Crystal and Molecular Structure and Absolute Configuration of Maytansine (3-Bromopropyl) Ether

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The molecular structure and absolute configuration of maytansine (Ia) have been found from a three-dimensional single-crystal *X*-ray analysis of its (3-bromopropyl) ether (Ib). Crystals are orthorhombic, space group $P2_12_12_1$ with $a = 24{\cdot}239(4)$, $b = 16{\cdot}044(4)$, $c = 10{\cdot}415(2)$ Å, and $Z = 4$. The structure was solved by the heavy-atom method and refined by Fourier and least-squares methods to R 0·101 for 927 independent reflections measured by counter diffractometry. The absolute configuration was established by the anomalous dispersion method.

The molecule contains a 19-membered ring with the nitrogen-containing aliphatic portion bridging a substituted phenyl group in a 1,3-ansa-fashion. The structure shows similarities to those of the ansamycin antibiotics, but has novel epoxide, carbinolamine ether, and aryl halide functions.

MAYTANSINE (Ia) is a powerful anti-leukaemic agent whose isolation from *Maytenus ovatus* Loes., and structural characterization by *X*-ray crystallographic analysis of its (3-bromopropyl) ether (Ib) have recently been reported briefly.[1] The compound is an active inhibitor, *in vitro*, of the growth of cells derived from human carcinoma of the nasopharynx (KB), and its shows *in vivo* activity at very low concentrations over a wide dosage range against murine P 388 leukaemia.[1]

Our *X*-ray analysis has shown that maytansine has a structure resembling those of the ansamycin antibiotics,[2-6] particularly geldanamycin.[7] It is the first molecule of this type shown to contain aryl halide, epoxide, or carbinolamine functions, and it is the first of

[1] S. M. Kupchan, Y. Komoda, W. A. Court, and G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger, and R. F. Bryan, *J. Amer. Chem. Soc.*, 1972, **94**, 1354.

[2] K. L. Rinehart, jun., *Accounts Chem. Res.*, 1972, **5**, 57.

[3] W. Oppolzer, V. Prelog, and P. Sensi, *Experientia*, 1964, **20**, 336; J. Leitich, W. Oppolzer, and V. Prelog, *ibid.*, p. 343; J. Leitich, V. Prelog, and P. Sensi, *ibid.*, 1967, **23**, 505; G. C. Lancini, G. G. Gallo, G. Sartori, and P. Sensi, *J. Antibiot.*, 1969, **22**, 369.

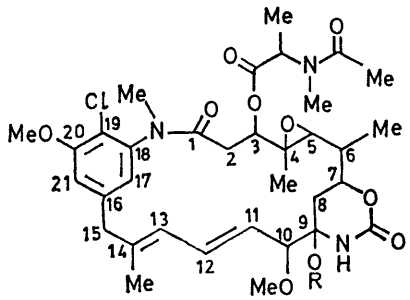
[4] M. Brufani, W. Fedeli, G. Giacomello, and A. Vaciago, *Experientia*, 1964, **20**, 339; 1967, **23**, 508.

[5] T. Kishi, S. Horanda, M. Asai, M. Muroi, and K. Mizuno, *Tetrahedron Letters*, 1969, 97; K. Kamiya, T. Sugiro, Y. Wada, M. Nishikawa, and T. Kishi, *Experientia*, 1969, **25**, 901.

[6] A. H.-J. Wang, I. C. Paul, K. L. Rinehart, jun., and F. J. Antosz, *J. Amer. Chem. Soc.*, 1971, **93**, 6275; K. L. Rinehart, jun., M. L. Mheshwari, F. J. Antosz, H. H. Mathur, K. Sasaki, and R. J. Schacht, *ibid.*, p. 6273.

[7] K. Sasaki, K. L. Rinehart, jun., G. Slomp, M. F. Grostic, and E. C. Olson, *J. Amer. Chem. Soc.*, 1970, **92**, 7591.

the class of ansa macrolides reported as showing significant *in vivo* tumour-inhibitory behaviour.[1]



(I) a; R = H
b; R = n-C_3H_6Br

EXPERIMENTAL

The bromopropyl ether of maytansine (m.p. 176—178 °C) was prepared as described previously.[1]

Crystal Data.—$C_{37}H_{51}BrClN_3O_{10}$, $M = 813{\cdot}2$. Orthorhombic, $a = 24{\cdot}239(4)$, $b = 16{\cdot}044(4)$, $c = 10{\cdot}415(2)$ Å, $U = 4050$ Å^3, $D_m = 1{\cdot}30$, $Z = 4$, $D_c = 1{\cdot}33$, $F(000) = 1704$. Space group $P2_12_12_1$, Cu-K_α radiation, $\lambda = 1{\cdot}5418$ Å; μ(Cu-K_α) = 27 cm^{-1}.

