THE MOLECULAR AND CRYSTAL STRUCTURE DETERMINATION OF BISANHYDROALTHIOMYCIN BY THE X-RAY DIFFRACTION METHOD[1)]

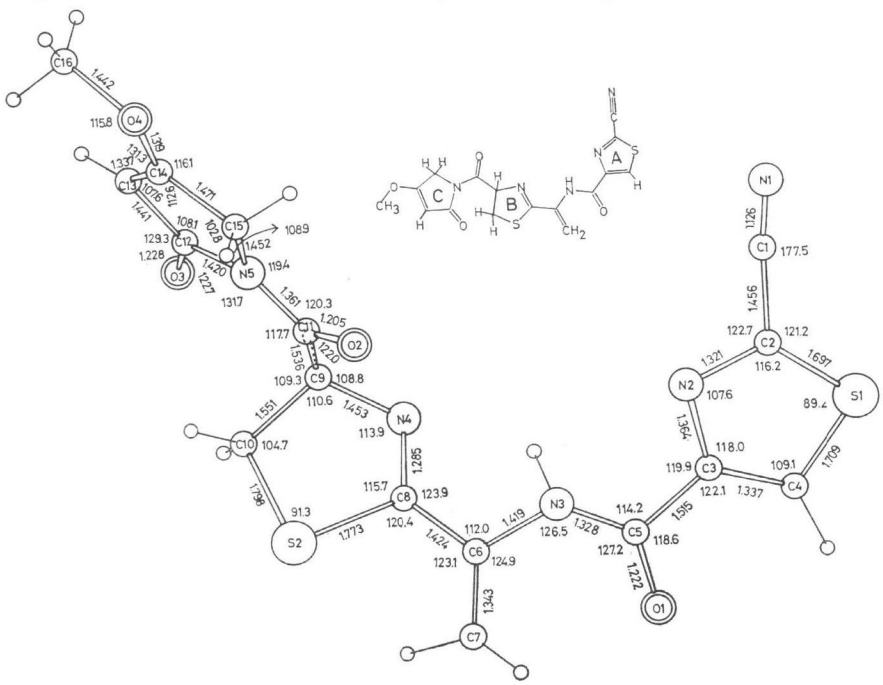
Sir:

Althiomycin is a sulfur-containing antibiotic isolated from *Streptomyces althioticus* in 1957[2)]. A structure for acetylalthiomycin was proposed by CRAM *et al.*[3)], but the proposed structure was not consistent with our chemical and spectroscopic data. However, we could not obtain enough information from our chemical studies to establish the structure. Though crystallization of althiomycin itself was unsuccessful, bisanhydroalthiomycin obtained by heating althiomycin in *n*-butanol followed by treatment with N-bromoacetoxysuccinimide in pyridine, gave well-developed crystals from dimethylformamide solution. Since this compound was considered to be a key degradation product, an X-ray structure determination has been carried out on it. The crystals are thick hexagonal-shaped plates with well-developed {100} faces and are transparent yellow in color. Oscillation and WEISSENBERG photographs indicated the space group to be $P2_1/c$. The lattice constants and intensity data were measured on a four-circle X-ray diffractometer using Ni-filtered CuKα radiation.

Crystal data: Bisanhydroalthiomycin, $C_{16}H_{13}O_4N_5S_2$, MW=403.44.
Monoclinic, $a=13.117\pm0.007$, $b=13.106\pm0.007$, $c=10.750\pm0.005$ Å,
$\beta=106.75\pm0.05°$, $U=1769.7$ Å^3.
$Z=4$, $D_x=1.513$ g·cm^{-3}.
Space group $P2_1/c$.

A total of 1610 structure amplitudes was obtained at the 3σ level, out of 3060 theoretically possible reflexions with 2θ value $\leqslant 130°$. Intensities were measured using the $\omega-2\theta$ scan method with a 2θ scan speed of 4°/min. The structure amplitudes were reduced to the normalized structure amplitudes E by use of the scale and temperature factors determined from a WILSON plot. The symbolic addition method was applied to the determination of the structure. Starting with the six reflexions (three origin specifying reflexions and three symbols), signs of 244 reflexions out of 255 having E values greater than 1.8 were determined. The resulting E map showed many peaks, and the 17 highest ones were included in a subsequent structure

Fig. 1. Molecular structure. Bond lengths (Å) and angles (°) are also shown.



factor and FOURIER calculation. The FOURIER map showed up the whole structure. Refinement was carried out by the block-diagonal least-squares method including anisotropic thermal parameters for each atom. Hyrogen atoms were located on a difference FOURIER map and their coordinates and isotropic thermal parameters were refined in the subsequent least-squares calculations. The final R value was 0.05 on a model which

