

## The Crystal and Molecular Structure of the Alkaloid Lycorine

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The crystal structure of the Amaryllidaceae alkaloid lycorine,  $C_{16}H_{17}O_4N$ , has been determined by direct methods from three-dimensional diffractometer data. The unit cell is orthorhombic, space group  $P2_12_12_1$ , with four molecules per unit cell and  $a=11.742$ ,  $b=13.986$ ,  $c=8.314$  Å. The final value of  $R$  over 1327 independent reflexions is 3.8%. The thermal motion has been analysed in terms of the rigid-body model and the hydrogen bonding is described.

### Introduction

*Crinum jagus* is one of the Amaryllidaceae of the Ivory Coast, used for local pharmacopœia, which are currently being examined by a research group of the University of Abidjan for their structural and medicinal properties. Lycorine (Fig. 1) is the most abundant alkaloid occurring in the Amaryllidaceae; this compound has been extracted from bulbs of *Crinum jagus* then purified and crystallized from a mixture of chloroform and methanol. The mass spectrum analysis confirmed the molecular formula  $C_{16}H_{17}O_4N$ . The absolute configuration of lycorine has previously been suggested by Nakagawa & Uyeo (1959), using Mill's rule (1952) and by the X-ray analysis of dihydrolycorine hydrobromide (Shiro, Sato & Koyama, 1968).

### Experimental

Lycorine  $C_{16}H_{17}NO_4$ , m.p. 519°K, M.W. 287.3, colourless prisms, orthorhombic.

$a=11.742$  (2) Å       $V=1365$  Å<sup>3</sup>  
 $b=13.986$  (2)       $D_x=1.40$  g cm<sup>-3</sup> for  $Z=4$   
 $c=8.314$  (1)       $D_m=1.39$  g cm<sup>-3</sup> (flotation)  
 $\lambda(\text{Cu } K\alpha)=1.54178$  Å       $F(000)=608$   
 $T=295^\circ\text{K}$        $\mu=8.44$  cm<sup>-1</sup>.

Absent reflexions:  $h00$  when  $h$  is odd,  $0k0$  when  $k$  is odd,  $00l$  when  $l$  is odd. Space group  $P2_12_12_1$ .

The intensities were collected on an on-line four-circle Siemens diffractometer, using nickel-filtered Cu  $K\alpha$  radiation. A crystal of approximate dimensions  $0.1 \times 0.2 \times 0.3$  mm<sup>3</sup> was aligned with its (001) axis along the  $\varphi$  axis of the diffractometer. Intensity data were taken up to  $\sin \theta/\lambda=0.61$  Å<sup>-1</sup> by the five-points method. The variation of a standard reflexion during the collection period did not indicate any significant crystal decomposition due to X-ray exposure. Of the 1503 reflexions, 1333 reflexions (89%) were considered as observed [ $I \geq 2\sigma(I)$ ]. Absorption corrections were not made because of the low  $\mu$  value and the small size of

the crystal. After application of the Lorentz and polarization corrections, an overall temperature factor and an absolute scale factor were computed by statistical methods.

### Structure determination

The structure was solved by applying a modification of the symbolic addition procedure (Karle & Karle, 1966). Three reflexions were fixed to define the origin of the cell; the numerical values of the phases of six additional reflexions were determined by the phase function method (Riche, 1970, 1972). The phases of 274 reflexions were obtained by an iterative application of the  $\Sigma_2$  relationship to the set of phases which gave the highest peak in the phase function map. The corresponding  $E$  map readily displayed the whole molecular skeleton. The starting set of phases is given in Table 1.

Table 1. Starting set for the application of  $\Sigma_2$

$h$	$k$	$l$	$E$	Phase (cycles)	
8	9	0	4.09	0.0000	} Origin
9	7	0	3.46	0.2500	
8	1	5	3.15	0.0000	
0	8	5	4.24	0.5000	} Most probable phases determined from the phase function map
0	10	7	2.90	0.5000	
6	15	1	2.60	0.2500	
6	3	8	2.49	0.2500	
8	4	3	2.48	0.7500	
6	7	4	2.44	0.2500	

The atomic coordinates thus obtained and isotropic temperature factors were refined by the full-matrix least-squares method. After three cycles of refinement, the residual index  $R = \sum |F_o| - |F_c| / \sum |F_o|$  was reduced to 0.11. The subsequent refinement was performed by introducing anisotropic temperature factors for all the non-hydrogen atoms. After two cycles, the  $R$  value was 0.09. The hydrogens were located on a difference electron density map and their contributions were included in the structure-factor calculations. At this