The density, measured by flotation in carbon tetrachloride–cyclohexane, gave the first reliable indication of the molecular weight of maytansine.

Preliminary unit-cell and space-group data were determined from 25° precession photographs of the reciprocal lattice taken with Mo-K_α radiation ($\lambda = 0{\cdot}7107$ Å). Unit cell parameters were then refined by a least-squares fit to the observed settings of $\pm 2\theta$ for 19 strong general reflections measured on the diffractometer.[8]

Intensity Measurements.—These were made from a single-crystal plate of dimensions $0{\cdot}05 \times 0{\cdot}25 \times 1{\cdot}2$ mm parallel to the cell axes, and mounted with c parallel to the ϕ axis of a Picker four-circle diffractometer controlled by an XDS Sigma 2 computer. Monochromatic Cu-K_α radiation was used, obtained by Bragg reflection of the direct beam from the (002) planes of a highly oriented graphite crystal. Measurements were made by use of the θ—2θ scanning technique with symmetrical 2° scan ranges and a scan speed of 2° min^{-1}. Background measurements were made by the stationary-crystal–stationary-counter method for intervals of 10s at the beginning and end of the scan ranges. True background was assumed to be linear between these points. The scattered radiation was detected by scintillation counting with pulse-height analysis. About 1200 reciprocal lattice points were surveyed within a single octant to 2θ 74°. Scattered intensity significantly above background was found at 927 locations where the net background corrected peak intensity, I, was $>3\sigma(I)$ where $I = C - (t_s/t_b)(B_1 + B_2)$ and $\sigma^2(I) = C + (t_s/t_b)^2(B_1 + B_2)$, and C and B are counts collected during the time of scan, t_s, and background, t_b, measurement.

Two reference reflections monitored after every 50 measurement cycles showed no significant change in intensity. No absorption corrections were applied, and structure amplitudes were derived in the usual way.

Structure Determination and Refinement.—Although the diffraction pattern of the ether derivative is of reasonable quality, it is very limited in extent being equivalent to a resolution of only *ca.* 1·3 Å. Thus, the 927 significant reflections obtained yield a ratio of observations to parameters of only slightly more than 4 : 1 when individual isotropic thermal parameters are assumed for the non-hydrogen atoms. This paucity of observed data affected the whole course of the structure determination and the correct solution was found only with difficulty.

The position of the bromine atom in the asymmetric unit was readily found from the Harker sections of the three-dimensional Patterson function, but over 30 cycles of Fourier refinement and structure-factor calculation were required to locate the remaining non-hydrogen atoms. The presence of the chlorine atom was unsuspected, and it was the last atom to be correctly identified. The phasing of the reflections was made no easier by the very high Debye thermal parameter of the bromine atom, B 11·0 Å^2. However, once all the atomic positions had been reliably fixed from the electron-density functions, the refinement of the atomic parameters proceeded smoothly by block-diagonal least-squares methods.

Assignment of chemical type was made by a careful analysis of the geometrical arrangement of the atoms and of the residual electron density at atomic sites when all light atoms were treated as carbon. All identifications were doubly checked for the absence of residual electron density after the assignment of type and the attribution of isotropic thermal parameters by least-squares refinement. Only in the case of the chlorine atom was it necessary to use chemical microanalysis to distinguish between the halogen and a possible sulphur atom at this site. All assignments are compatible with measurements of the u.v., i.r., and n.m.r. spectra of maytansine and with the results of high-resolution mass spectrometric measurements.[1]

With the bromine and chlorine atoms only given anisotropic thermal parameters, the final R was 0·101. A final three-dimensional difference electron-density synthesis showed no structurally significant features. The weighting scheme used in the least-squares process was based on counting statistics with some allowance made for the non-random errors of measurement associated with the stronger reflections, *etc.*[9] The scattering functions used were for neutral atoms.[10] All calculations were carried out with programs written in this laboratory for the XDS Sigma 2 computer.

