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(37) See, e.g., discussion and references in 31a.
(38) See, e.g., A. Veillard in "Internal Rotation in Molecules", Orville-Thomas, Ed., Wiley, New York, N.Y., 1974, p 385.
(39) See, e.g., N. D. Epiotis, S. Sarkanen, D. Bjorkquist, L. Bjorkquist, and R. Yates, *J. Am. Chem. Soc.*, **96**, 4075 (1974).
(40) In some cases an exponential of the type $A \exp(br_{ij})$ is used instead of the reciprocal nth power dependence to describe the nonbonded repulsions (see discussion in ref 28). In addition, explicit terms to represent the hydrogen bond may be included (e.g., ref 15), but these are not involved in any case in the energetics of the methyl rotation.
(41) R. Gopal and S. A. Rizvi, *J. Indian Chem. Soc.*, **45**, 13 (1968).
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Structure of a Derivative of Streptovaricin C Triacetate. Crystal and Molecular Structure of the Atropisomer of the Cyclic *p*-Bromobenzeneboronate Ester of Streptovaricin C Triacetate: Methylene Dichloride 1:1 Solvate

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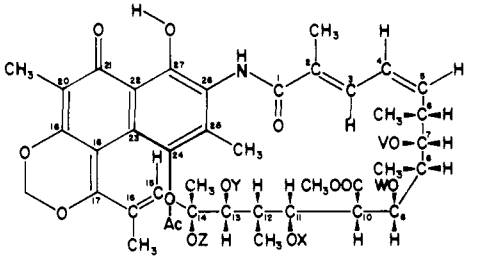
Abstract: The crystal and molecular structure of a *p*-bromobenzeneboronate ester of streptovaricin C triacetate has been determined by single-crystal x-ray methods. The derivative studied was of the atropisomer of the naturally occurring form of streptovaricin C triacetate and it crystallized as a 1:1 methylene dichloride solvate. The crystals are orthorhombic, $a = 22.487$ (8), $b = 12.678$ (5), and $c = 19.723$ (6) Å, with four molecules of $C_{52}H_{59}BBrNO_{17}\cdot CH_2Cl_2$ in the space group $P2_12_12_1$. The structure has been refined to an R factor of 0.106 on 2148 nonzero reflections. A strong indication of the absolute configuration was obtained from the x-ray study. The relative configuration, absolute configuration, and conformation of the ansa ring in this derivative of streptovaricin are compared with those found in other derivatives of ansamycins that have been studied by x-rays. Some structural features that may have a bearing on the biological activity of these macrocyclic antibiotics are also described and discussed.

The streptovaricins are a class of antibiotics that contain a naphthoquinone nucleus and a macrocyclic aliphatic ansa bridge, i.e., one connecting two nonadjacent positions in an aromatic nucleus.[1] The streptovaricins, along with the related rifamycins, have been shown to have important biological activity, such as the inhibition of RNA-dependent DNA polymerase (reverse transcriptase) from RNA tumor virus, the inhibition of DNA-dependent RNA polymerase from *Escherichia coli*, and general antiviral and antibacterial properties, especially against mycobacteria.[2] Different members of the streptovaricin class have varying activities in these separate areas of biological action. In particular, the level of acetylation of the several hydroxyl groups in the molecule has a significant effect on activity.

We are planning to undertake a study of the relationship of the detailed three-dimensional structure of molecules of the streptovaricin family to their biological function with the aim of ascertaining some of the factors that govern such activity. As the first step in this direction, we now describe the three-dimensional structure of a *p*-bromobenzeneboronate ester of streptovaricin C triacetate. This work also served to confirm the earlier chemical work of Rinehart and colleagues as to gross structure[3] and to establish the complete stereochemistry. A preliminary communication has been published.[4] Some more recent studies[5] have shown that the compound studied was in fact the atropisomer of the derivative of streptovaricin C triacetate, rather than the form corresponding to naturally occurring streptovaricin C. Atropisomers in the ansamycins arise due to a reversal of the sense or helicity of the ansa ring (see Figure 1).

Experimental Section

Streptovaricin C triacetate (**1**) upon reaction with *p*-bromobenzeneboronic acid gave two derivatives. One of these esters, **2**, was obtained in 16% yield and melted at 215–220°, while the other, **3**, was obtained in 14% yield and melted at 214–217°. The first derivative was originally thought to be an acyclic ester,[4] but the two esters are now recognized to be the two atropisomeric cyclic *p*-bromobenzeneboronate esters ($C_{52}H_{59}BBrNO_{17}$) of **1** (Figure 1).[5] The helicity of the ansa ring in the ester **2** is now known to correspond to that of naturally occurring streptovaricin C; the x-ray analysis was carried out on a solvate of the atropisomeric ester **3.**



3, V = W = X = Ac, Y + Z = >BC$_6$H$_4$Br(*p*)

The ester **3** was crystallized from methylene dichloride–ether to give a methylene dichloride solvate, $C_{52}H_{59}BBrNO_{17}\ CH_2Cl_2$ (mp 275–278°), crystals of which were adequate for x-ray structure determination.

Structure Determination of the *p*-Bromobenzeneboronate Ester of Streptovaricin C Triacetate: Methylene Dichloride 1:1 Solvate. The crystals of the methylene dichloride solvate are red and transparent with a rectangular bar shape, elongated along the *b* axis. A relatively

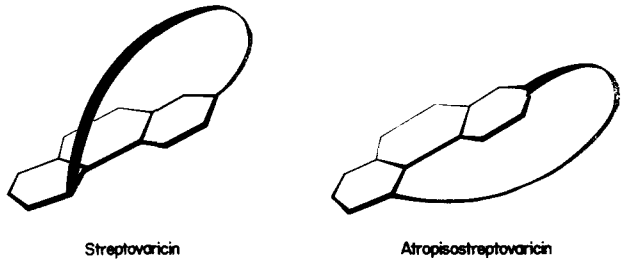


Figure 1. Schematic view of streptovaricin and atropisostreptovaricin.

small, but untwinned crystal with dimensions ca. 0.10 × 0.10 × 0.20 mm was mounted on a Picker FACS-1 diffractometer with the *b* axis along the ϕ axis.