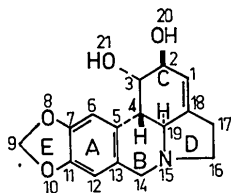


Fig. 1. The lycorine molecule.

point, six strong low-angle reflexions which appeared to be affected by extinction were discarded and two cycles of full-matrix anisotropic refinement with all hydrogen

Table 2. Coordinates of nonhydrogen atoms with *e.s.d.*'s in parentheses

Coordinates represent the true absolute configuration in a right-handed reference frame.

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
C(1)	0.10378 (27)	0.61063 (24)	0.59251 (40)
C(2)	0.14646 (26)	0.54420 (23)	0.46200 (40)
C(3)	0.27469 (26)	0.55466 (21)	0.41910 (36)
C(4)	0.34228 (25)	0.57871 (21)	0.57020 (36)
C(5)	0.47152 (25)	0.58530 (21)	0.55806 (38)
C(6)	0.53235 (26)	0.51761 (24)	0.46640 (42)
C(7)	0.64820 (27)	0.52553 (24)	0.46658 (44)
O(8)	0.72599 (19)	0.46872 (18)	0.38609 (34)
C(9)	0.83460 (28)	0.49949 (28)	0.44094 (55)
O(10)	0.82060 (18)	0.58930 (18)	0.52171 (34)
C(11)	0.70489 (25)	0.59687 (24)	0.54831 (43)
C(12)	0.64874 (29)	0.66296 (23)	0.63911 (42)
C(13)	0.52910 (27)	0.65590 (22)	0.64637 (38)
C(14)	0.46792 (28)	0.72859 (23)	0.75195 (43)
N(15)	0.35072 (22)	0.69749 (17)	0.78570 (30)
C(16)	0.27451 (33)	0.77110 (23)	0.85425 (44)
C(17)	0.15351 (31)	0.73578 (26)	0.81141 (47)
C(18)	0.17255 (27)	0.66937 (23)	0.66991 (41)
C(19)	0.29755 (26)	0.67272 (21)	0.63179 (37)
O(20)	0.12352 (18)	0.44820 (15)	0.51897 (25)
O(21)	0.28701 (20)	0.62817 (15)	0.30133 (27)

Table 4. Thermal parameters of non-hydrogen atoms with *e.s.d.*'s in parentheses

The parameters are in the form:  $\exp [-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$ .

	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
C(1)	0.00359 (21)	0.00400 (17)	0.01001 (49)	0.00040 (18)	0.00037 (30)	-0.00012 (25)
C(2)	0.00371 (21)	0.00362 (17)	0.00862 (45)	0.00023 (17)	-0.00087 (29)	0.00006 (25)
C(3)	0.00406 (21)	0.00296 (15)	0.00685 (42)	0.00001 (16)	-0.00036 (27)	0.00000 (22)
C(4)	0.00362 (22)	0.00255 (15)	0.00677 (42)	0.00008 (15)	0.00012 (26)	-0.00016 (21)
C(5)	0.00343 (21)	0.00265 (15)	0.00820 (45)	-0.00023 (15)	0.00018 (28)	0.00011 (24)
C(6)	0.00387 (21)	0.00349 (17)	0.01010 (50)	-0.00032 (16)	-0.00014 (29)	-0.00095 (27)
C(7)	0.00415 (22)	0.00357 (17)	0.01039 (50)	0.00023 (18)	0.00068 (30)	-0.00057 (26)
O(8)	0.00358 (16)	0.00581 (16)	0.01861 (50)	0.00014 (14)	0.00123 (26)	-0.00388 (24)
C(9)	0.00344 (24)	0.00527 (22)	0.02052 (78)	0.00034 (20)	0.00059 (37)	-0.00134 (38)
O(10)	0.00328 (16)	0.00489 (14)	0.01725 (48)	-0.00060 (12)	0.00031 (24)	-0.00094 (23)
C(11)	0.00303 (21)	0.00387 (17)	0.01057 (51)	-0.00050 (16)	0.00005 (28)	0.00095 (28)
C(12)	0.00461 (24)	0.00326 (16)	0.01046 (50)	-0.00102 (16)	-0.00114 (32)	0.00023 (27)
C(13)	0.00449 (23)	0.00272 (15)	0.00716 (42)	-0.00011 (16)	-0.00047 (28)	0.00039 (24)
C(14)	0.00525 (26)	0.00299 (16)	0.01069 (50)	-0.00069 (18)	0.00044 (33)	-0.00138 (26)
N(15)	0.00493 (20)	0.00279 (13)	0.00661 (36)	0.00012 (15)	0.00045 (24)	-0.00094 (19)
C(16)	0.00720 (30)	0.00343 (17)	0.01140 (56)	0.00031 (20)	0.00105 (37)	-0.00200 (27)
C(17)	0.00574 (28)	0.00478 (20)	0.01302 (56)	0.00059 (21)	0.00239 (36)	-0.00251 (31)
C(18)	0.00440 (24)	0.00327 (16)	0.00955 (51)	0.00103 (16)	0.00117 (29)	-0.00033 (25)
C(19)	0.00419 (24)	0.00276 (15)	0.00714 (43)	0.00024 (16)	-0.00023 (27)	-0.00045 (23)
O(20)	0.00532 (18)	0.00363 (12)	0.00814 (32)	-0.00073 (12)	-0.00067 (21)	0.00001 (17)
O(21)	0.00651 (19)	0.00364 (12)	0.00762 (31)	0.00030 (14)	0.00084 (22)	0.00063 (17)