Assignment of Absolute Configuration.—When the real and imaginary components of the anomalous scattering terms for bromine and chlorine [11] are included in two separate structure-factor calculations with co-ordinates corresponding to the two possible enantiomers, R values of 0·101 and 0·103 result. This indicates a distinction between the two configurations at the 99·5% confidence level.[12] To check the correctness of this choice the intensities of 23 Bijvoet pairs of reflections, chosen at random from among the stronger intensities, were carefully remeasured. All eight contributors were measured in each case and the mean values of each set taken. In all cases the observed differences in intensity corresponded very closely to those

[8] U. W. Arndt and B. T. M. Willis, ' Single Crystal Diffractometry,' Cambridge University Press, Cambridge, 1966, p. 262.
[9] W. R. Busing and H. A. Levy, *J. Chem. Phys.*, 1957, **26**, 563; D. F. Grant, R. C. G. Killean, and J. L. Lawrence, *Acta Cryst.*, 1969, *B*, **25**, 374.
[10] H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.
[11] ' International Tables for *X*-Ray Crystallography,' vol. 3, Kynoch Press, Birmingham, 1968.
[12] W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.

expected.[13] A list of the observed and calculated structure amplitudes for these reflections is given in Table 1.†

TABLE 1

Bijvoet pairs of reflections used in the determination of the absolute configuration. The superscripts + and − refer to the index triples *hkl* and $\bar{h}\bar{k}\bar{l}$, respectively

h	*k*	*l*	$\lvert F_o^+\rvert$	$\lvert F_c^-\rvert$	Δ_o	Δ_c
1	1	1	71·2	76·8	−5·6	−4·4
1	1	2	113·7	117·3	−3·6	−2·7
1	1	3	138·3	137·2	1·1	1·3
1	2	2	127·5	130·3	−2·8	−2·1
1	2	3	132·9	132·6	0·3	1·0
1	3	2	154·5	154·4	0·1	0·0
1	3	3	114·6	117·6	−3·0	−2·3
2	2	3	110·2	108·0	2·2	2·6
2	3	1	144·1	152·2	−8·1	−7·8
2	3	2	123·6	126·3	−2·7	−2·3
2	4	2	129·8	130·8	−1·0	−0·3
2	4	3	118·8	117·9	0·8	0·5
3	1	1	66·4	69·9	−3·5	−3·2
3	1	2	128·2	128·9	−0·7	0·4
3	1	3	126·9	127·3	−0·4	−0·7
3	2	2	113·5	107·8	5·7	5·4
3	3	1	141·4	144·7	−3·3	−2·6
3	4	1	106·6	106·2	0·4	−0·2
4	1	1	87·8	85·6	2·2	2·1
4	1	2	117·5	115·5	2·0	1·5
4	2	1	84·1	85·7	−1·6	−1·7
5	1	1	112·5	112·8	−0·3	−0·2
5	3	2	94·9	98·7	−3·8	−3·2

DESCRIPTION OF THE STRUCTURE AND DISCUSSION

The atomic parameters with their estimated standard deviations [14] are given in Table 2. A view of the molecular structure as found in the crystal is shown in Figure 1, while Figure 2 shows the bond lengths and angles found and the numbering scheme adopted for the atoms. Torsion angles about certain bonds in the molecule are shown in Figure 3. The observed geometry leads directly to the structural assignments (Ia) for maytansine and (Ib) for the bromopropyl derivative.

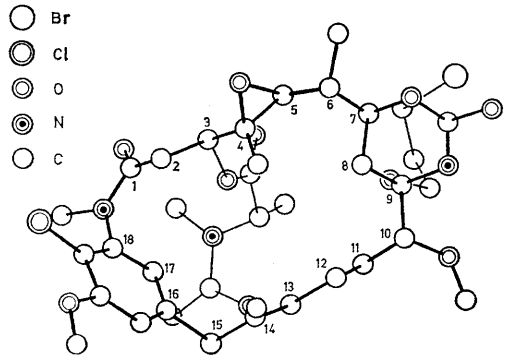


FIGURE 1 A view of the molecular structure, as found in the crystal, projected onto the plane of the 19-membered ring; only the ring atoms are numbered

Based on the root-mean-square deviations in chemically equivalent parameters,[15] the standard deviation in a C–C bond is *ca.* 0·06 Å and in a C–C–C angle *ca.* 4°.

† Complete observed and calculated structure amplitudes are listed in Supplementary Publication No. SUP 20606 (3 pp., 1 microfiche). For details see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20 (items less than 10 pp. are sent as full size copies).

