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The Crystal and Molecular Structure of Demycarosyl Leucomycin A_3 Hydrobromide

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The stereochemically-complete molecular structure of demycarosyl leucomycin A_3, $C_{30}H_{49}NO_{11}$, has been determined by means of an X-ray crystal analysis of its hydrobromide. The crystals of the hydrobromide are orthorhombic with four chemical units in a unit cell with the dimensions of $a=19.52\pm0.03$, $b=20.63\pm0.03$, and $c=9.28\pm0.03$ Å. The space group is $P2_12_12_1$. As a result of the present study, it has been found that the crystals contain about 0.6 mole of ethanol per mole of the hydrobromide as alcohol of crystallization. The intensity data were obtained from equi-inclination integrating Weissenberg photographs taken with Cu$K\alpha$ radiation around the b and c axes. The structure was elucidated by means of the minimum function, least-squares, and Fourier methods. The atomic coordinates obtained were refined by the block-diagonal least-squares method, anisotropic thermal motion being assumed for only the bromine atom. The final R factor is 14.6%. The molecular structure thus obtained corresponds exactly to that proposed in 1967 by Hata *et al.* on the chemical evidence, considering the allylic rearrangement in the hydrolysis of leucomycin A_3 with dilute hydrochloric acid. The conjugated diene system in the macro ring has the *trans-trans* configuration. The sugar component, mycaminose, forms a β-glycosidic linkage with the lactone ring.

Leucomycin A_3 is a basic macrolide antibiotic obtained from the broth-filtrate of *Streptomyces Kitasatoensis* Hata.[1] A partial structure was reported by Watanabe *et al.* for the compound,[2] which contains, as sugar components, the mycaminose and 4-*O*-isovaleryl mycarose found in many other antibiotics.[3] Later, the total structure

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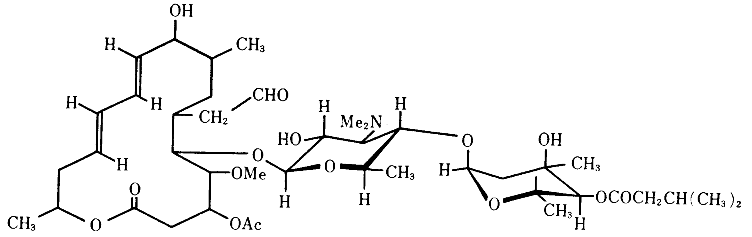
1) T. Hata and Y. Sano *J. Antibiotics, Ser. A*, **6**, 87 (1953).

2) T. Watanabe, T. Fujii, H. Sakurai, J. Abe and K. Satake, Abstracts of papers, International Symposium on the Chemistry of Natural Products, Kyoto (1964), p. 145.

3) W. D. Celmer, *J. Amer. Chem. Soc.*, **87**, 1799 (1965).



shown below was proposed by Hata *et al.* on the basis of a comparison with those of magnamycin B and spiramycin A.[4] For the purpose of confirming the proposed structure, an X-ray study of leucomycin A_3 hydrobromide has recently been undertaken by some of the present authors. However, it has been found that the bromine atom is placed at an unfavorable position in the crystal with the space group $P2_12_12_1$; thus, the analysis has been led to difficulty. Therefore, an X-ray structure determination has been tried for the hydrobromide of demycarosyl leucomycin A_3 instead of leucomycin A_3 itself. The crystal analysis of the derivative has proved successful, and the present paper will describe in detail the complete molecular structure, including the absolute configuration.

Experimental

Demycarosyl leucomycin A_3 (I) was derived from leucomycin A_3 by hydrolysis with 0.3 N hydrochloric acid and then further converted into its hydrobromide by the neutralization of an ethanol solution of I with a water-ethanol solution of hydrobromic acid. Single crystals of the hydrobromide were obtained in colorless prisms by adding ether to a methanol-ethanol solution and by then letting it stand overnight in an icebox. The crystal data determined from the present experiment are summarized in Table 1. The cell dimensions were determined from Weissenberg photographs calibrated with the standard silicon powder lines. The crystal density was measured by flotation in a mixture of carbon tetrachloride and cyclohexane.

Table 1. Crystal data

Formula	$C_{30}H_{49}NO_{11}\cdot HBr\cdot xC_2H_5OH$	
Orthorhombic		
	$a = 19.52\pm0.03$ Å	
	$b = 20.63\pm0.03$	
	$c = 9.28\pm0.03$	
Space group	$P2_12_12_1$	
U	3737 ± 23 Å	
Z	4	
D_m	1.258 g/cm³	(at 26°C)
D_x	1.209 g/cm³	(for $x=0.0$)
	1.258	(for $x=0.6$)
	1.291	(for $x=1.0$)

The intensities of reflections were visually measured from equi-inclination integrating Weissenberg photographs around the b and c axes taken with Ni-filtered Cu $K\alpha$ radiation. These intensities were corrected for the Lorentz-polarization factor, but not for the absorption effect, though the crystals used were not sufficiently small. The relative values of the observed structure factors of the 2450 reflections thus obtained were put on an absolute scale by Wilson's method, the estimated overall temperature factor, B, being 7.27 Å².

