(23) | 1·443 (7) | C(24)–O(25) | 1·202 (12) |
| C(9)–O(10) | 1·450 (9) | C(24)–C(26) | 1·471 (13) |
| O(10)–C(11) | 1·356 (9) | C(26)–C(27) | 1·66* |
| C(11)–O(12) | 1·193 (10) | C(26)–C(28) | 1·09* |
| C(11)–C(13) | 1·524 (12) | C(28)–C(29) | 1·54* |
| C(2)–C(1)–C(8) | 110·0 (6) | C(11)–C(13)–C(14) | 112·6 (6) |
| C(2)–C(1)–C(9) | 126·1 (6) | C(11)–C(13)–C(18) | 107·2 (6) |
| C(8)–C(1)–C(9) | 123·8 (5) | C(14)–C(13)–C(18) | 115·6 (6) |
| C(1)–C(2)–C(3) | 111·8 (6) | C(14)–C(13)–O(17) | 106·9 (6) |
| C(2)–C(3)–N(4) | 103·7 (6) | C(18)–C(13)–O(17) | 109·0 (6) |
| C(3)–N(4)–C(5) | 113·1 (5) | C(13)–C(14)–C(15) | 112·3 (7) |
| C(3)–N(4)–C(8) | 107·8 (5) | C(13)–C(14)–C(16) | 107·7 (7) |
| C(5)–N(4)–C(8) | 105·6 (5) | C(13)–C(14)–O(22) | 108·4 (6) |
| N(4)–C(5)–C(6) | 105·5 (6) | C(15)–C(14)–C(16) | 111·1 (7) |
| C(5)–C(6)–C(7) | 101·5 (6) | C(15)–C(14)–O(22) | 105·8 (6) |
| C(6)–C(7)–C(8) | 104·6 (5) | C(16)–C(14)–O(22) | 111·6 (7) |
| C(6)–C(7)–O(23) | 105·7 (6) | C(13)–C(18)–C(19) | 115·3 (7) |
| C(8)–C(7)–O(23) | 110·3 (5) | C(13)–C(18)–O(20) | 107·6 (6) |
| C(1)–C(8)–N(4) | 103·7 (5) | C(19)–C(18)–O(20) | 107·8 (7) |
| C(1)–C(8)–C(7) | 114·5 (5) | C(18)–O(20)–C(21) | 113·5 (6) |
| N(4)–C(8)–C(7) | 107·1 (5) | C(7)–O(23)–C(24) | 115·3 (6) |
| C(1)–C(9)–O(10) | 106·4 (5) | O(23)–C(24)–O(25) | 123·4 (9) |
| C(9)–O(10)–C(11) | 115·2 (5) | O(23)–C(24)–C(26) | 113·1 (9) |
| C(10)–C(11)–O(12) | 122·2 (7) | O(25)–C(24)–C(26) | 123·4 (10) |
| C(10)–C(11)–C(13) | 111·8 (6) | C(24)–C(26)–C(27) | 113* |
| C(12)–C(11)–C(13) | 126·0 (7) | C(24)–C(26)–C(28) | 131* |
| C(11)–C(13)–O(17) | 104·9 (6) | C(27)–C(26)–C(28) | 115* |
| | | C(26)–C(28)–C(29) | 125* |

* Systematic errors associated with the high thermal motion of atoms C(26) to C(29) have almost certainly caused an underestimate of the e.s.d.'s derived from the least-squares refinement, which are 0·02 Å and 2° respectively in bond lengths and angles involving these atoms.

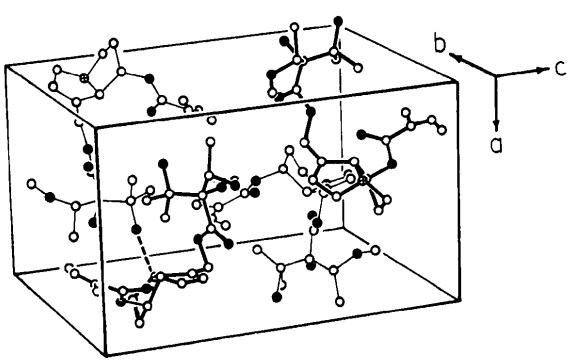


Fig. 2. The molecular packing in the crystal.

## Description of the structure

The absolute molecular structure of lasiocarpine, assigned by comparison with that of heliotridine (II), is illustrated in Fig. 1. Bond lengths and angles given in Table 2 and torsional angles in Table 3 define the conformational detail in the molecule. The relative configuration at the asymmetric centres C(7), C(8), C(13) and C(18) is the same as observed in the related alkaloid heliotrine (Wodak, 1975). Consequently, the absolute configuration of (+)-lasiocarpic acid* is (2*R*,1′*R*).