Crystal data: $C_{52}H_{59}BBrNO_{17}\cdot CH_2Cl_2$, mol wt = 1145.7; orthorhombic; a = 22.487 (8), b = 12.678 (5), c = 19.723 (6) Å; V = 5623 Å^3; ρ_{measd} = 1.31 g cm^{-3}; Z = 4; ρ_{calcd} = 1.35 g cm^{-3}; $F(000)$ = 2384; systematic absences, $h = 2n + 1$ for $h00$, $k = 2n + 1$ for $0k0$, and $l = 2n + 1$ for $00l$; space group = $P2_12_12_1$; μ (Cu Kα) = 18.9 cm^{-1}.

The unit cell dimensions were determined from a least-squares fit to the angular settings for nine independent reflections on the diffractometer. The density of the crystal was measured by flotation in aqueous zinc chloride solution at room temperature. A total of 3945 reflections in the octant hkl was collected out to 2θ = 110° with Ni-filtered Cu Kα (λ = 1.5418 Å) radiation using a θ–2θ scan.

The general procedures for data collection have been described previously.[6] Using the criterion of a 1.5σ level based on counting statistics, 2148 of these reflections were considered to be significantly nonzero. Beyond 2θ of 110°, virtually no significant net intensity could be detected due to the small size of the crystal and probably also due to its mosaic characteristics. After a period of 7 days for data collection, there was a small decrease (7%) in the intensities of the three standards.

The structure was solved by three-dimensional Patterson and Fourier methods. The methylene dichloride molecule, whose presence had not hitherto been suspected, was revealed from a difference map. Full-matrix least-squares refinement of the positional and isotropic thermal parameters for all nonhydrogen atoms reduced the R factor to 0.152.[7] From the bond length and angle calculations, there were no ambiguities in assigning the oxygen and carbon atoms of the acetate groups in the molecule. Refinement was continued with anisotropic thermal parameters for the bromine atom and the three nonhydrogen atoms of the methylene dichloride molecule and gave an R factor of 0.106 and R_2 of 0.108 for all nonzero reflections. In the final cycle of refinement, no individual parameter shifted by more than its estimated standard deviation.

The nonzero reflections were weighted on the basis of assigned errors, $\sigma(F_o)$, that were given the values 1.20, 1.10, or 1.00 depending on whether $\sigma_{counting}(F_o)/|F_o|$ exceeded 0.10 and 0.03, or was equal to or less than 0.03, respectively.[8] A difference map based on the final atomic parameters showed some peaks with electron density ranging from 0.3 to 0.5 e/Å^3. Some of these peaks lie at the expected positions for the hydrogen atoms. The two largest peaks, both with electron density of 0.5 e/Å^3, are very close to the O(39) atom which presumably has highly anisotropic thermal motion.

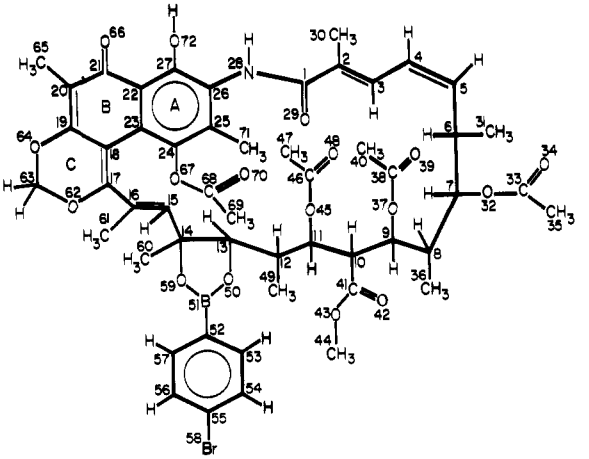


Figure 3. Schematic drawing of the molecule of **3** showing atom numbering used in this study; absolute stereochemistry is not implied in this drawing.

Because of the relatively small number of experimental data (the ratio of the number of reflections to the number of parameters varied was 6.7), further refinement was not attempted nor were hydrogen atoms included in the model, although two peaks were interpreted as hydrogen atoms to clarify the hydrogen bonding scheme (see later). The atomic scattering curves used were those listed in the International Tables for X-Ray Crystallography.[9] The final atomic coordinates and temperature factors are listed in Table I.[10,11]

Results and Discussion

The structure of the streptovaricin derivative obtained from the x-ray analysis of the solvate of **3** is in close agreement with the structure assigned to streptovaricin C from chemical evidence.[3] A stereoscopic view of the molecule of **3** is shown in Figure 2, while the atom numbering used in this study is shown in Figure 3. The complete list of bond lengths and bond angles has been deposited;[10] the values are, in general, consistent with the structure for **3** within the limits of error of the analysis. The estimated standard deviations of the bond lengths and angles are ca. 0.03 Å and 2°, respectively.

An unambiguous assignment of absolute configuration on the basis of the anomalous dispersion effect was not possible for these crystals. However, comparison of the configurations at the centers C(8)–C(14) with those for another family of ansamycins, the rifamycins,[12-15] implied the absolute configuration shown in Figure 2 and this indication was supported by the results of the refinement of the two enantiomers.[11] This conclusion, however, predicted the opposite helicity for the ansa ring in the molecule of **3** from that found in the rifamycins,[12-14] in rifampicin,[16] and in tolypomycin.[17,18]

The entire picture became clearer, however, with the recognition that **2** and **3** are not an acyclic and a cyclic pair of boronate esters but are, in fact, atropisomers (Figure 1) of the