Structure Determination

As the first step in the structure analysis, a three-dimensional Patterson function, $P(u, v, w)$, was calculated at intervals of 1/120 for u and v and at intervals of 1/60 for w. Since all the three peaks corresponding to the Br–Br vectors were sufficiently separated from the other high peaks, though they were not always the highest in the Harker sections, it was easily found that the bromine atom might be situated at the position, (0.144, 0.098, 0.171). Five cycles of the least-squares treatment were then carried out. As a result of this treatment, it was found that the bromine position was adequate, since the temperature factor converged into a reasonable value of 6.28 Å²; the coordinates also converged into (0.144, 0.097, 0.177). At this stage, the discrepancy factor, R, was 0.48 for all the observed reflections. In order to seek for positions of light atoms, the minimum-function method was applied by using the three independent Br–Br vectors. Out of many maxima in the minimum function diagram, forty-nine were selected as the positions of light atoms on the basis of their heights; they were tested for adequacy by means of the least-squares method, with the coordinates fixed and using the atomic scattering factor of carbon for all.[5] After five cycles it was found that, out of the forty-nine positions, only eighteen were adequate. Then, the first Fourier synthesis was carried out with phases based on these eighteen positions in addition to the bromine. By applying again the above-mentioned method, it was found that thirty-one maxima in the Fourier map were adequate, five other peaks being excluded as false.

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[4] S. Omura, H. Ogura and T. Hata, *Tetrahedron Lett.*, **1967**, 1267.

[5] M. Nishikawa, K. Kamiya, M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, Y. Tomiie, I. Nitta and K. Goto, *J. Chem. Soc.*, *B*, **1968**, 652.

Out of these thirty-one rechosen positions, five were taken as those of oxygen atoms on the basis of their very small temperature factors. The second Fourier map thus calculated contained forty-one significant peaks, out of which seven were regarded as oxygen, one as nitrogen, and the remaining thirty-three as carbon, on the basis of both their heights and the chemical information. After three cycles of the usual least-squares refinement using the block-diagonal matrix approximation, it was further found that one of the carbon positions was inadequate and that three others were probably oxygen positions because their temperature factors were definitely small as compared with those of the carbon atoms previously established. The discrepancy factor, *R*, was 0.28 at this stage.

In order to look for the two atoms of I which had not yet been found, a difference synthesis was carried out. The map obtained had five peaks, with heights ranging from 1.3 to 1.7 e/Å^3. Of these peaks, two could be taken as an oxygen and a carbon atom of I on the basis of the chemical information. On the other hand, the remaining three seemed to correspond to a nonlinear triatomic molecule independent of I, judging from the calculated distances. The presence of the molecule was also supported by the consideration of the molecular packing. Thus, this was considered to be an ethanol molecule which is contained as alcohol of crystallization. However, after three cycles of the least-squares refinement, it turned out that the temperature factors of the three atoms in the alcohol molecule became abnormally large, though the *R* factor dropped from 0.27 to 0.24. Accordingly, excluding the parameters of the alcohol molecule for a while, six cycles of the least-squares method were repeated, assuming the anisotropic thermal motion for the bromine atom, the *R* factor calculated being 0.19. In the third Fourier map, computed with the parameters from the refinement, three peaks, with heights of from 1.0 to 1.7 e/Å^3, appeared again at almost the same positions as the peaks in the difference map already mentioned. Thus, it became certain that these peaks were not mere ghost peaks. The least-squares refinement including the ethanol parameters decreased the *R* factor to 0.177, but again made greater the thermal parameters of the alcohol molecule (20.8 Å^2 for O_E, 16.5 Å^2 for $C_E(1)$ and 20.1 Å^2 for $C_E(2)$). While so far it had been assumed that the mol ratio of ethanol to I was 1 : 1, this assumption no longer seemed to be reasonable. Accordingly, we attempted to estimate the mol ratio from a careful measurement of the crystal density and the unit-cell volume; the estimated value was about 0.6. Using, for the ethanol molecule, 0.6 times the usual values of the atomic scattering factors, three cycles of the refinement were carried out. The *R* factor thus reached a value of 0.152. Though four more cycles of the finement were performed in consideration of the anomalous dispersion correction of bromine for Cu *Kα* radiation, the *R* factor did not drop ap-

Table 2. The final atomic parameters

Atom	*x*/*a*	*y*/*b*	*z*/*c*	*B*	Atom	*x*/*a*	*y*/*b*	*z*/*c*	*B*
Br	0.6422	0.4034	0.1823	*	C (10)	0.2638	0.5294	0.2048	4.26
O (1)	0.2875	0.2592	0.2292	5.88	C (11)	0.3210	0.4874	0.1533	4.33
O (2)	0.1505	0.3150	0.1903	4.01	C (12)	0.3814	0.4877	0.2287	3.98
O (3)	0.2110	0.3651	0.0218	6.43	C (13)	0.4405	0.4455	0.1781	4.85
O (4)	0.0859	0.3262	0.4686	3.30	C (14)	0.4552	0.3840	0.2709	5.29
O (5)	−0.0045	0.4259	0.3826	2.68	C (15)	0.4035	0.3280	0.2402	4.83
O (6)	0.0245	0.3744	−0.0487	6.78	C (16)	−0.0587	0.3821	0.4025	3.01
O (7)	0.5003	0.4847	0.1998	5.96	C (17)	−0.1085	0.4125	0.5071	3.33
O (8)	0.3425	0.3427	0.3317	3.54	C (18)	−0.1748	0.3685	0.5092	2.85
O (9)	−0.0901	0.3741	0.2601	4.15	C (19)	−0.2008	0.3580	0.3616	4.27
O (10)	−0.0800	0.4121	0.6378	4.29	C (20)	−0.1431	0.3271	0.2703	3.97
O (11)	−0.2571	0.3138	0.3757	4.85	C (21)	0.1746	0.3191	0.0522	5.35
O_E	0.1432	0.1738	0.3437	9.15	C (22)	0.1530	0.2663	−0.0354	6.31
N	−0.2326	0.3973	0.5984	5.11	C (23)	0.0927	0.3335	0.6173	5.61
C (1)	0.2871	0.3071	0.3085	4.00	C (24)	0.0061	0.4754	0.0843	4.30
C (2)	0.2277	0.3295	0.3992	3.67	C (25)	−0.0101	0.4196	−0.0228	5.39
C (3)	0.1729	0.3617	0.3093	2.94	C (26)	0.1550	0.6282	0.2619	5.35
C (4)	0.1110	0.3808	0.3973	2.97	C (27)	0.4398	0.2653	0.2974	7.64
C (5)	0.0493	0.4026	0.2983	3.49	C (28)	−0.1620	0.3135	0.0996	6.75
C (6)	0.0696	0.4591	0.1897	3.48	C (29)	−0.2179	0.3943	0.7591	6.66
C (7)	0.0926	0.5196	0.2670	3.25	C (30)	−0.2563	0.4640	0.5574	6.85
C (8)	0.1391	0.5630	0.1744	3.87	C_E(1)	0.0916	0.1523	0.4074	10.69
C (9)	0.2040	0.5293	0.1312	3.70	C_E(2)	0.0430	0.1794	0.3127	8.55