Table 1. Final atomic parameters

	x	y	z	$\beta 11$	$\beta 22$	$\beta 33$	$\beta 12$	$\beta 13$	$\beta 23$
S(1)	1.2290(1)	0.3516(2)	0.4214(2)	0.0047(1)	0.0091(2)	0.0149(3)	−0.0003(1)	0.0025(1)	0.0008(2)
S(2)	0.6159(2)	0.3753(2)	0.6039(2)	0.0081(1)	0.0104(2)	0.0105(2)	0.0017(1)	0.0057(1)	0.0007(2)
O(1)	1.0643(4)	0.3610(4)	0.7341(4)	0.0080(4)	0.0102(5)	0.0090(5)	0.0009(4)	0.0010(4)	0.0003(4)
O(2)	0.6265(4)	0.5232(4)	0.3062(5)	0.0083(4)	0.0065(4)	0.0132(6)	−0.0028(3)	0.0006(4)	0.0002(4)
O(3)	0.3962(4)	0.2969(4)	0.1756(5)	0.0083(4)	0.0061(4)	0.0182(8)	−0.0022(3)	0.0009(4)	0.0011(4)
O(4)	0.2975(4)	0.6023(4)	−0.0607(4)	0.0078(4)	0.0073(4)	0.0118(6)	0.0012(3)	0.0025(4)	0.0002(4)
N(1)	1.0595(5)	0.3865(6)	0.0799(6)	0.0110(6)	0.0121(7)	0.0137(8)	0.0011(5)	0.0058(6)	0.0002(6)
N(2)	1.0291(4)	0.3761(4)	0.3919(5)	0.0054(4)	0.0061(4)	0.0101(6)	0.0003(3)	0.0021(4)	0.0003(4)
N(3)	0.9115(4)	0.3665(4)	0.5652(5)	0.0055(4)	0.0074(5)	0.0083(6)	0.0007(3)	0.0020(4)	0.0006(4)
N(4)	0.7075(4)	0.3468(4)	0.4218(5)	0.0056(4)	0.0067(4)	0.0088(6)	0.0005(3)	0.0032(4)	−0.0004(4)
N(5)	0.4749(4)	0.4565(4)	0.1825(5)	0.0050(4)	0.0043(4)	0.0085(6)	−0.0006(3)	0.0019(4)	−0.0008(4)
C(1)	1.0758(6)	0.3800(6)	0.1883(7)	0.0078(6)	0.0069(6)	0.0127(9)	0.0009(5)	0.0042(6)	0.0005(6)
C(2)	1.1018(5)	0.3710(5)	0.3290(6)	0.0060(5)	0.0058(5)	0.0114(8)	−0.0000(4)	0.0028(5)	−0.0002(5)
C(3)	1.0799(5)	0.3644(5)	0.5210(6)	0.0050(4)	0.0057(5)	0.0094(8)	0.0002(4)	0.0012(5)	0.0007(5)
C(4)	1.1854(5)	0.3504(6)	0.5566(7)	0.0050(5)	0.0080(6)	0.0123(9)	−0.0005(4)	0.0012(5)	0.0012(6)
C(5)	1.0163(5)	0.3640(5)	0.6184(6)	0.0062(5)	0.0057(5)	0.0095(8)	0.0004(4)	0.0010(5)	0.0010(5)
C(6)	0.8329(5)	0.3629(5)	0.6322(6)	0.0066(5)	0.0057(5)	0.0086(7)	0.0008(4)	0.0023(5)	0.0003(5)
C(7)	0.8530(6)	0.3643(7)	0.7619(7)	0.0088(6)	0.0103(7)	0.0094(8)	0.0004(6)	0.0029(6)	0.0002(6)
C(8)	0.7280(5)	0.3591(5)	0.5451(6)	0.0060(4)	0.0049(5)	0.0093(7)	0.0008(4)	0.0039(5)	0.0010(5)
C(9)	0.5945(5)	0.3487(5)	0.3528(6)	0.0060(5)	0.0050(5)	0.0099(8)	−0.0001(4)	0.0032(5)	−0.0003(5)
C(10)	0.5270(5)	0.3388(6)	0.4493(7)	0.0067(5)	0.0066(5)	0.0143(9)	−0.0007(4)	0.0051(6)	0.0006(6)
C(11)	0.5683(5)	0.4503(5)	0.2792(6)	0.0054(5)	0.0059(5)	0.0087(7)	−0.0008(4)	0.0029(5)	−0.0015(5)
C(12)	0.3923(5)	0.3844(5)	0.1336(7)	0.0062(5)	0.0060(5)	0.0113(8)	−0.0012(4)	0.0031(5)	−0.0012(5)
C(13)	0.3110(5)	0.4325(6)	0.0309(7)	0.0050(5)	0.0076(6)	0.0120(9)	−0.0006(4)	0.0022(5)	−0.0007(6)
C(14)	0.3426(5)	0.5281(5)	0.0191(6)	0.0061(5)	0.0057(5)	0.0090(8)	0.0009(4)	0.0035(5)	−0.0011(5)
C(15)	0.4463(5)	0.5518(5)	0.1121(6)	0.0068(5)	0.0051(5)	0.0091(7)	−0.0005(4)	0.0040(5)	−0.0014(5)
C(16)	0.1955(6)	0.5787(7)	−0.1511(8)	0.0080(7)	0.0103(8)	0.0157(12)	0.0018(6)	0.0020(7)	0.0012(8)
H(N3)	0.8727(55)	0.3590(56)	0.4806(68)	7.79(2.02)					
H(C4)	1.2464(51)	0.3350(53)	0.6531(63)	6.59(1.82)					
H(C7)	0.7852(65)	0.3461(67)	0.7818(78)	10.70(2.57)					
H′(C7)	0.9249(44)	0.3665(45)	0.8232(53)	4.55(1.46)					
H(C9)	0.5716(42)	0.2904(44)	0.2858(52)	4.11(1.39)					
H(C10)	0.4600(41)	0.3729(42)	0.4233(50)	3.79(1.29)					
H′(C10)	0.5057(47)	0.2717(46)	0.4587(55)	4.81(1.52)					
H(C13)	0.2457(52)	0.4054(55)	−0.0116(64)	6.86(1.86)					
H(C15)	0.4492(54)	0.5966(55)	0.1563(65)	7.26(1.93)					
H′(C15)	0.5045(46)	0.5684(47)	0.0663(55)	5.09(1.52)					
H(C16)	0.1464(55)	0.5459(55)	−0.1029(66)	7.86(1.99)					
H′(C16)	0.1659(58)	0.6326(60)	−0.1886(71)	8.52(2.19)					
H∼(16)	0.1979(57)	0.5170(58)	−0.2210(68)	8.07(2.08)					