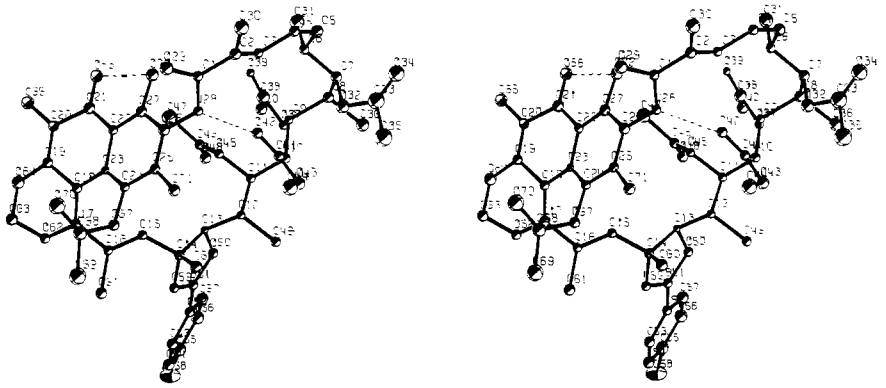


Figure 2. Stereoscopic view of a molecule of the cyclic *p*-bromobenzeneboronate ester of streptovaricin C triacetate (**3**).

Table I. Final Atomic Coordinates for the Solvate of **3** in Fractions of the Unit Cell Edge and Thermal Parameters Expressed as $\exp(-B_\theta \sin^2\theta/\lambda^2)$. Standard Deviations in Parentheses

	x	y	z	B_θ, Å^2		x	y	z	B_θ, Å^2
C(1)	0.4942 (9)	0.564 (2)	0.6630 (11)	2.9 (5)	C(49)	0.6852 (9)	1.081 (2)	0.5540 (11)	3.2 (5)
C(2)	0.4407 (10)	0.587 (2)	0.6242 (11)	3.5 (5)	C(52)	0.8966 (10)	1.088 (2)	0.5934 (12)	3.2 (5)
C(3)	0.4491 (9)	0.634 (2)	0.5617 (10)	2.5 (4)	C(53)	0.9355 (10)	1.120 (2)	0.6406 (12)	4.0 (5)
C(4)	0.4016 (9)	0.657 (2)	0.5167 (11)	3.0 (5)	C(54)	0.9894 (10)	1.170 (2)	0.6238 (12)	4.5 (5)
C(5)	0.4087 (10)	0.706 (2)	0.4550 (12)	4.3 (5)	C(55)	1.0040 (12)	1.176 (2)	0.5580 (14)	5.6 (7)
C(6)	0.4695 (9)	0.728 (2)	0.4231 (11)	3.0 (4)	C(56)	0.9686 (12)	1.147 (2)	0.5022 (13)	5.8 (6)
C(7)	0.4716 (10)	0.848 (2)	0.4053 (12)	3.8 (5)	C(57)	0.9125 (11)	1.101 (2)	0.5238 (13)	4.8 (6)
C(8)	0.5303 (10)	0.886 (2)	0.3734 (12)	3.6 (5)	C(60)	0.7233 (10)	0.957 (2)	0.7083 (13)	4.1 (6)
C(9)	0.5897 (9)	0.857 (2)	0.4176 (10)	2.4 (4)	C(61)	0.8492 (10)	0.838 (2)	0.7814 (12)	4.0 (5)
C(10)	0.6054 (9)	0.924 (2)	0.4795 (11)	3.0 (5)	C(63)	0.8850 (10)	0.520 (2)	0.7748 (12)	4.2 (5)
C(11)	0.6740 (9)	0.904 (2)	0.4956 (11)	2.7 (5)	C(65)	0.8152 (11)	0.313 (2)	0.6190 (13)	5.0 (6)
C(12)	0.6920 (8)	0.955 (2)	0.5647 (10)	2.3 (4)	C(68)	0.7224 (12)	0.655 (2)	0.8622 (14)	5.3 (6)
C(13)	0.7569 (8)	0.923 (1)	0.5811 (9)	1.7 (4)	C(69)	0.7394 (13)	0.730 (3)	0.9186 (15)	7.3 (8)
C(14)	0.7718 (9)	0.916 (2)	0.6588 (11)	3.1 (5)	C(71)	0.5884 (10)	0.736 (2)	0.7842 (12)	3.8 (5)
C(15)	0.7860 (9)	0.803 (2)	0.6759 (10)	2.7 (4)	B(51)	0.8372 (11)	1.025 (2)	0.6064 (14)	3.1 (6)
C(16)	0.8168 (9)	0.766 (2)	0.7306 (11)	2.7 (5)	N(28)	0.5396 (7)	0.635 (1)	0.6624 (8)	2.5 (4)
C(17)	0.8246 (10)	0.650 (2)	0.7366 (11)	3.3 (5)	O(29)	0.4973 (7)	0.490 (1)	0.7051 (8)	4.6 (4)
C(18)	0.7837 (9)	0.576 (2)	0.7173 (11)	3.1 (5)	O(32)	0.4614 (7)	0.909 (1)	0.4682 (9)	5.1 (4)
C(19)	0.8102 (9)	0.471 (2)	0.6950 (11)	3.2 (5)	O(34)	0.3648 (9)	0.935 (2)	0.4375 (11)	7.4 (5)
C(20)	0.7851 (10)	0.409 (2)	0.6490 (12)	3.3 (5)	O(37)	0.6377 (6)	0.871 (1)	0.3684 (7)	2.9 (3)
C(21)	0.7250 (11)	0.441 (2)	0.6220 (13)	4.0 (6)	O(39)	0.6332 (8)	0.696 (2)	0.3399 (10)	2.0 (4)
C(22)	0.6935 (9)	0.526 (2)	0.6567 (11)	2.7 (5)	O(42)	0.5587 (6)	0.802 (1)	0.5563 (7)	3.4 (3)
C(23)	0.7214 (8)	0.590 (2)	0.7083 (10)	1.8 (4)	O(43)	0.5534 (6)	0.978 (1)	0.5759 (8)	4.3 (4)
C(24)	0.6841 (9)	0.652 (2)	0.7485 (11)	2.6 (4)	O(45)	0.6804 (5)	0.790 (1)	0.5054 (7)	2.7 (3)
C(25)	0.6220 (9)	0.668 (2)	0.7387 (11)	2.8 (5)	O(48)	0.7579 (7)	0.789 (1)	0.4358 (8)	4.5 (4)
C(26)	0.5995 (10)	0.612 (2)	0.6814 (12)	3.7 (5)	O(50)	0.7994 (6)	1.000 (1)	0.5539 (7)	3.1 (3)
C(27)	0.6335 (10)	0.540 (2)	0.6465 (12)	3.5 (5)	O(59)	0.8239 (6)	0.982 (1)	0.6659 (7)	2.8 (3)
C(30)	0.3830 (12)	0.542 (2)	0.6492 (14)	5.7 (7)	O(62)	0.8804 (6)	0.624 (1)	0.7527 (7)	3.2 (3)
C(31)	0.4813 (12)	0.665 (1)	0.3621 (15)	6.2 (7)	O(64)	0.8692 (7)	0.457 (1)	0.7159 (9)	5.1 (4)
C(33)	0.4035 (14)	0.951 (2)	0.4751 (17)	7.7 (8)	O(66)	0.7032 (7)	0.390 (1)	0.5761 (9)	4.7 (4)
C(35)	0.4000 (14)	1.024 (3)	0.5391 (17)	8.7 (9)	O(67)	0.7093 (6)	0.706 (1)	0.8046 (7)	3.3 (3)
C(36)	0.5270 (11)	1.013 (2)	0.3578 (13)	5.2 (6)	O(70)	0.7179 (9)	0.560 (2)	0.8624 (11)	7.5 (5)
C(38)	0.6527 (12)	0.776 (2)	0.3334 (14)	5.5 (7)	O(72)	0.6059 (7)	0.489 (1)	0.5937 (8)	4.5 (4)
C(40)	0.7044 (10)	0.810 (2)	0.2860 (12)	4.7 (6)	Br(58)	1.0821 (2)	1.2332 (3)	0.5377 (2)	*a*
C(41)	0.5686 (9)	0.892 (2)	0.5420 (11)	3.0 (4)	C(73)	0.5827 (15)	0.309 (3)	0.7435 (19)	*a*
C(44)	0.5249 (13)	0.953 (2)	0.6426 (15)	6.8 (8)	Cl(74)	0.6078 (7)	0.224 (1)	0.6866 (6)	*a*
C(46)	0.7240 (9)	0.742 (2)	0.4681 (11)	3.2 (5)	Cl(75)	0.6405 (5)	0.345 (1)	0.7990 (7)	*a*
C(47)	0.7230 (13)	0.623 (2)	0.4790 (15)	6.5 (7)					