TABLE 2

Atomic parameters defining the crystal structure. Positional parameters are given as fractional co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses

	x/a	*y/b*	*z/c*	*B*/Å²
Br	6440(2)	5301(3)	1977(4)	*
Cl	2242(4)	7900(6)	9136(10)	*
O(1)	2837(8)	6463(12)	5358(23)	8·3(6)
O(2)	4074(5)	6131(10)	6141(16)	3·5(3)
O(3)	4230(7)	5622(11)	4154(21)	7·2(5)
O(4)	4110(7)	3856(12)	8082(22)	7·4(5)
O(5)	4433(7)	8157(12)	4793(22)	6·9(5)
O(6)	6303(3)	7142(9)	4326(17)	4·8(4)
O(7)	7232(7)	6795(12)	4349(21)	7·4(5)
O(8)	5815(6)	5121(9)	5159(17)	4·7(4)
O(9)	6595(7)	4791(11)	7315(20)	6·5(5)
O(10)	2729(8)	7832(13)	11609(23)	8·4(6)
N(1)	2713(8)	6514(13)	7437(24)	5·9(6)
N(2)	3683(8)	4407(12)	6511(21)	4·9(5)
N(3)	6656(7)	5984(12)	5475(22)	4·4(5)
C(1)	3017(13)	6780(20)	6349(35)	7·9(9)
C(2)	3457(10)	7293(15)	6500(27)	4·7(6)
C(3)	3916(10)	6952(17)	5574(29)	5·5(7)
C(4)	4443(9)	7454(14)	5643(25)	3·4(6)
C(5)	4832(9)	7461(14)	4555(24)	3·4(6)
C(6)	5419(10)	7711(16)	4537(30)	5·5(7)
C(7)	5756(9)	6820(14)	4548(26)	3·8(6)
C(8)	5714(8)	6489(13)	5920(22)	2·5(5)
C(9)	6085(10)	5766(15)	5912(28)	4·3(6)
C(10)	6168(11)	5474(17)	7354(31)	6·4(7)
C(11)	5656(10)	5126(15)	7872(28)	4·8(6)
C(12)	5453(11)	5634(17)	8771(34)	6·4(8)
C(13)	4910(11)	5387(19)	9401(32)	6·7(8)
C(14)	4596(10)	5824(15)	10231(29)	4·8(7)
C(15)	4049(10)	5484(16)	10726(28)	5·4(7)
C(16)	3569(10)	6051(14)	10226(26)	4·3(6)
C(17)	3330(9)	6038(15)	9001(30)	4·8(7)
C(18)	2910(13)	6568(19)	8759(35)	7·4(8)
C(19)	2701(10)	7197(16)	9517(29)	5·6(7)
C(20)	2964(10)	7195(15)	10820(29)	5·4(7)
C(21)	3395(10)	6666(17)	11170(31)	5·6(7)
C(22)	2155(13)	6108(21)	7314(39)	8·8(9)
C(23)	4191(11)	5469(17)	5359(30)	6·3(7)
C(24)	4244(9)	4689(15)	6024(25)	3·9(6)
C(25)	4386(15)	4047(22)	5006(42)	9·6(10)
C(26)	3195(11)	4510(17)	5606(30)	6·1(7)
C(27)	3643(10)	3942(16)	7610(29)	5·6(7)
C(28)	3176(13)	3613(19)	8239(39)	8·3(9)
C(29)	4709(11)	7749(18)	7048(34)	6·8(7)
C(30)	5510(10)	8176(17)	3228(31)	5·6(7)
C(31)	6699(11)	6681(17)	4694(33)	6·3(7)
C(32)	6173(10)	4389(16)	4764(28)	5·2(7)
C(33)	5856(9)	4030(14)	3539(25)	3·5(6)
C(34)	5744(14)	4706(21)	2497(38)	9·3(10)
C(35)	6862(14)	4737(20)	8613(35)	8·6(9)
C(36)	4760(15)	6706(24)	10721(40)	9·8(10)
C(37)	2882(11)	7838(18)	12919(36)	7·3(8)

* Anisotropic thermal parameters for Br and Cl in the form: $exp - (h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})$. Values of β_{ij} ($\times 10^4$), given in that order, are as follows:

Br	79(2)	126(3)	97(5)	−47(2)	18(3)	−39(4)
Cl	45(2)	109(6)	154(14)	31(4)	15(5)	51(8)

These values are greater, by a factor of 1·5, than those calculated from the errors in the atomic positions given by the least-squares process.[14] The low level of accuracy achieved in this analysis is due to the low ratio of observations to parameters noted earlier. However there is no reason to believe that any of our conclusions as to the chemical structure of maytansine are incorrect,

[13] J. M. Bijvoet, A. F. Peerdeman, and A. T. van Bommel, *Nature*, 1951, **168**, 271.
[14] L. I. Hodgson and J. S. Rollett, *Acta Cryst.*, 1963, **16**, 329.
[15] A. McL. Mathieson, *Perspectives in Structural Chem.*, 1967, **1**, 44.

although any discussion of the finer details of the molecular geometry would not be worthwhile.