*	B_{11}	B_{22}	B_{33}	B_{12}	B_{23}	B_{31}
	0.00298	0.00547	0.06022	0.00211	−0.00066	0.00778

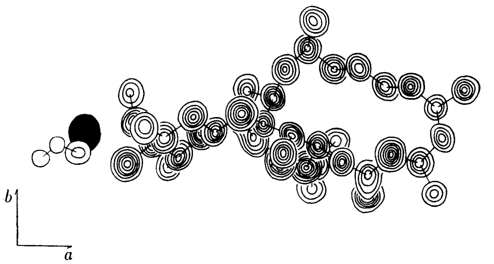

Fig. 1. A composite electron density map viewed along the c axis. Contours are at an interval of 2 e/Å^3, beginning at 2 e/Å^3. For the bromine atom, the region with a density above 2 e/Å^3 is blacked out.

preciably, the final value being 0.146. The final atomic parameters thus obtained are listed in Table 2, while the final electron-density distribution computed from these parameters is shown in Fig. 1. Tables of the observed and calculated structure factors are preserved by the Chemical Society of Japan.[*2]

The Absolute Configuration of I

When a non-centric crystal contains atoms which give rise to an observable anomalous scattering of X-rays, Friedel's law $|F(hkl)|^2=|F(\bar{h}\bar{k}\bar{l})|^2$ no longer holds.[6] Since, for the $P2_12_12_1$ space group, $|F(hkl)|^2=|F(\bar{h}\bar{k}l)|^2=|F(h\bar{k}\bar{l})|^2=|F(\bar{h}k\bar{l})|^2$ and $|F(\bar{h}\bar{k}\bar{l})|^2=|F(hk\bar{l})|^2=|F(\bar{h}kl)|^2=|F(h\bar{k}l)|^2$, pairs of (hkl) and $(\bar{h}\bar{k}\bar{l})$ reflections need not be selected for a study of the absolute configuration. In the

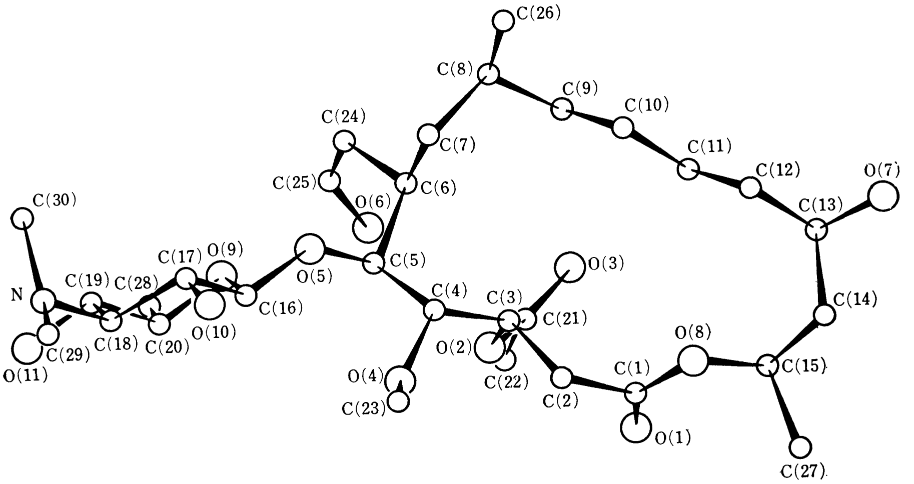

Fig. 2. The absolute configuration of the demycarosyl leucomycin A_3 molecule viewed along the normal of the mean plane of the macro ring.

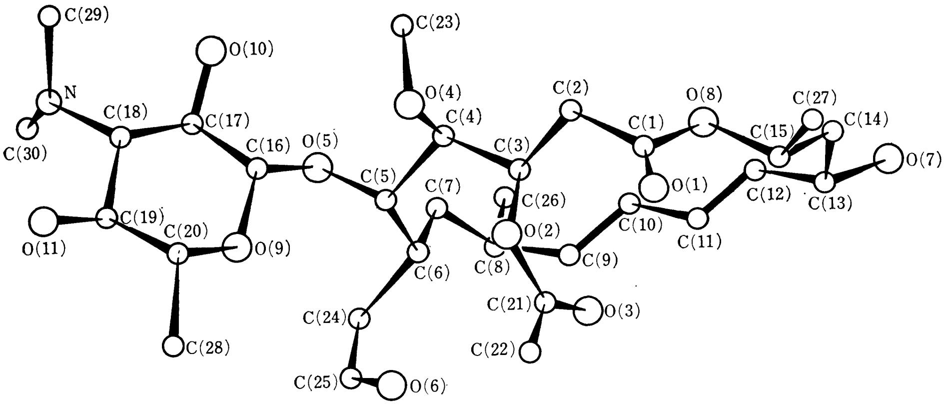

Fig. 3. The absolute configuration of the demycarosyl leucomycin A_3 molecule viewed along the b axis.