	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br(58)	0.0030 (1)	0.0174 (4)	0.0079 (2)	−0.0042 (2)	0.0014 (1)	−0.0024 (3)
C(73)	0.0039 (9)	0.010 (4)	0.007 (2)	0.002 (2)	0.002 (2)	0.001 (2)
Cl(74)	0.0128 (8)	0.018 (1)	0.0064 (5)	0.0045 (9)	0.0017 (5)	−0.0006 (7)
Cl(75)	0.0054 (4)	0.022 (1)	0.0094 (6)	−0.0007 (7)	−0.0012 (4)	−0.0001 (8)

[a] Anisotropic temperature factors expressed as $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

cyclic boronate ester and that **2** corresponds to the naturally occurring form of streptovaricin C.[5] Hence the x-ray study was carried out on a solvate of a derivative of the unnatural atropisomer. Thus, Figure 2 represents the true absolute configuration of derivative **3** which is 6*R*,7*R*,8*R*,9*R*,10*S*,-11*S*,12*R*,13*S*,14*R*, but the helicity of the ansa ring in **3** is the opposite of that found in the naturally occurring streptovaricins. The helicity of the ansa ring in the natural form of the streptovaricins and the stereochemistry at the centers C(8)-C(14) are identical with those of the rifamycins, but the stereochemistry at C(6) and C(7) is opposite to that for the rifamycins.

Naphthoquinone Chromophore. In the naphthoquinone ring system, ring B, unlike ring A, is markedly nonplanar (Table II), and the bonds C(17)-C(18), C(18)-C(19), C(19)-C(20), C(20)-C(21), and C(21)-O(66) provide evidence of alternating double and single bond character. Ring B is clearly considerably distorted due to ring strain, with C(18) lying 0.31 Å from the best plane through the other five ring atoms (plane V in Table II). An appreciation of the extent of distortion can be obtained from Figure 4 which shows the Newman projections along the C(17)-C(18) and C(18)-C(23) bonds.

The C(15)-C(16) and C(17)-C(18) double bonds are in a cisoid arrangement with torsion angles of −35° about the C(16)-C(17) single bond that is between the two double bonds. The C(16)-C(17)-C(18)-C(23) and C(17)-C(18)-C(23)-C(24) torsion angles are −21 and −38° Some of these distortions presumably arise from overcrowding between the substituents on C(16) and C(24); the distance between two of these atoms, C(15) and O(67), is 3.31 (3) Å. It is interesting to note that in the process of changing the helicity of the ansa bridge, the atoms C(15) and O(67) must somehow pass each other in space. A somewhat similar phenomenon is observed in the thermal racemization of [7]-, [8]-, and [9]helicenes.[19,20]

The alkylidenedioxacyclohexane ring is markedly nonplanar, with the methylene carbon atom, C(63), lying 0.77 Å out of the best plane through the other five atoms.