E.s.d.'s are given in parentheses denoting the least significant digits. Temperature factors are of the form: $T=\exp\{-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\}$.

included hydrogen atoms. The atomic parameters are shown in Table 1. Fig. 1 shows the molecular structure in which bond lengths and angles are also shown. The estimated standard deviations of C-C, C-O, C-S lengths are 0.010, 0.008, 0.007 Å and those of C-C-C, C-S-C, C-C-S angles are 0.6, 0.4, 0.5°, respectively.

The molecule contains three five-membered rings: thiazole ring (A), thiazolin ring (B) and Δ^3-pyrrolin ring (C). A and B rings are linked through a vinyl amide group, B and C rings through a carbonyl carbon atom. Each of the A and C rings is planar within ± 0.003 Å, while the B ring is in a twist form, C(9) and C(10) deviating from the mean plane by 0.12 and -0.13 Å respectively. It should be noted that the crystal belonged to a centrosymmetric space group and hence was a racemate (at the C(9) atom).

The 2-cyano-thiazole group, vinyl amide group and (4-methoxy-2-oxo-3-pyrrolin-1-yl) carbonyl group all adopt conjugated planar conformations but a certain degree of rotational freedom is seen about the bonds C(3)-C(5) and C(9)-C(11). The internal torsion angle around the C(3)-C(5) bond, N(2)-C(3)-C(5)-N(3), is only 5.7°, and the angle of the plane of the (4-methoxy-2-oxo-3-pyrrolin-1-yl)carbonyl group to the mean plane of the B ring is 77.3°. A full account of the structure of althiomycin will be published in the accompanying paper.[4]

HIKARU NAKAMURA
YOICHI IITAKA

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Tokyo 113 Japan

HIDEO SAKAKIBARA*
HAMAO UMEZAWA

National Institute of Health, Kami-osaki, Shinagawa-ku, Tokyo 141 Japan

(Received June 17, 1974)

References

1) A preliminary account of this work was presented at the Symposium on the Chemistry of Natural Products held in 1973, in Tokyo, Abs. p. 213
2) YAMAGUCHI, H.; Y. NAKAYAMA, K. TAKEDA, K. TAWARA, K. MAEDA, T. TAKEUCHI & H. UMEZAWA: A new antibiotic, althiomycin. J. Antibiotics, Ser. A 10: 195~200, 1957
3) CRAM, D. J.; O. THEANDER, H. JAGER & M. K. STANFIELD: Mold metabolites. IX. Contribution to the elucidation of the structure of althiomycin. J. Amer. Chem. Soc. 85: 1430~1437, 1963
4) SAKAKIBARA, H.; H. NAGANAWA, M. OHNO, K. MAEDA & H. UMEZAWA: The structure of althiomycin. J. Antibiotics 27: 897~899, 1974

* Present address: Toyo Jozo Co., Ltd., Ōhito, Shizuoka-pref., Japan.