[*2] The complete data of the F_o-F_c table are kept as Document No. 7002 at the office of the Bulletin of the Chemical Society of Japan. A copy may be secured by citing the document number and by remitting, in advance, ¥ 1,000 for photoprints. Payment may be made by check or money order payable to: Chemical Society of Japan.

6) S. Nishikawa and K. Matsukawa, *Proc. Imp. Acad. Jap.*, **4**, 96 (1928).

present study, the intensities of pairs of (hkl) and $(h\bar{k}l)$ reflections were compared with each other on the above-mentioned Weissenberg photographs around the c axis. On the other hand, the structure factors of these reflections were calculated using the atomic parameters shown in Table 2 and the imaginary part of the dispersion correction, $\Delta f''=+1.5$, for the bromine atom. The results are given in Table 3. A comparison between the observed and calculated intensities indicates that the absolute configuration of I corresponds exactly to the structure given in Table 2. The complete molecular structure thus determined is shown in Figs. 2 and 3.

Table 3. The observed and calculated intensity ratios of the reflections $(h\bar{k}l)$ to (hkl)

h	k	l	$\frac{\lvert F_c(h\bar{k}l)\rvert^2}{\lvert F_c(hkl)\rvert^2}$	$\frac{I_0(h\bar{k}l)}{I_0(hkl)}$	h	k	l	$\frac{\lvert F_c(h\bar{k}l)\rvert^2}{\lvert F_c(hkl)\rvert^2}$	$\frac{I_0(h\bar{k}l)}{I_0(hkl)}$
1	13	1	1.59	>1	1	8	3	0.91	<1
1	14	1	0.88	<1	6	1	3	1.12	>1
1	15	1	1.08	>1	6	3	3	1.16	>1
2	12	1	1.33	>1	8	1	3	1.07	>1
2	13	1	1.05	>1	9	2	3	0.95	>1*
7	1	1	1.23	>1	9	4	3	0.97	>1*
7	6	1	0.64	<1	10	1	3	1.42	>1
8	3	1	0.92	<1	10	3	3	1.01	>1
8	4	1	1.27	>1	10	9	3	0.95	<1
10	1	1	1.06	<1*	1	7	4	0.68	<1
11	1	1	0.76	<1	3	12	4	0.98	<1
11	2	1	0.97	>1*	5	2	4	1.01	>1
13	1	1	0.66	<1	5	6	4	1.11	>1
5	1	2	1.03	>1	9	4	4	1.02	<1*
5	4	2	1.00	>1*	10	2	4	1.06	>1
8	6	2	1.13	>1	11	5	4	1.00	<1*
9	1	2	0.69	<1	1	7	5	1.28	>1
10	1	2	1.02	<1*	1	13	5	1.01	>1
10	5	2	0.99	>1*	2	12	5	1.30	>1
12	1	2	0.47	<1	3	12	5	0.83	<1
13	1	2	0.81	<1	12	1	5	1.00	>1*

* The observations marked with an asterisk are not in accord with the results of the calculation.

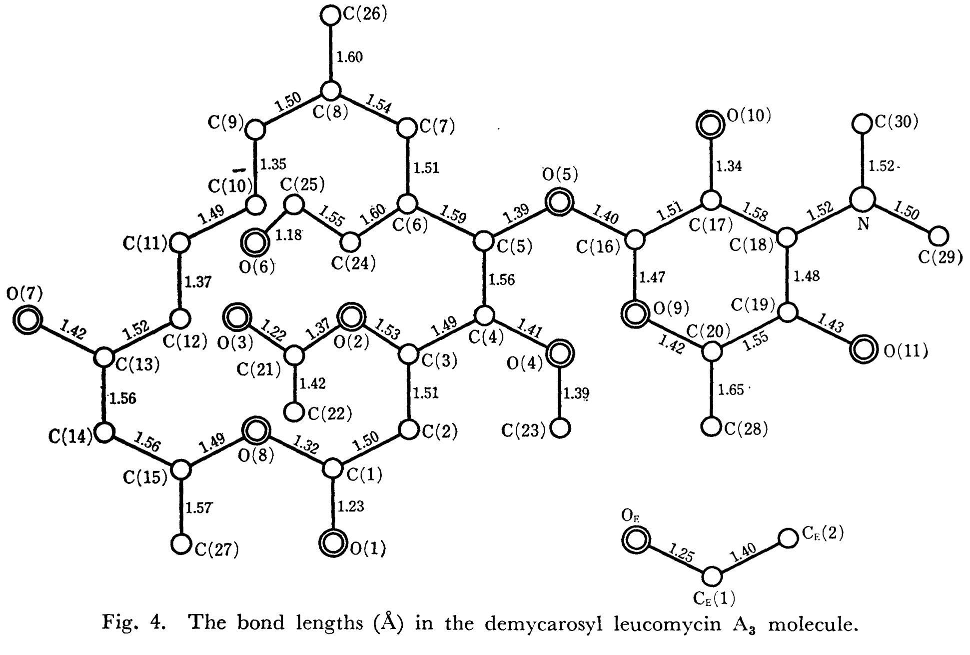

Fig. 4. The bond lengths (Å) in the demycarosyl leucomycin A_3 molecule.