The hydrogen bond between O(66) and O(72) is supported

Table II. Best planes[a,b] through Various Groups of Atoms and Derivatives (Å) of Atoms from These Planes

I	*C(18)*, 0.26; *C(19)*, −0.18; *C(20)*, −0.23; *C(21)*, 0.07; *C(22)*, 0.14; *C(23)*, 0.14; *C(24)*, −0.09; *C(25)*, −0.18; *C(26)*, −0.00; *C(27)*, 0.05; $\chi^2 = 503.0$, $P^c \ll 0.01$
II	*C(22)*, −0.03; *C(23)*, 0.05; *C(24)*, −0.03, *C(25)*, −0.03; *C(26)*, 0.07; *C(27)*, −0.03; C(18), 0.08; C(21), −0.26; N(28), 0.26; O(29), −1.83; O(67), −0.11; C(71), −0.10; O(72), 0.03; $\chi^2 = 21.8$, $P < 0.01$
III	*C(18)*, 0.16; *C(19)*, −0.08; *C(20)*, −0.05; *C(21)*, 0.12; *C(22)*, −0.01; *C(23)*, −0.09; C(17), 0.73; C(24), −0.51; C(27), −0.22; O(64), −0.03; C(65), −0.08; O(66), 0.25; $\chi^2 = 113.6$, $P < 0.005$
IV	*C(17)*, 0.07; *C(18)*, −0.09; *C(19)*, 0.08; *O(62)*, −0.01; *O(64)*, −0.02; C(63), −0.77; $\chi^2 = 38.8$, $P < 0.005$
V	*C(19)*, 0.02; *C(20)*, −0.05; *C(21)*, 0.06; *C(22)*, −0.03; *C(23)*, 0.00; C(17), 0.97; C(18), 0.31; C(24), −0.38; C(27), −0.29; O(64), 0.13; C(65), −0.12; O(66), 0.10; $\chi^2 = 12.0$, $p < 0.01$
VI	*C(17)*, 0.02; *C(18)*, −0.04; *C(19)*, 0.01; *C(23)*, 0.01; C(20), 0.54; C(22), 0.63; C(24), −0.58; O(62), −0.24; C(63), −1.06; O(64), −0.27; $\chi^2 = 4.7$, $P \sim 0.025$
VII	*C(1)*, 0.01; *C(2)*, 0.01; *C(3)*, −0.02; *C(4)*, 0.03; *C(5)*, −0.03; *C(6)*, 0.02; N(28), −0.78; O(29), 0.52; C(30), 0.28; $\chi^2 = 6.5$, $P \sim 0.10$
VIII	*C(1)*, 0.05; *C(2)*, 0.09; *C(26)*, 0.17; *N(28)*, −0.13; *O(29)*, −0.03; $\chi^2 = 147.4$, $P < 0.005$
IX	*C(13)*, 0.03; *C(14)*, −0.04; *O(50)*, −0.02; *B(51)*, 0.03; *O(59)*, 0.01; C(52), 0.28; $\chi^2 = 9.9$, $P \sim 0.01$
X	*O(50)*, 0.000; *B(51)*, −0.05; *C(52)*, 0.01; *O(59)*, 0.00; C(13), 0.22; C(14), 0.13; $\chi^2 = 3.3$, $P \sim 0.05$

[a] Atoms included in the plane calculation are shown in italics. [b] In these calculations, the atoms were weighted as $1/\sigma^2$, when σ is the standard deviation from the least-squares results. [c] Probability (on the basis of the χ^2 test) that distances from plane form a normal distribution.

by the presence of a peak at $x = 0.629$, $y = 0.452$, $z = 0.564$ with a height of 0.40 e/Å^3 in the final difference map; this peak could be interpreted as a hydrogen atom attached to O(72). The O(72)···O(66) and O(72)–H(72) distances are 2.55 (2) and 0.91 Å, and the O(72)–H(72)···O(66) angle is 130°. These values are similar to those found in other 8-hydroxynaphthoquinone derivatives.[21]

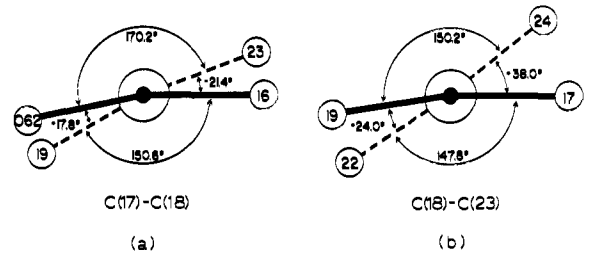


Figure 4. Newman projections looking along (a) the C(17)–C(18) bond and (b) the C(18)–C(23) bond.

Ansa Bridge. Comparisons of the conformations of the ansa bridge may provide useful information on the structure–activity relationships among different ansamycins. Among ansamycins, in addition to **3**, x-ray structural data are available for derivatives of rifamycin B,[12,14] rifamycin Y,[13,14] rifampicin,[16] tolypomycin,[17] maytansine,[22] and geldanamycin.[23] While the number of atoms comprising the macrocyclic ring is 23 in streptovaricin C triacetate, and 24 in the case of the two rifamycins, rifampicin, and tolypomycin, there are 17 atoms in the ansa bridge (i.e., that are not part of the fused ring system) in these five derivatives. Maytansine[22] and geldanamycin[23] have only 16 atoms in the ansa bridge and 19 atoms in the macrocyclic ring.

Table III lists the torsion angles along the ansa chain backbone in the derivatives of streptovaricin C triacetate, rifamycin B, rifamycin Y, rifampicin, and tolypomycin.[24] Figure 5 shows stereoscopic views of the macrocyclic rings in these molecules looking approximately normal to the direction of the naphthoquinone ring, together also with views of maytansine and geldanamycin. It should be noted that the helicity of the ansa ring in **3** is opposite that of the 24-membered rings.