The nucleus of the molecule is a roughly rectangular 19-membered ring with the aliphatic portion bridging in a 1,3-ansa-fashion a substituted phenyl group, and having an amide group directly linked through the nitrogen atom is also of bacterial origin, but experiments to test this possibility have given negative results so far.

Three results, found for maytansine, have not previously been observed for this type of compound: (i) the ring nitrogen is methylated, [as are also C(4), C(6), and C(14)], (ii) there is an epoxide ring at C(4)–C(5), and (iii)

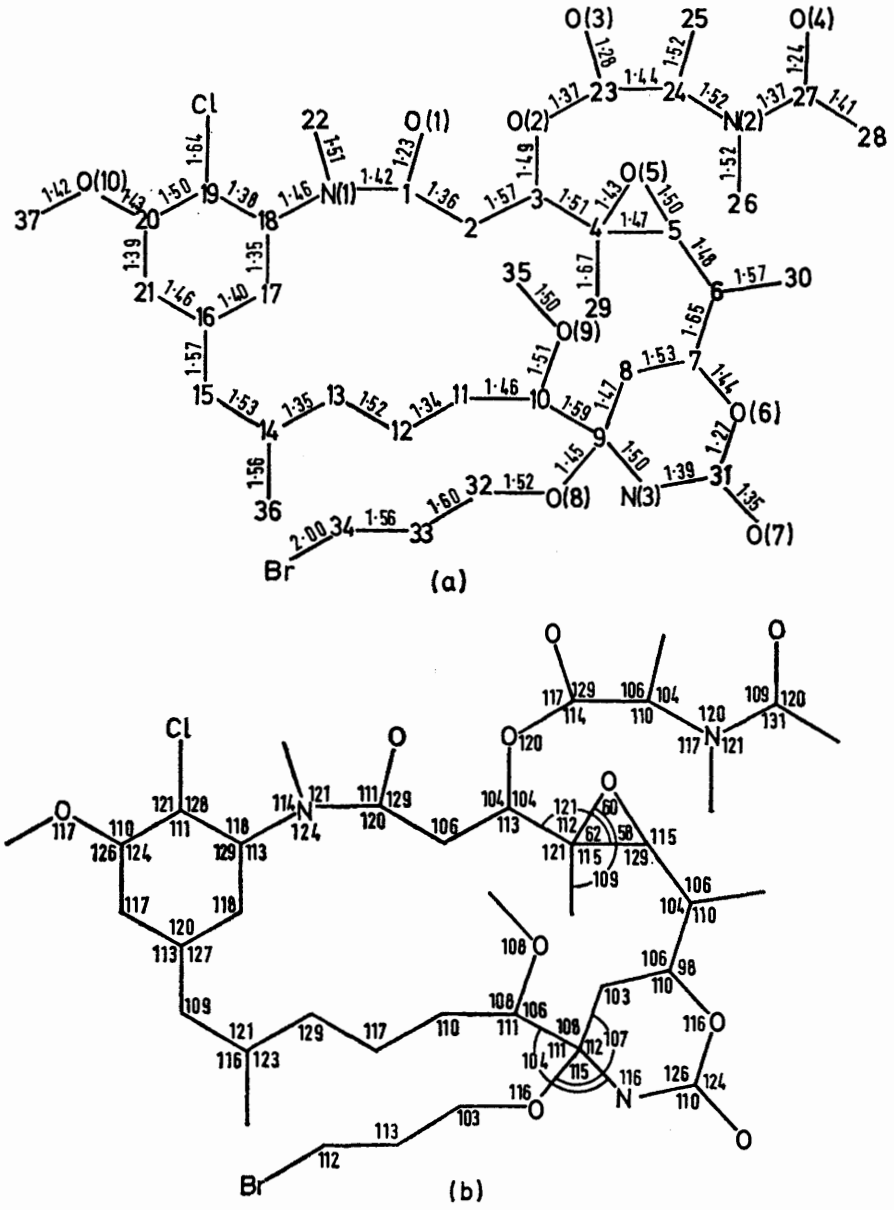


FIGURE 2 (a) Bond lengths (Å); the atom numbering scheme is shown. (b) Bond angles (deg.)