The pucker of the pyrrolizidine nucleus is *endo*; the unsaturated five-membered ring and atom C(6) lie on the same side of the plane defined by atoms N(4), C(5) and C(7). A similar conformation is also observed in heliotrine, both alkaloids being derived from the diol, heliotridine. However, in lasiocarpine, the puckering angle of 34·0 (8)° is significantly smaller than the value of 45° in heliotrine, and the angle between the mean planes defined by the atoms C(1), C(2), C(3), N(4), C(8) and C(5), N(4), C(8), C(7) is 120·6 (7)°, compared with 130° in the latter. In solution, lasiocarpine and other heliotridine esters apparently undergo flipping between *endo*- and *exo*-puckered forms, according to the evidence of NMR measurements in deuterochloroform (Culvenor & Woods, 1965).

There are no close contacts between the two ester groups in the molecule both of which adopt extended conformations. The orientation of the lasiocarpic acid moiety differs from that of the heliotric acid moiety in heliotrine by a rotation of approximately 165° about the C(11)–C(13) bond. The torsional angle O(10)–C(9)–C(1)–C(2) is +121·4 (7)° so that O(10) lies away from the double bond between C(1) and C(2). The value for this torsional angle in a number of macrocyclic di-ester pyrrolizidine alkaloids, for example, is −63° in monocrotaline (Stoeckli-Evans, 1979*a*), −64°

* See Culvenor, Drummond & Price (1954) for specific rotation.

Table 3. *Torsional angles* (°)

E.s.d.'s range between 0·6 and 1·1°

| Pyrrolizidine nucleus | | Lasiocarpic acid moiety | |
|---|---|---|---|
| C(1)–C(2)–C(3)–C(4) | 8·9 | C(2)–C(1)–C(9)–O(10) | 121·4 |
| C(1)–C(8)–N(4)–C(3) | 17·6 | C(8)–C(1)–C(9)–O(10) | −62·5 |
| C(1)–C(8)–N(4)–C(5) | 138·8 | C(1)–C(9)–O(10)–C(11) | −178·1 |
| C(1)–C(8)–C(7)–C(6) | −106·6 | C(9)–O(10)–C(11)–O(12) | −2·4 |
| C(1)–C(8)–C(7)–O(23) | 140·1 | C(9)–O(10)–C(11)–C(13) | 175·2 |
| C(2)–C(3)–N(4)–C(5) | −132·8 | O(10)–C(11)–C(13)–C(14) | 72·1 |
| C(2)–C(3)–N(4)–C(8) | −16·4 | O(10)–C(11)–C(13)–O(17) | −172·0 |
| C(2)–C(1)–C(8)–N(4) | −12·2 | O(10)–C(11)–C(13)–C(18) | −56·2 |
| C(2)–C(1)–C(8)–C(7) | 104·0 | C(11)–C(13)–C(14)–C(15) | −72·8 |
| C(3)–N(4)–C(5)–C(6) | 81·8 | C(11)–C(13)–C(14)–C(16) | 49·8 |
| C(3)–N(4)–C(8)–C(7) | −103·8 | C(11)–C(13)–C(14)–O(22) | 170·6 |
| C(3)–C(2)–C(1)–C(8) | 2·1 | C(11)–C(13)–C(18)–C(19) | −158·9 |
| C(3)–C(2)–C(1)–C(9) | 178·7 | C(11)–C(13)–C(18)–O(20) | −38·6 |
| N(4)–C(5)–C(6)–C(7) | 39·9 | O(12)–C(11)–C(13)–C(14) | −110·4 |
| N(4)–C(8)–C(1)–C(9) | 171·1 | O(12)–C(11)–C(13)–O(17) | 5·5 |
| N(4)–C(8)–C(7)–C(6) | 7·6 | O(12)–C(11)–C(13)–C(18) | 121·3 |
| N(4)–C(8)–C(7)–O(23) | −105·6 | C(13)–C(18)–O(20)–C(21) | 141·8 |
| C(5)–N(4)–C(8)–C(7) | 17·4 | C(14)–C(13)–C(18)–C(19) | 74·5 |
| C(5)–C(6)–C(7)–C(8) | −27·8 | C(14)–C(13)–C(18)–O(20) | −165·1 |
| C(5)–C(6)–C(7)–O(23) | 88·6 | C(15)–C(14)–C(13)–O(17) | 172·5 |
| C(7)–C(8)–C(1)–C(9) | −72·6 | C(15)–C(14)–C(13)–C(18) | 50·9 |
| | | C(16)–C(14)–C(13)–O(17) | 64·9 |
| Angelic acid moiety | | C(16)–C(14)–C(13)–C(18) | 173·6 |
| | | O(17)–C(13)–C(18)–C(19) | −45·8 |
| C(6)–C(7)–O(23)–C(24) | 166·1 | O(17)–C(13)–C(18)–O(20) | 74·5 |
| C(8)–C(7)–O(23)–C(24) | −81·3 | C(18)–C(13)–C(14)–O(22) | −65·6 |
| C(7)–O(23)–C(24)–O(25) | −3·9 | C(19)–C(18)–O(20)–C(21) | −93·2 |
| C(7)–O(23)–C(24)–C(26) | 179·8 | | |
| O(23)–C(24)–C(26)–C(27) | 148·9 | | |
| O(23)–C(24)–C(26)–C(28) | −40·5 | | |
| C(24)–C(26)–C(28)–C(29) | 13·8 | | |
| O(25)–C(24)–C(26)–C(27) | −27·3 | | |
| O(25)–C(24)–C(26)–C(28) | 143·3 | | |
| C(27)–C(26)–C(28)–C(29) | −175·7 | | |