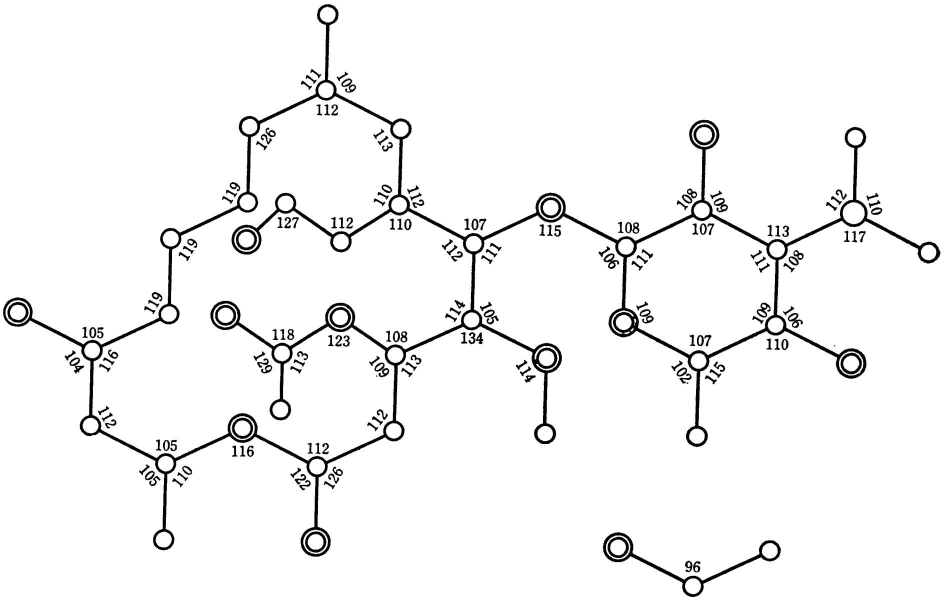

Fig. 5. The bond angles (°) in the demycarosyl leucomycin A_3 molecule.

Results and Discussion

The bond lengths and angles calculated from the final coordinates are shown in Figs. 4 and 5 respectively. The mean estimated standard deviations in the atomic distances of I are 0.025 Å for C–O, 0.028 Å for C–N, and 0.030 Å for C–C, while those of the ethanol molecule are 0.066 Å for C–O and 0.079 Å for C–C. From these lengths and angles, it is now found that demycarosyl leucomycin A_3 has the structural formula shown in Fig. 6. This is different in part from the corresponding part of the structure proposed by Hata *et al.*; that is, in the present case, the two conjugated double bonds in the macro ring are C(9)–C(10) and C(11)–C(12) and a hydroxyl oxygen, O(7), is attached to C(13), while in the latter, the diene system is C(10)=C(11)–C(12)=C(13) and O(7) is at C(9). Since, in the latter structure, the O(7)–H hydroxyl group is situated at the allylic position with respect to the C(10)=C(11) double bond, it can easily be eliminated as a hydroxide ion. If the elimination of the hydroxyl group occurs, the conjugated diene system changes easily from C(10)=C(11)–C(12)=C(13) to C(9)=C(10)–C(11)=C(12) by the successive migration of the two π-bonds, and lastly a hydroxide ion, OH^-, is connected to C(13). The new system thus formed corresponds exactly to the structure established by the present study. In fact, an organic chemical investigation has recently established that such structural changes occur in the process of the hydrolysis of leucomycin A_3 with dilute hydrochloric acid.[7] Table 4 gives the bond distances of I grouped in accordance with the chemical bond nature. In every group, the individual values deviate to some extent from the ordinary value, but the average of these is in good agreement with it.

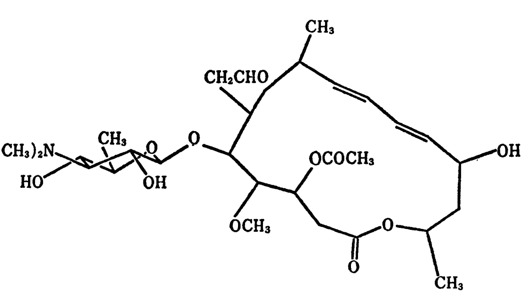

Fig. 6. The structural formula of demycarosyl leucomycin A_3 corresponding to the absolute configuration in Fig. 2.

The aglycone of demycarosyl leucomycin A_3 is composed of a sixteen-membered lactone ring with a conjugated diene system and its seven substituents, *i.e.*, a methoxyl, an acetyl, a formylmethyl, two methyl and two hydroxyl groups. The mean plane of the macro ring is represented by the equation; $0.1031\,x+0.3567\,y+0.9285\,z=5.850$ and is inclined by about 22° from the crystallographic *c* plane. The deviations of some atoms from the plane are given in Table 5. As may be seen from this table, the sixteen ring atoms deviate alternately in opposite directions except for two pairs, C(5)–C(6) and C(7)–C(8). It is of great interest to compare the conformation of the present sixteen-membered ring with that of

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[7] S. Omura, M. Katagiri, T. Hata, M. Hiramatsu, T. Kimura and K. Naya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1402 (1968).