to the aromatic group. This kind of macrocyclic ring system is characteristic of the ansamycin antibiotics,[2] and maytansine most closely resembles geldanamycin [7] (II) which also has a 19-membered ring and where the aromatic group is a methoxy-substituted *p*-quinone. All the other representatives of this class of compound are of bacterial origin, and maytansine is the first to be isolated from a plant source. It may be that maytansine a carbinolamine function in the ring system bridging C(7) and C(9). A planar *trans,trans*-diene system is formed by C(11)–(14) and attached to C(3) is an *N*-acetyl-*N*-methylalanine residue. The presence of a halogen substituent on the aromatic group is also novel in these compounds. The absolute configurations at the asymmetric centres are: 3*S*,4*S*,5*S*,6*R*,7*S*,9*S*,10*R*,23*S*.

The overall molecular shape is best described in terms

of the angles which the least-squares mean-planes through certain groups of atoms make with one another

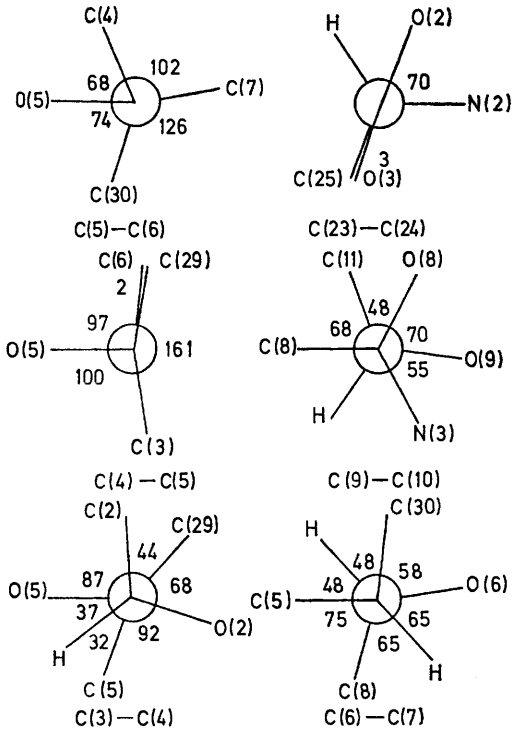
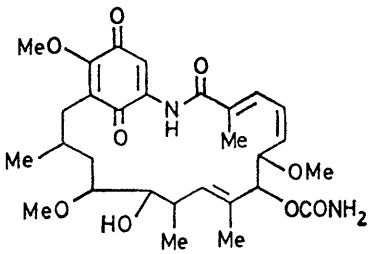


FIGURE 3 Torsion angles

and with that through the 19-membered ring (Figure 4, and Table 3).



(II)

The two longer sides of the ring are roughly parallel and separated by *ca.* 5·4 Å so that there is a hole in the centre of the ring. The two faces of the ring have a different character, the lower surface, opposite the amino-acid residue, is predominantly hydrophobic while the upper face is more hydrophilic. This may be important to the way in which maytansine binds to cell constituents.[1]

TABLE 3

Least-squares mean planes through selected groups of atoms (see Figure 4)

(*a*) Coefficients of the equations of the planes in the form: $aX + bY + cZ = d$, where X, Y, and Z are in Å and the axial system is the same as the cell axial system

Plane	*a*	*b*	*c*	*d*
(I)	−0·6878	−0·6476	0·3279	−8·7488
(II)	0·3403	−0·5929	0·7298	0·8594
(III)	0·2677	−0·9399	0·2120	−7·1101
(IV)	0·8440	0·5220	0·1229	18·0515
(V)	0·4944	−0·4755	0·7277	8·8373
(VI)	−0·1510	0·8629	0·4823	7·9500
(VII)	0·9703	0·2118	0·1173	12·3359
(VIII)	0·2227	0·8461	0·4842	14·7742

TABLE 3 (*Continued*)

(*b*) Deviations (Å) of atoms from the planes

(I) C(15) 0·01, C(16) −0·01, C(17) 0·00, C(18) −0·05, C(19) 0·01, C(20) −0·01, C(21) 0·02, N(1) 0·03

(II) C(1) −0·01, C(2) 0·00, C(3) 0·01, C(4) 0·00

(III) C(4)—C(6)