Despite the opposite helicity of the ansa ring in the molecule of **3** from the others, the torsion angles along the backbone from C(8) to C(13) in all five molecules are quite similar. The aliphatic chain from C(8) to C(13) of **3** is almost in a trans "fully extended" conformation. Owing to the ring closure caused by the formation of the boronate ester at O(50) and O(59) in **3**, some conformational change about the C(13)–C(14) bond could be anticipated as compared to streptovaricin

Table III. Torsion Angles (Deg) along the Ansa Chain Backbone in the Derivatives of Streptovaricin C, Rifamycin B and Y, Rifampicin, and Tolypomycin[a]

	3	Rifamycin B[b]	Rifamycin Y[b]	Rifampicin[d]	Tolypomycin[e]
C(27)–C(26)–N(28)–C(1)	63	−32	−26	−55	−153
C(25)–C(26)–N(28)–C(1)	−117	146[c]	143[c]	131	16
C(26)–N(28)–C(1)–C(2)	−162	180	168	179	175
N(28)–C(1)–C(2)–C(3)	39	−43	−47	−31	77
C(1)–C(2)–C(3)–C(4)	177	5	−8	4	7
C(2)–C(3)–C(4)–C(5)	178	168	180	155	−179
C(3)–C(4)–C(5)–C(6)	9	−175	171	−165	124
C(4)–C(5)–C(6)–C(7)	−127	−11	111	−19	−2
C(5)–C(6)–C(7)–C(8)	179	170	−76	169	150
C(6)–C(7)–C(8)–C(9)	−54	−179	−84	−176	−162
C(7)–C(8)–C(9)–C(10)	−79	53	143	62	52
C(8)–C(9)–C(10)–C(11)	−161	174	180	165	−177
C(9)–C(10)–C(11)–C(12)	−171	155	159	159	168
C(10)–C(11)–C(12)–C(13)	174	174	151	153	−169
C(11)–C(12)–C(13)–C(14)	−151	−170	−174	−171	178
C(12)–C(13)–C(14)–C(15)	115	117	113	118	−139
C(13)–C(14)–C(15)–C(16)	160	−168	−176	−175	−161
C(14)–C(15)–C(16)–C(17)	179	49	78	65	−111

[a] The torsion angle A–B–C–D is considered positive if, when looking along the bond from B to C, atom A has to be rotated clockwise to eclipse atom D. [b] Torsion angles given in ref 14. [c] Calculated from coordinates listed in ref 14. [d] Calculated from coordinates listed in ref 16. [e] Calculated from coordinates listed in ref 17.

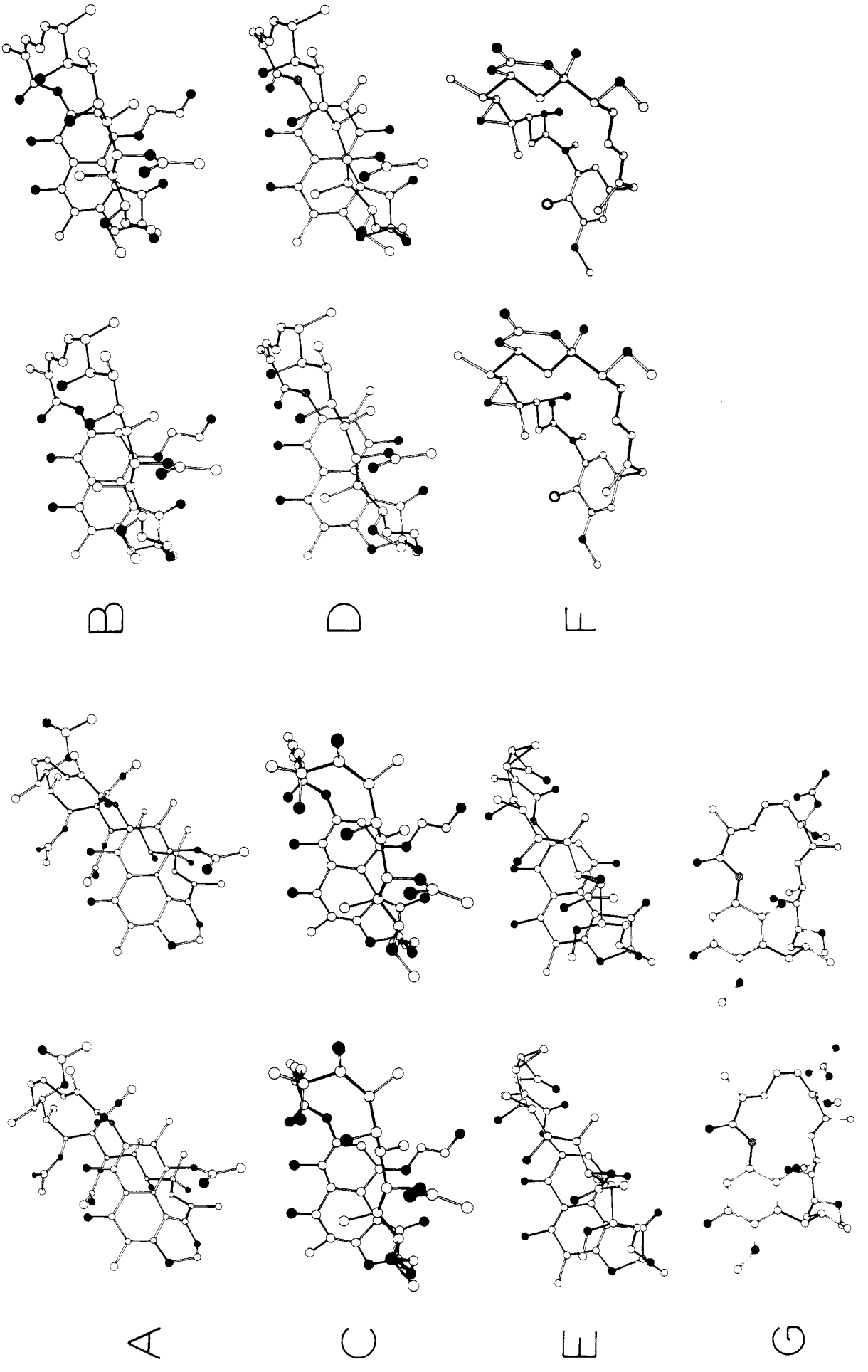


Figure 5. Stereoscopic views looking across the macrocyclic ring for (A) the atropisomer of the *p*-bromobenzeneboronate ester of streptovaricin C triacetate, (B) rifamycin B *p*-iodoanilide,[14] (C) rifamycin Y *p*-iodoanilide,[14] (D) rifampicin,[16] (E) tolypomycinone tri-*m*-bromobenzoate,[17] (F) maytansine (3-bromopropyl) ether,[22] and (G) geldanamycin.[23] These pictures were drawn by us from coordinates in references cited. Large side chains used to form crystalline derivative have been omitted for clarity. The ansa bridge is shaded in each drawing.