TABLE 4. THE BOND DISTANCES (Å) GROUPED IN ACCORDANCE WITH THE BOND NATURE

1. C-C distances

(1) $\geqslant C{-}C\leqslant$

C(2)-C(3)	1.51
C(3)-C(4)	1.49
C(4)-C(5)	1.56
C(5)-C(6)	1.59
C(6)-C(7)	1.51
C(7)-C(8)	1.54
C(13)-C(14)	1.56
C(14)-C(15)	1.56
C(16)-C(17)	1.51
C(17)-C(18)	1.58
C(18)-C(19)	1.48
C(19)-C(20)	1.55
C(6)-C(24)	1.61
C(8)-C(26)	1.60
C(15)-C(27)	1.57
C(20)-C(28)	1.65
av.	1.55±0.05

(2) $\geqslant C{-}\overset{|}{C}{=}$

C(24)-C(25)	1.55
C(1)-C(2)	1.50
C(8)-C(9)	1.50
C(12)-C(13)	1.52
C(21)-C(22)	1.42
av.	1.50±0.04

(3) $-\overset{|}{C}{=}\overset{|}{C}-$

C(9)-C(10)	1.35
C(11)-C(12)	1.37
av.	1.36

(4) $=\overset{|}{C}{-}\overset{|}{C}=$

C(10)-C(11)	1.49

2. C-O distances

(1) $\geqslant C{-}O$

C(3)-O(2)	1.53
C(4)-O(4)	1.41
C(23)-O(4)	1.39
C(13)-O(7)	1.42
C(15)-O(8)	1.49
C(5)-O(5)	1.39
C(16)-O(5)	1.40
C(16)-O(9)	1.47
C(17)-O(10)	1.34
C(19)-O(11)	1.43
C(20)-O(9)	1.42
av.	1.43±0.05

(2) $=\overset{|}{C}{-}O$

C(1)-O(8)	1.32
C(21)-O(2)	1.37
av.	1.35

(3) $C{=}O$

C(1)-O(1)	1.23
C(21)-O(3)	1.22
C(25)-O(6)	1.18
av.	1.21

3. C-N distances

(1) $\geqslant C{-}N$

C(18)-N	1.52
C(29)-N	1.50
C(30)-N	1.52
av.	1.51

the twelve-membered ring in cyclododecane[8] and that of the thirty-four-membered ring in cyclotetratriacontane.[9] When viewed along the normal of the ring plane, the cyclododecane ring looks nearly like a square with a side of three C–C bonds, while the cyclotetratriacontane ring appears to be almost a rectangle, with one side of three bonds and the other of fourteen bonds. It is worth noticing that, in either of these cases, one side of the square or rectangle is made of three bonds. Such a partial molecular form may be the most compact and most stable one that molecules with a large ring can take. The four corners of the square or rectangle are made in such a way that two adjacent bonds take the *gauche* conformation. As may be seen from Fig. 2 and Table 6, in the present ring also, one half (from C(4) to C(13)) has a conformation very similar to that found in cyclododecane or cyclotetratriacontane, in spite of its containing

TABLE 5. THE DEVIATIONS FROM THE MEAN PLANE OF THE LACTONE RING

Atom	Deviation	Atom	Deviation
C(1)	−0.35 Å	C(13)	−0.15 Å
C(2)	0.47	C(14)	0.23
C(3)	−0.18	C(15)	−0.56
C(4)	0.60	O(8)	0.22
C(5)	−0.22	C(24)	−1.61
C(6)	−0.70	C(26)	1.34
C(7)	0.46	C(27)	−0.45
C(8)	0.08	O(1)	−1.39
C(9)	−0.41	O(2)	−1.59
C(10)	0.34	O(4)	0.76
C(11)	−0.30	C(5)	0.57
C(12)	0.48	O(7)	0.44

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8) J. D. Dunitz and H. M. M. Shearer, *Helv. Chim. Acta*, **43**, 18 (1960).

9) H. F. Kay and B. A. Newman, *Acta Crystallogr.*, **B24**, 615 (1968).

TABLE 6. THE CONFORMATIONS OF THE SIXTEEN BONDS IN THE LACTONE RING

A-B	Angle*	Conformation**	Deviation***
C (1)-C (2)	65°	G	5°
C (2)-C (3)	177°	T	3°
C (3)-C (4)	−170°	T	10°
C (4)-C (5)	−55°	$\bar{\mathrm{G}}$	5°
C (5)-C (6)	−61°	$\bar{\mathrm{G}}$	1°
C (6)-C (7)	156°	T	24°
C (7)-C (8)	−61°	$\bar{\mathrm{G}}$	1°
C (8)-C (9)	−90°	$\bar{\mathrm{G}}$	30°
C (9)-C (10)	174°	T	6°
C (10)-C (11)	180°	T	0°
C (11)-C (12)	180°	T	0°
C (12)-C (13)	−74°	$\bar{\mathrm{G}}$	14°
C (13)-C (14)	78°	G	18°
C (14)-C (15)	−84°	$\bar{\mathrm{G}}$	24°
C (15)-O (8)	170°	T	10°
O (8)-C (1)	−173°	T	7°

* This is the azimuthal angle which, in the part -X-A-B-Y- of the ring, X-A and B-Y make around A-B. The positive sign denotes that the angle is measured in the right-handed way, while the negative sign denotes the measurement in the other way.

** T, G and $\bar{\mathrm{G}}$ mean the *trans*, right-handed *gauche* and left-handed *gauche* conformations respectively.