(IV) C(6) 0·07, C(7) 0·02, C(8) −0·17, C(9) −0·02, C(10) 0·09

(V) C(10) −0·05, C(11) 0·00, C(12) 0·05, C(13) 0·06, C(14) −0·02, C(15) −0·04

(VI) C(24) −0·01, C(26) 0·06, C(27) 0·00, C(28) −0·03, N(2) −0·07, O(4) 0·06

(VII) C(3) 0·08, O(2) −0·08, O(3) −0·03, C(23) −0·03, C(24) 0·03, C(25) 0·03

(VIII) From C(6) −0·91 to C(11) 0·79. This is the mean plane though the 19-membered ring

(*c*) Interplanar angles (deg.) for the angle between the labelled plane and the succeeding planes, in numerical order

(I) 66, 60, 151, 77, 108, 139, 123
(II) 37, 86, 11, 102, 73, 94
(III) 104, 43, 138, 85, 129
(VI) 75, 68, 19, 46
(V) 98, 62, 87
(VI) 85, 22
(VII) 63

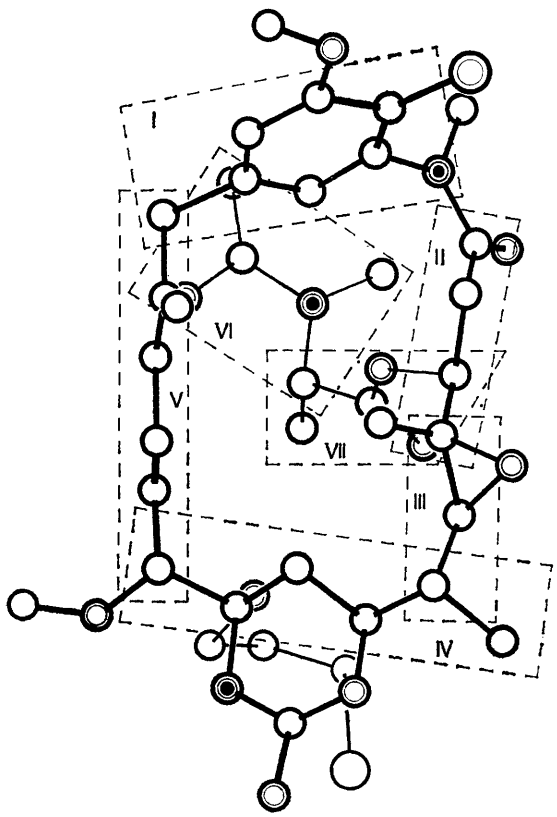


FIGURE 4 The molecular structure blocked into the planar regions (see text and Table 3). Plane (VIII) is the mean plane through the atoms of the 19-membered ring