in fulvine (Sussman & Wodak, 1973), −79° in incanine (Tashkodzhaev, Telezhenetskaya & Yunusov, 1979), −87° in retrorsine (Stoeckli-Evans, 1979*b*), −88° in axillarine (Stoeckli-Evans & Crout, 1976), −90° in doronenine (Kirfel, Will, Wiedenfeld & Roeder, 1980), −106° in jacobine (Pérez-Salazar, Cano & García-Blanco, 1978), −108° in swazine (Laing & Sommerville, 1972) and −124° in trichodesmine (Tashkhodzhaev, Yagudaev & Yunusov, 1979). In these alkaloids, as in lasiocarpine, O(10) lies away from the C(1)–C(2) double bond whereas in heliotrine, where the torsional angle is only +12°, O(10) lies adjacent to it. Both carbonyl groups in lasiocarpine point away from the H atom at C(8), and the dihedral angle between the C(11)–O(12) and C(24)–O(25) bonds is 40·8 (5)°. This contrasts with the situation in monocrotaline, fulvine, incanine and axillarine where the carbonyl groups are synparallel and point in the same direction as the H atom at C(8), whereas in retrorsine, doronenine, jacobine, swazine and trichodesmine the carbonyl groups are antiparallel.

The atoms in the ester groups, C(9), O(10), C(11), O(12), C(13) and C(7), O(23), C(24), O(25), C(26), are coplanar within ±0·03 and ±0·02 Å respectively, and the dihedral angle between the two planes is 55·1 (7)°. The relative positions of the ester planes, the systems $CH_2OC{=}O$ and $CHOC{=}O$, are close to those predicted as the preferred conformations of primary and secondary esters from NMR data (Culvenor, 1966). The plane of the *trans*-2-butene group of the angelic acid moiety is rotated by about 30° from the plane of its associated group, the torsional angle O(25)–C(24)–C(26)–C(27) being −27·3 (10)°.

The apparent high thermal motion of atoms C(26) to C(29) (see Table 1), and consequent lack of resolution at these sites in the electron-density maps, has severely reduced the accuracy of the bond lengths and angles in the end chain of the angelic moiety (see Table 2). A similar effect was noted recently in the angelyl groups in the structure of acetylated napoleogenin* (Spirlet, Dupont, Dideberg & Kapundu, 1980), while Porte & Robertson (1959) reported a high temperature factor and possible disorder for their angelic acid structure. The bond lengths and angles in the remainder of the molecule are relatively normal and compare reasonably with those reported for other pyrrolizidine alkaloids. The pyrrolizidine ring-fusion distance, N(4)–C(8), is 1·485 (8) Å which is similar to the value 1·494 (3) Å observed for this distance in heliotrine and to the mean value 1·51 Å in the macrocyclic pyrrolizidine alkaloids.

In the lasiocarpic acid moiety the hydroxyl substituent at C(13) forms an intramolecular hydrogen bond with the carbonyl oxygen atom, O(12). The O(7)···O(12) and H(17)···O(12) distances are 2·63 (1) and 2·01 Å respectively and the O(17)–H(17)···O(12) angle is 122°. The atom H(17) lies 0·94 Å from O(17) and the angle subtended at the latter is 106°.

* No satisfactory explanation can be offered as this stage as to why anomalous dimensions appear to be associated in these cases with the angelyl components.