C triacetate itself. O(50) and O(59) are brought into an eclipsed orientation from what would presumably be a gauche orientation. In the C(4)-C(8) region of the ring, where the greatest differences in torsion angles occur between the active rifamycin B and the inactive rifamycin Y, the molecule of **3** has a different geometry from either (Table III).

The C(1)-C(6) portion of the molecule is quite planar (see Table II, plane VI) with the atoms N(28) and O(29) lying on opposite sides of this plane. The geometry about the $\Delta^{2,3}$ and $\Delta^{4,5}$ bonds in molecule **3** is trans,cis, whereas in rifamycin A, rifamycin Y, and rifampicin, it is cis,trans, while the $\Delta^{2,3}$ bond in tolypomycin is cis (this bond is adjacent to a ketone group). In geldanamycin, the $\Delta^{2,3}$ and $\Delta^{4,5}$ bonds are trans,cis. There is no corresponding region with C=C double bonds in maytansine.

In all five compounds listed in Table III and in the smaller geldanamycin, the amide group assumes a trans arrangement. In contrast, the amide group in maytansine is N-methylated and has a cis arrangement. In **3**, the amide group, which consists of the C(26), N(28), C(1), C(2), and O(29) atoms, is very significantly nonplanar, with deviations ranging from −0.13 to 0.17 Å (Table II, plane VIII). This nonplanarity also is very evident from the C(26)-N(28)-C(1)-C(2) torsion angle of −162°. While the corresponding amide groups in the derivatives of the rifamycins and of tolypomycin are also nonplanar, the one in **3** shows the greatest deviation from planarity. The C(27)-C(26)-N(28)-C(1) torsion angle in **3** is 63°, while those in the rifamycin B and Y and tolypomycin derivatives are −32, −26, and −153°, respectively; however in rifampicin, this torsion angle is −55°. Thus, the angle between the plane of the amide group and that of the aromatic ring is greater in **3** than in many of the others. In the ansa rings in these five compounds, the way in which the amide links to either the aromatic ring or to the conjugated double bond sequence in the ansa bridge serves to provide a significant "hinge" or "turning point" for the macrocyclic ring. In the cases of the rifamycins and tolypomycin, this is mainly achieved by twist around the C(1)-C(2) bond, whereas in **3** and also in the rifampicin derivative there is, in addition, a very large twist of the amide group out of the plane of the aromatic nucleus.

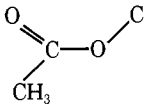
In view of the large angle (ca. 60°) between the amide group and ring A of the naphthoquinone system, the delocalization of the π electrons between these two groups will be minimal. The C(26)-N(28) bond length of 1.43 (3) Å is slightly longer than that in acetanilide, 1.413 Å,[25] but shorter than that in *N*-methylacetanilide (1.481 Å).[26] The change of C-N bond length can be correlated with either the C-C-N-C (carbonyl) torsion angles, for example, 63° for the C(27)-C(26)-N(28)-C(1) torsion angle in **3**, and 20 and 93° for the corresponding torsion angles in acetanilide[25] and *N*-methylacetanilide,[26] respectively. The large twist of the C(26)-N(28) bond has the effect of pointing the carbonyl group to the outside of the molecule and at a large angle to the plane of the naphthoquinone ring. The carbonyl group may therefore be in a position to interact with other molecules and, in this crystal, does so with the methylene dichloride solvent molecule (see below).

The arrangement of the amide group and alternating double and single C-C bonds in the ansa bridge is such that it would be possible to imagine a delocalized structure that would tend to make the atoms N(28), O(29), C(30), and C(1)-C(6) lie in the plane of ring A. However, such a geometrical arrangement would be inconsistent with the formation of the macrocyclic ring.

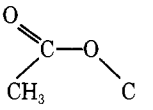
There is probably an intramolecular hydrogen bond between N(28) and O(42) with an N(28)···O(42) distance of 3.01 (2) Å. In the final difference map, there was a peak of 0.40 e/Å^3 near N(28) and it probably represents a hydrogen atom, H(28), attached to N(28). The N(28)-H(28) and H(28)···O(42) distances would be 1.22 and 1.82 Å, respectively, and the N(28)-**H**(28)···O(42) angle would be 163°. This intramolecular hydrogen bond may be partly responsible for the apparent conformational rigidity of the molecule. This type of transannular N-H···O hydrogen bond has been found in many cyclic peptides.[27-30] There are no equivalent transannular hydrogen bonds in any of the other ansamycins whose structures have been determined,[12-14,16,17,22,23] although in rifamycin Y there is an O-H···O hydrogen bond between groups substituted on carbon atoms C(6) and C(9) of the macrocyclic ring, while in rifamycin B and rifampicin there appears to be an O-H···O hydrogen bond between the OH groups attached to C(7) and C(9). These types of hydrogen bonding are not possible in the tolypomycin molecule because of the derivatization.

The *p*-bromobenzeneboronate ester in the crystal of the solvate of **3** was formed by complexing the 1,2-diol [O(50) and O(59)] group. The entire five-membered boronate ring approaches planarity (Table II, plane IX) and the dihedral angle between the boronate and phenyl rings is 19°. Boron and its three-bonded atoms are nearly planar with an endocyclic O-B-O [115 (2°)] angle considerably less than 120°.[31-33]

The acetate groups have some noteworthy features. Not only are the acetate groups closely planar, but they all adopt the conformation (**4a**) with the carbonyl oxygen eclipsed by the



4a



4b

carbon attached to the hydroxyl oxygen, rather than the alternative planar arrangement (**4b**). This is in agreement with previous findings on esters.[34] All the acetate groups have the terminal acetyl residue aligned almost normal to the direction of the backbone of the ansa ring. The derivatives of rifamycin B, rifamycin Y, rifampicin, and of tolypomycin that have been studied by x-ray methods each had only one acetate group (see Figure 5). In all these cases, the plane of the group is again almost normal to the direction of the backbone of the ring and the group adopts conformation **4a** in the crystal.[35] Thus, whereas streptovaricin triacetate may appear to be a very "floppy" molecule, in fact the conformation found for the acetate groups in the crystal appears to be favored thermodynamically.