*** This is the deviation from the perfect *trans* or *gauche* conformation.

a conjugated diene system. The diene part is incorporated into the longer side of the rectangle form because if its property of keeping six of the ring carbon atoms zig-zag in a plane. On the other hand, the conformation of the remaining half is considerably different from that of the regular part. The main difference is that the conformations of four bonds, C(1)–C(2), C(14)–C(15), C(15)–O(8), and O(8)–C(1), are, respectively, *gauche*, *gauche*, *trans*, and *trans*, while in the regular ring conformation, such as in cyclododecane or cyclotetratriacontane, they should be, respectively, *trans*, *trans*, *gauche*, and *gauche*. Such a deviating behavior of the conformations seems to be attributable mainly to the existence of the lactone group. That the C(2), C(1), O(8), C(15), and O(1) atoms lie on a plane with the C(1)–O(8) *trans* bond is due to the interaction of the π-orbitals of the C(1) and O(8) of the lactone group. The *gauche* nature of the C(1)–C(2) bond would be more favorable than the possible *trans* conformation, which makes the C(2)–C(3) bond *cis* oriented with the C(1)–O(1) bond.

The orientation of the acetyl group attached to the C(3) from the macro-ring plane is on the same side as O(1). Accordingly, some atoms of the group are near to the oxygen atom; the distances are 2.93 Å for O(2)···O(1), 3.01 Å for C(21)···O(1), and 3.27 Å for O(3)···O(1). The C(3) atom lies nearly on the mean plane of the acetyl group; its deviation from the plane is only 0.15 Å. As in the case of the lactone group, this shows that the energy of the conjugation between the C(21)–O(3) double bond and the O(2) oxygen atom is superior to the energy loss due to the close contact of 2.77 Å between C(3) and O(3). The mean plane of the acetyl makes an angle of about 82° with the macro-ring plane, and one of about 85° with the plane through C(2), C(3), and C(4). The O(2) oxygen atom has a *gauche* relation with both C(5) and O(4), and also with C(1).

The methoxyl group, O(4)–C(23), is placed on the opposite side of the ring plane from the acetyl. The plane through C(4)–O(4)–C(23) is almost perpendicular to the ring plane, the dihedral angle being about 85°. The O(4) oxygen atom has a *gauche* relation with C(2), O(2), and O(5), and a *trans* relation with C(6).

Though the formylmethyl group, O(6)–C(25)–C(24), lies on the same side of the ring as the acetyl, these two groups are not extremely close to each other; for example, the distances of O(6) from C(21), C(22), O(2), and O(3) are, respectively, 3.28, 3.36, 3.53, and 3.70 Å. Nevertheless, it must be taken into account that the two groups exert on each other some considerable attractive forces, such as electrostatic; we may thus understand the fact that the aldehydic carbonyl oxygen, O(6), is almost in a *cis* conformation with C(6) around C(24)–C(25) - in other words, the azimuthal angle for O(6) and C(6) is only 13° and, consequently, the distance between O(6) and C(6) is no more than 2.95 Å. The methylene carbon, C(24), takes a *gauche* conformation with both C(8) and O(5) around C(6)–C(7) and C(5)–C(6) respectively.

The diene system has a nearly planar *trans-trans* conformation. The mean plane of the diene part, C(9)–C(10)–C(11)–C(12), makes an angle of about 77° with the macro-ring plane. As may be seen from Table 6, one of the two double bonds, C(9)=C(10), is somewhat twisted, while the other, C(11)=C(12), is not. This twisting may be due to the incorporation into the regular part of the large ring. Since C(7)–C(8) and C(9)–C(10) make an azimuthal angle of about 90° around C(8)–C(9), though, roughly speaking, they are *gauche*, C(26) is very close to C(10), the distance being only 2.99 Å.

From Fig. 2, it can also be seen that the sugar component, mycaminose, is connected to the C(5) of the macro ring through a β-glycosidic linkage. The six-membered ring takes a regular chair form similar to that of cyclohexane, and its mean plane makes an angle of about 86° with the macro-ring plane. The five groups in the ring occupy the five possible equatorial positions, one by one. The

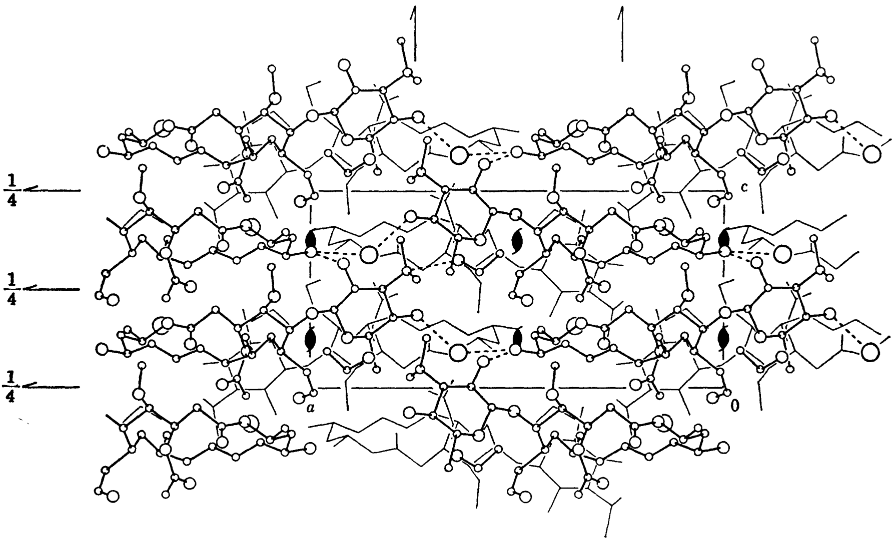

Fig. 7. The molecular arrangement viewed down along the *b* axis.