Table 3. Coordinates of hydrogen atoms

( $B=3.5 \text{ \AA}^2$  for all atoms.)

	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>
H(1)	0.0128	0.6185	0.6071
H(2)	0.1035	0.5538	0.3486
H(3)	0.2982	0.4926	0.3539
H(4)	0.3303	0.5247	0.6526
H(6)	0.4885	0.4653	0.3941
H(9)	0.8899	0.5056	0.3458
H'(9)	0.8676	0.4488	0.5190
H(12)	0.7037	0.7123	0.6961
H(14)	0.4725	0.7975	0.7092
H'(14)	0.5094	0.7277	0.8818
H(16)	0.2834	0.7643	0.9856
H'(16)	0.2926	0.8316	0.8177
H(17)	0.1074	0.7991	0.7670
H'(17)	0.1059	0.7064	0.8928
H(19)	0.3129	0.7296	0.5484
H(20)	0.1298	0.3990	0.4370
H(21)	0.3192	0.5963	0.2143

atom parameters held constant reduced the *R* value to 0.038; the corresponding weighted residual  $wR = [\sum w(|F_o| - |F_c|)^2 / \sum w|F_o|^2]^{1/2}$  was 0.039. The weighting scheme was  $w=1$  for the observed reflexions and  $w=0$  for those unobserved. The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1962). A final difference map showed no features above  $0.21 \text{ e \AA}^{-3}$ . The positional and thermal parameters together with their standard deviations are given in Tables 2, 3 and 4.\*

\* The list of observed and calculated structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30230 (5 pp.). Copies are available from: The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

## Thermal motion analysis

Fig. 2 gives a stereoscopic view of the molecule (Johnson, 1965) and shows the shape and orientation of the thermal vibration ellipsoids. When the thermal motion is analysed in terms of the rigid-body motion (Scho-

Table 5. *Interatomic distances (Å) and angles (°)*  
*E.s.d.'s are in parentheses*