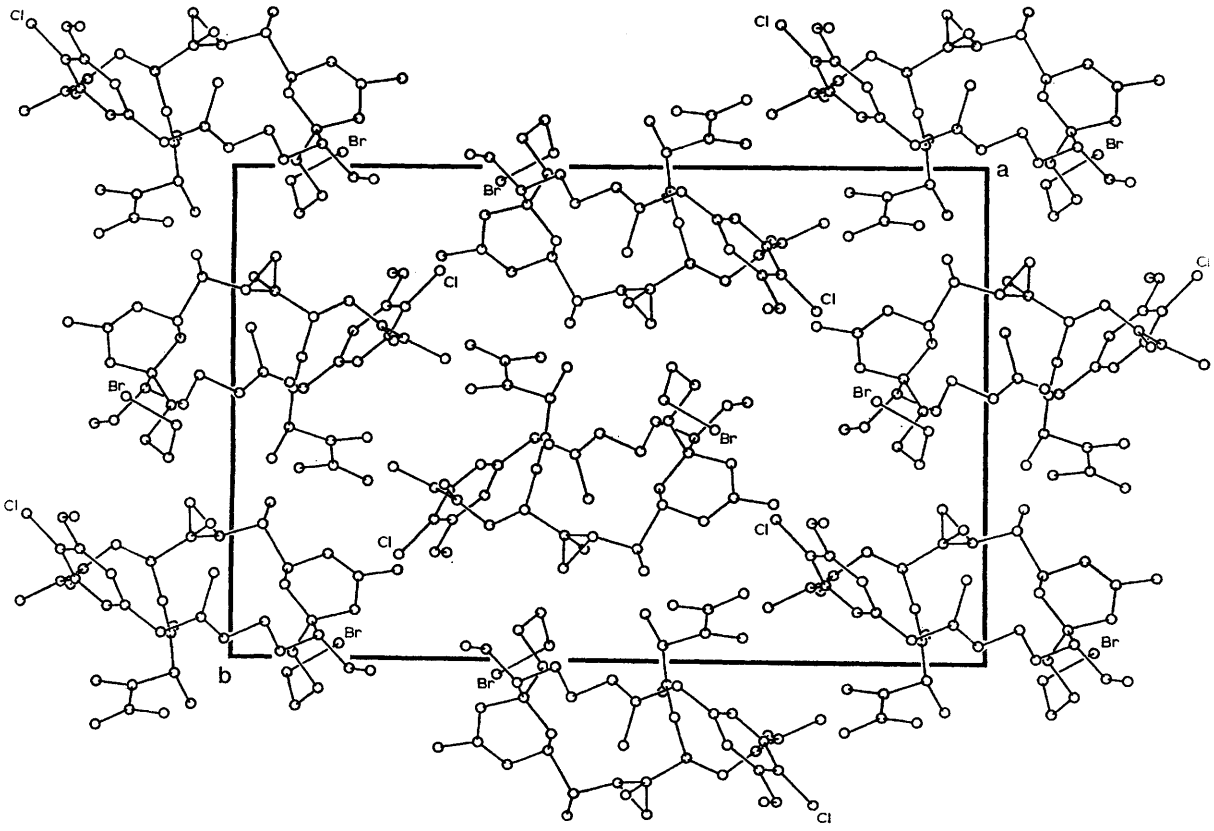


FIGURE 5 The arrangement of molecules in the unit cell

Some of the shorter intramolecular approach distances between atoms are given in Table 4. These distances and the observed torsion angles suggest that there is very little strain in the molecular structure as found in the crystal, and there are no abnormally short intermolecular contacts. The symmetrical nature of the molecular structure, coupled with the chemically enforced rigidity of many of its parts, and the absence of serious strain, suggests that this structure may well be maintained in solution.

TABLE 4

Selected shorter intramolecular approach distances (Å)

Br · · · O(8)	3·66	O(3) · · · C(5)	3·32
Br · · · C(31)	3·65	O(4) · · · C(25)	3·29
Cl · · · C(22)	3·45	O(9) · · · C(32)	2·92
O(1) · · · O(2)	3·15	C(2) · · · C(17)	3·31
O(1) · · · C(26)	3·26	C(4) · · · C(8)	3·46
O(2) · · · N(1)	3·62	C(8) · · · C(29)	3·38
O(2) · · · C(17)	3·48	C(12) · · · C(36)	3·15
O(3) · · · C(4)	3·36	C(21) · · · C(36)	3·34

The arrangement of molecules in the unit cell is shown in Figure 5 and the shorter intermolecular contacts are given in Table 5. These contacts are of normal van der Waals type.

TABLE 5

Shorter intermolecular contacts (Å)

Br · · · C(35^{I})	3·76	O(5) · · · C(34^{V})	3·47
Br · · · Cl^{VI}	3·67	O(7) · · · N(1^{VI})	3·49
Cl · · · O(7^{II})	3·66	O(7) · · · C(1^{VI})	3·06
O(1) · · · C(37^{I})	3·37	O(7) · · · C(2^{VI})	3·43
O(1) · · · C(28^{III})	3·30	C(18) · · · C(26^{VII})	3·72
O(1) · · · O(7^{II})	3·17	C(19) · · · C(26^{VII})	3·68
O(3) · · · C(15^{I})	3·60	C(22) · · · C(26^{VII})	3·67
O(4) · · · C(6^{IV})	3·29	C(25) · · · C(30^{VIII})	3·66
O(4) · · · C(29^{IV})	3·37	C(28) · · · C(37^{III})	3·48

Roman numerals as superscripts denote the following symmetry related positions relative to atoms at x, y, z:

I	$x, y, z - 1$	V	$1 - x, 0.5 + y, 0.5 - z$
II	$x - 0.5, 1.5 - y, 1 - z$	VI	$0.5 + x, 1.5 - y, z$
III	$0.5 - x, 1 - y, z - 0.5$	VII	$0.5 - x, 1 - y, 0.5 + z$
IV	$1 - x, y - 0.5, 0.5 + z$	VIII	$1 - x, y - 0.5, 0.5 - z$

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