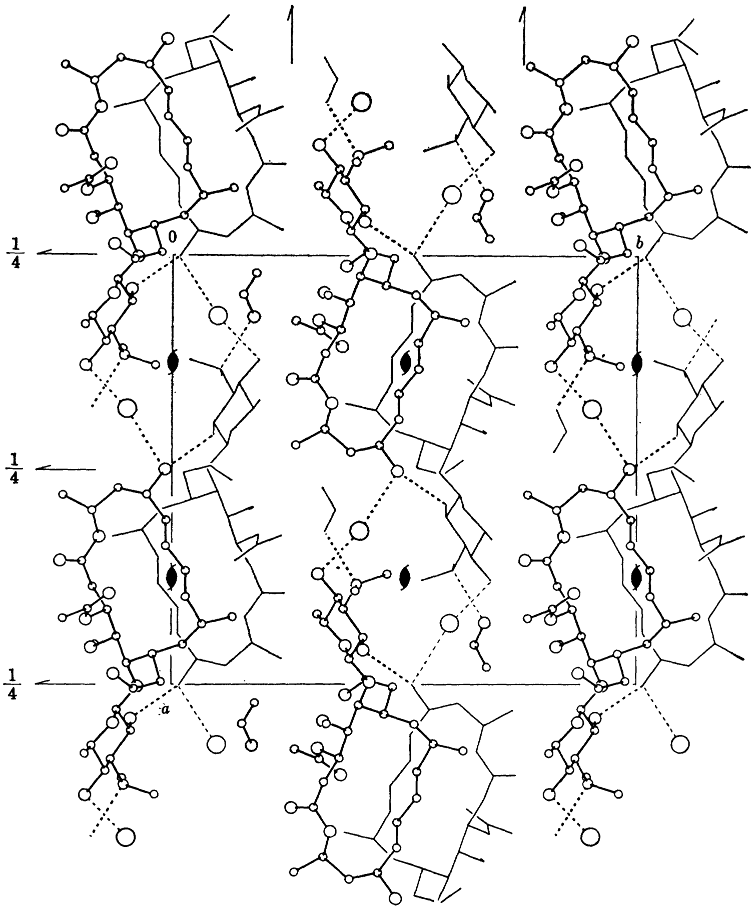

Fig. 8. The molecular arrangement viewed down along the *c* axis.

dimethylamino group takes such a conformation around N–C(18) that C(30) has a *gauche* relation with either C(17) or C(19), and C(29) also has one with C(17). As a result, the C(29) and O(10) atoms approach each other somewhat closely, the distance being 2.95 Å. As for the C(16)–O(5) bond, C(17) and O(9) are, respectively, *trans* and *gauche* with C(5).

The molecular arrangements viewed along the *b* and *c* axes are shown in Figs. 7 and 8 respectively. The macro rings of the molecules are arranged near to one another around the screw axis along the *c* axis at $x=1/4$ and $y=1/2$. The principal interatomic distances in this kind of intermolecular contact are listed in Table 7. All of these correspond to the usual van der Waals contacts except for the distance, 2.70 Å, of the O(10)-H···O(7)′ hydrogen bond. Through this hydrogen bonding, the molecules are one-dimensionally connected together around the screw axis. The molecular chains thus formed are further held together by two hydrogen bonds of the bromide ion, O(11)–H···Br^- (3.24 Å) and O(7)–H···Br^- (3.25 Å), finally making a hydrogen-bonded molecular layer parallel to the (010) plane.

TABLE 7. INTERMOLECULAR DISTANCES WITHIN THE HYDROGEN-BONDED MOLECULAR LAYER

O(3)···C(10)	3.69 Å	O(7)···C(24)	3.66 Å
O(3)···C(26)	3.56	O(7)···C(25)	3.25
O(5)···O(7)	3.48	O(8)···C(8)	3.75
O(6)···O(7)	3.76	C(2)···C(9)	3.86
O(7)···O(10)	2.70	C(4)···C(11)	3.87
O(7)···C(17)	3.50	C(12)···C(23)	3.86

Besides these strong contacts, the bromide ion is in contact with C(14), C(19), and C(30) at distances of 3.76, 3.61, and 3.71 Å respectively. The ethanol molecules are connected to the glycoside molecules only by the hydrogen bond of the N^+–H···O_E type, with a distance of 2.88 Å. The intermolecular distances from the ethanol are given in Table 8. As may be seen from this table, the hydrogen atom of the ethanol hydroxyl group does not take part in the formation of the hydrogen bonding at all. This may be one of the reasons why the ethanol molecule is easy to get out of the crystal. Between the glycoside molecules about the screw axis at $x=3/4$ and $y=1/2$, there is no intermolecular contact with a distance smaller than 4.0 Å.

TABLE 8. DISTANCES FROM THE ETHANOL MOLECULE

O_E···O(1)	3.49 Å	O_E···C(30)	3.57 Å
O_E···O(2)	3.25	C_E(1)···O(2)	3.68
O_E···O(4)	3.53	C_E(1)···O(4)	3.46
O_E···O(11)	3.26	C_E(2)···O(4)	3.63
O_E···N	2.88	C_E(2)···O(11)	3.64
O_E···C(2)	3.65	C_E(2)···N	3.58
O_E···C(29)	3.20	C_E(2)···C(30)	3.83

TABLE 9. INTERMOLECULAR DISTANCES BETWEEN THE HYDROGEN-BONDED MOLECULAR LAYERS

O(1)···N	3.62 Å	O(11)···C(2)	3.63 Å
O(1)···C(18)	3.66	O(10)···C(27)	3.73
O(1)···C(29)	3.17	C(23)···C(27)	3.70

The relatively small interatomic distances between the molecular layers parallel to the (010) plane are listed in Table 9. These distances correspond to the ordinary van der Waals interaction, and all but one are found between the aglycone part of one molecule and the sugar part of another molecule related with the first one by the screw axis along the *a* axis.