C(1)—C(18)	1.319 (5)	O(8)—C(9)	1.421 (4)
C(1)—C(2)	1.514 (5)	C(9)—C(10)	1.434 (5)
C(2)—O(20)	1.449 (4)	O(10)—C(11)	1.381 (4)
C(2)—C(3)	1.554 (4)	C(11)—C(12)	1.363 (5)
C(3)—O(21)	1.427 (4)	C(12)—C(13)	1.410 (5)
C(3)—C(4)	1.524 (4)	C(13)—C(14)	1.523 (5)
C(4)—C(19)	1.506 (4)	C(14)—N(15)	1.470 (4)
C(4)—C(5)	1.524 (4)	N(15)—C(19)	1.465 (4)
C(5)—C(13)	1.404 (4)	N(15)—C(16)	1.478 (4)
C(5)—C(6)	1.410 (4)	C(16)—C(17)	1.546 (5)
C(6)—C(7)	1.365 (4)	C(17)—C(18)	1.515 (5)
C(7)—C(11)	1.379 (5)	C(18)—C(19)	1.502 (4)
C(7)—O(8)	1.383 (4)		
C(2)—C(1)—C(18)	121.9 (3)		
C(3)—C(2)—C(1)	115.3 (3)		
C(1)—C(2)—O(20)	105.8 (3)		
C(3)—C(2)—O(20)	110.0 (2)		
C(2)—C(3)—C(4)	109.7 (3)		
C(2)—C(3)—O(21)	108.9 (2)		
C(4)—C(3)—O(21)	110.7 (2)		
C(3)—C(4)—C(19)	106.9 (2)		
C(19)—C(4)—C(5)	108.5 (2)		
C(4)—C(5)—C(13)	119.2 (3)		
C(13)—C(5)—C(6)	120.7 (3)		
C(5)—C(6)—C(7)	116.7 (3)		
C(6)—C(7)—C(11)	122.7 (3)		
C(11)—C(7)—O(8)	109.6 (3)		
C(7)—O(8)—C(9)	105.3 (3)		
O(8)—C(9)—O(10)	108.2 (3)		
C(9)—O(10)—C(11)	104.8 (3)		
O(10)—C(11)—C(7)	109.9 (3)		
C(7)—C(11)—C(12)	122.0 (3)		
C(11)—C(12)—C(13)	117.3 (3)		
C(12)—C(13)—C(5)	120.5 (3)		
C(5)—C(13)—C(14)	122.9 (3)		
C(13)—C(14)—N(15)	110.7 (3)		
C(14)—N(15)—C(19)	107.6 (2)		
C(19)—N(15)—C(16)	104.1 (2)		
C(15)—C(16)—C(17)	104.2 (3)		
C(16)—C(17)—C(18)	103.8 (3)		
C(17)—C(18)—C(19)	106.8 (3)		
C(19)—C(18)—C(1)	121.0 (3)		
C(18)—C(19)—N(15)	103.9 (3)		
N(15)—C(19)—C(4)	110.8 (2)		
C(18)—C(19)—C(4)	112.7 (3)		

Table 6. *Equations of best planes through selected parts of the lycorine molecule and displacements of the atoms from these planes*

$X, Y, Z$  are the fractional coordinates in the direct cell.  
Hydrogen atoms are omitted.

Rings  $A$  and  $E$

$$-0.5411X + 8.2668Y - 6.6952Z = 0.8537$$

C(5)	-0.007 Å
C(6)	0.015
C(7)	0.016
O(8)	0.043
C(9)	-0.128
O(10)	0.081
C(11)	0.028
C(12)	-0.003
C(13)	-0.054

Ring  $B$

$$-0.2923X + 9.4284Y - 6.1373Z = 2.0038$$

C(4)	-0.147 Å
C(5)	-0.048
C(13)	0.059
C(14)	0.114
N(15)	-0.352
C(19)	0.374

Ring  $C$

$$-0.3636X + 10.0760Y - 5.7602Z = 2.8036$$

C(1)	-0.102 Å
C(2)	-0.035
C(3)	0.271
C(4)	-0.381
C(18)	0.019
C(19)	0.227

maker & Trueblood, 1968), we find that the lycorine molecule behaves nearly as a rigid body. The root mean square difference between the observed  $U_{ij}$  and those calculated from the derived T, L, S molecular tensors is only  $0.0034 \text{ \AA}^2$  for all non-hydrogen atoms. Observed and calculated ellipsoids were compared according to the tests suggested by Burns, Ferrier & McMullan (1967); no remarkable features were then noticed, except for the atom O(21) which has a small amount of independent motion. The rigid-body motions are principally translational and are almost isotropic with an average amplitude of  $0.16 \text{ \AA}$ . Rotational motion is limited by the molecular close packing and the hydrogen bonding.

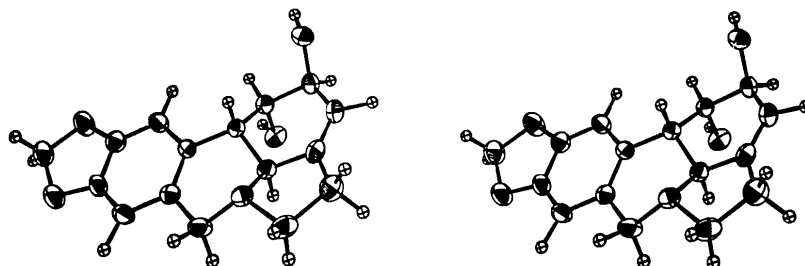


Fig. 2. Stereoscopic plot of the lycorine molecule. Thermal ellipsoids are scaled to include 50% probability.