Table 4. *Intermolecular approaches* <3·8 Å *with e.s.d.'s in parentheses*

Transformations of the coordinates (*x*,*y*,*z*) are denoted by superscripts: (i) $\frac{1}{2}+x, \frac{1}{2}-y, 1-z$; (ii) $1+x, y, z$; (iii) $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; (iv) $1\frac{1}{2}-x, -y, -\frac{1}{2}+z$; (v) $1\frac{1}{2}-x, 1-y, -\frac{1}{2}+z$.

| | | | |
|---|---|---|---|
| C(2)···O(20$^{i}$) | 3·64 (1) | C(7)···O(22$^{ii}$) | 3·72 (1) |
| C(2)···C(19$^{ii}$) | 3·76 (1) | C(9)···O(20$^{i}$) | 3·79 (1) |
| C(3)···O(22$^{iii}$) | 3·36 (1) | C(9)···C(21$^{i}$) | 3·75 (1) |
| N(4)···C(14$^{iii}$) | 3·80 (1) | C(27)···O(12$^{iv}$) | 3·72 (1) |
| N(4)···O(17$^{iii}$) | 3·57 (1) | C(29)···C(2$^{v}$) | 3·61 (2) |
| N(4)···O(22$^{iii}$) | 2·81 (1) | C(29)···C(3$^{v}$) | 3·70 (2) |
| C(5)···O(22$^{iii}$) | 3·45 (1) | C(29)···O(17$^{iii}$) | 3·52 (2) |
| C(6)···O(22$^{ii}$) | 3·69 (1) | | |

The crystal packing is illustrated in Fig. 2 and intermolecular approaches less than 3·8 Å are listed in Table 4. There is indication of only one intermolecular hydrogen bond in the structure. In this, the hydroxyl substituent at C(14) is hydrogen bonded to N(4) of an adjacent molecule related by the twofold screw axis along (010) at $x = \frac{1}{2}$, $z = \frac{1}{2}$, with the O(22)···N(4) distance 2·81 (1) Å. These interactions link the molecules into helices with the long axis parallel to the crystallographic *b* axis. In the heliotrine structure, it is the hydroxyl substituent at C(13) which forms an intermolecular hydrogen bond with N(4) in which the O(17)···N(4) distance is 2·734 Å.

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# The Structure of 6,9-Dichloro-2-methoxyacridine

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## Abstract

6,9-Dichloro-2-methoxyacridine (DCMA), $C_{14}H_9Cl_2NO$, is triclinic, $P\bar{1}$, with $a = 7{\cdot}735$ (1), $b = 8{\cdot}651$ (1), $c = 10{\cdot}344$ (1) Å, $\alpha = 95{\cdot}63$ (1), $\beta = 101{\cdot}80$ (1), $\gamma = 113{\cdot}25$ (1)°, $U = 603{\cdot}7$ Å$^3$, $Z = 2$; $D_m = 1{\cdot}52$ (2), $D_c = 1{\cdot}530$ Mg m$^{-3}$, $F(000) = 284$, $\lambda$(Cu $K\alpha$) = 1·5418 Å, $\mu = 4{\cdot}701$ mm$^{-1}$. 2428 reflections were measured, of which 1999 had significant intensities. Refinement by full-matrix least-squares methods gave a final $R$ factor of 0·040. The structure consists of centrosymmetrically related, stacked molecules. The acridine mucleus is slightly buckled, and does not show mirror symmetry along the C(9)–N(10) line. The addition of the Cl atom at C(9) has produced significant shortening in adjacent bonds, compared to acridines with a Cl atom at C(6) alone.

## Introduction

The biological activity of acridine derivatives is often manifest in their mutagenic properties. These have been attributed (Albert, 1966; Waring, 1972; Neidle, 1979), at least in part, to interactions with nucleic acids, particularly DNA. The hypothesis (Lerman, 1961) that the planar chromophore common to the acridines is involved in stacking interactions with the planar pyrimidine–purine base-pairs, has received support from a large body of physical and biological data, including X-ray crystallographic studies on dinucleoside complex-model systems [for example Berman *et al.* (1979)].

The present study reports crystallographic data on an acridine derivative with two chlorine substituents; several analyses have been documented on 6-chloro-substituted acridines (for references see the discussion section), and one on 9-chloroacridine (Achari & Neidle, 1977). This analysis reveals the electronic effect of dichloro substitution on the acridine-ring-system geometry and the stacking properties of the planar chromophore. The relationship of these to mutagenic activity is currently being explored in these laboratories.

## Experimental

Pale-yellow elongated prisms of DCMA were grown from ethanolic solution. Preliminary oscillation and Weissenberg photographs indicated triclinic symmetry. Accurate cell dimensions were obtained from measure-

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