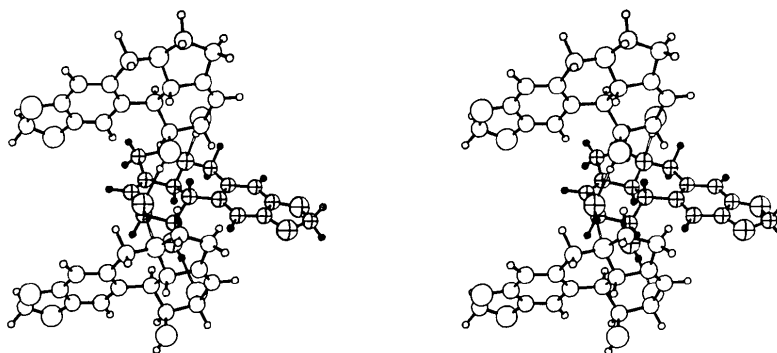


Fig. 3. Stereoscopic plot of the hydrogen bonding in lycorine structure.

### Molecular structure

Interatomic distances and valency angles of the lycorine molecule are given in Table 5. No attempt has been made to establish the absolute configuration, suggested by Nakagawa & Uyeo (1959) and by the X-ray analysis of dihydrolycorine hydrobromide (Shiro, Sato & Koyama, 1968). The bond lengths and angles do not differ significantly from normal values. The junction between rings *B* and *C* is *trans* and between *C* and *D*, *cis*. Best planes through selected atoms are given in Table 6 with the displacements of the atoms from these planes. The fragment including atoms from C(5) to C(13) is nearly planar. The *B* ring is a distorted boat.

### Molecular packing

Hydrogen bonding exists in this structure (Table 7). Each hydroxyl group O(20)–H(20) is involved in two hydrogen bonds and acts both as a proton donor and as a proton acceptor (Fig. 3). In both cases, these bonds are nearly linear.

Table 7. *Geometry of the hydrogen bonding between the molecules*

Symmetry code <i>c</i> : 0.5 - x, 1 - y, 0.5 + z			
Hydrogen bond	Distance H...N	Distance O...N	Angle O-H...N
O(20)–H(20)···N(15) ( <i>c</i> )	1.859	2.829	176.8°
Hydrogen bond	Distance H...O	Distance O...O	Angle O-H...O
O(21)–H(21)···O(20) ( <i>c</i> )	1.865	2.785	169.8°

The packing is efficient and several other distances between atoms are approximately equal to the sum of the van der Waals radii. In all these contacts at least one hydrogen atom is involved (Table 8).

The calculations were carried out with a local version of the X-RAY 70 System of crystallographic programs (Stewart, Kundell & Baldwin, 1970) on a UNIVAC 1108 Computer (Centre de Calcul de l'Université Paris-Sud). The program *DEVIN*, written by C. Riche, was used to choose the set of symbolic phases and the pro-

Table 8. *Shortest intramolecular distances in lycorine structure (Å)*

Symmetry code:				<i>a</i> : 1 + x	<i>y</i>	<i>z</i>
				<i>b</i> : 0.5 + x	1.5 - y	1 - z
				<i>c</i> : 0.5 - x	1 - y	0.5 + z
C(1)	H(3) ( <i>c</i> )	2.852	C(18)	H(3) ( <i>c</i> )	2.875	
C(2)	H(21) ( <i>c</i> )	2.902	C(19)	H(20) ( <i>c</i> )	2.859	
O(10)	H(1) ( <i>a</i> )	2.401	H(4)	C(2) ( <i>c</i> )	2.760	
O(10)	H(19) ( <i>b</i> )	2.601	H(4)	C(3) ( <i>c</i> )	2.768	
C(11)	H(19) ( <i>b</i> )	2.854	H(4)	H(3) ( <i>c</i> )	2.266	
C(12)	H(19) ( <i>b</i> )	2.899	H(4)	H(2) ( <i>c</i> )	2.113	
C(14)	H(20) ( <i>c</i> )	2.621	H(12)	O(21) ( <i>b</i> )	2.436	
			H(20)	H(21) ( <i>c</i> )	2.383	

gram *ORTEP* (Johnson, 1965) to make stereoscopic drawings.

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