Molecular Packing. The crystal structure of the methylene chloride solvate of **3** as seen along the *b* axis is shown in Figure 6. A table with some of the short intermolecular contacts has been deposited.[10] The contacts between molecules of **3** appear largely to be of the van der Waals type. There are, however, some short C···O contacts between molecules. In particular C(19) and C(20) of the naphthoquinone nucleus lie 3.12 and 3.17 Å from O(34) (acetate carbonyl oxygen) in the molecule at $\frac{1}{2} + x, 1\frac{1}{2} - y, 1 - z$, the six-membered ring methylene carbon, C(63), and the ether oxygen, O(64), lie 3.05 and 3.12 Å from the acetate oxygen, O(39), in the molecule at $1\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$, and the terminal methyl of an acetate group, C(44), lies 3.07 Å from the amide oxygen, O(29), in the molecule at $1 - x, \frac{1}{2} + y, 1\frac{1}{2} - z$.

The methylene dichloride molecules occupy well-defined positions surrounded by several antibiotic molecules. The solvent molecule is so oriented that there is a C···O(29) distance of 3.09 (4) Å and the two Cl-C···O(29) angles are 115 (2) and 122 (2)°; these dimensions suggest a C-H···O (amide) hydrogen bond. Such C-H···O hydrogen bonds have been noted to occur with chloroform and with dichlorobromomethane.[36]

Relation of Structure to Biological Activity. Although the

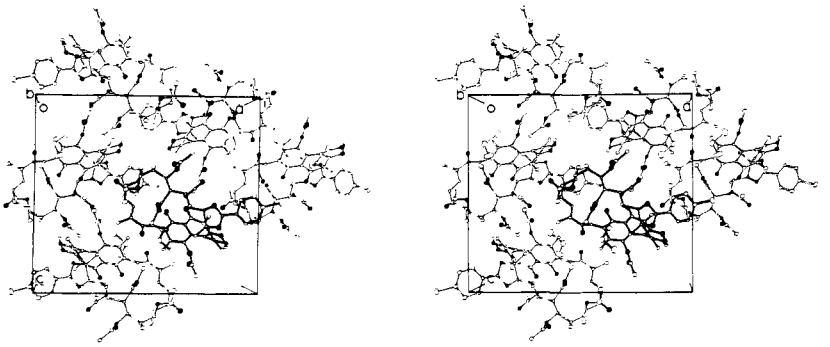


Figure 6. The stereoscopic view of the packing in the crystal of the solvate of **3** looking along the *b* axis. The bonds in the reference molecule are shaded. The oxygen atom bonds in the drawing are given in black.

families of the streptovaricins, rifamycins, and tolypomycins have similar types of biological activity, this activity can be greatly affected by some apparently minor variations in chemical structure.[2] For example, the only differences in chemical structure between rifamycin B and rifamycin Y are the replacement of a hydrogen on the ansa chain carbon adjacent to the diene group in the former by a hydroxyl and the oxidation in the former of a secondary alcohol to a ketone on the next carbon. Yet rifamycin B forms a complex with DNA-dependent RNA polymerase and inhibits its action in bacteria, whereas rifamycin Y does neither.[1b] However, as can be appreciated from Figure 5, even this slight change in chemical structure causes a significant difference in the disposition of the ansa ring. Whereas in rifamycin B, the plane through the four carbon atoms of the conjugated diene group runs at an angle of 65° to the plane of the naphthoquinone nucleus; in rifamycin Y it is nearly normal (84°) to it. Streptovaricin F, which has very low antibacterial activity and activity against *E. coli* DNA-dependent RNA polymerase, differs from streptovaricin C in having a direct covalent bond between C(41) and O(32). [It is of interest that these two atoms are only 2.82 (3) Å apart in **3** and would appear to be well disposed for bond formation.] It is also clear that such bond formation would prevent the N(28)-H···O(42) hydrogen bridge across the macrocyclic ring. Breaking this hydrogen bond could have a significant effect on the conformation of the ansa ring as the orientation of the amide group and that of the carbomethoxyl group on C(10) are such as to favor this bond.

The *p*-bromobenzeneboronate esters of streptovaricin C triacetate show some activity against DNA-dependent RNA polymerase and are quite active against reverse transcriptase.[5] Somewhat surprisingly, the two atropisomers of various streptovaricin benzeneboronate esters showed little difference in bioactivity.[5]

It should be noted that the streptovaricins, the rifamycins, and tolypomycin all have certain common features and it is probable that at least some of these are essential for activity:[1b] a naphthoquinone chromophore with an intramolecular O-H···O hydrogen bond; an ansa ring containing an amide group; an adjacent conjugated diene (or related planar group, as in tolypomycin); and several attached acetate or carbomethoxy groups. However, it is only in the molecule of **3** that the amide group, by being twisted out of the plane of the chromophore, is involved in a transannular hydrogen bond.

In the present compound, the electronic nature of much of the surface of the molecule is determined by the placement of the acetate groups and this placement is in turn influenced by the conformation of the ansa ring. One side of the exterior of the molecule of **3** (the lower side in Figure 5, A) is largely nonpolar, whereas the other side is partially polar and partially nonpolar. The methylene dichloride solvent molecule sits in the nonpolar cushion provided by one side of the molecule of **3**; the side of the methylene dichloride that participates in this nonpolar interaction is opposite to that involved in the C-H···O interaction.

In conclusion, the complete three-dimensional structure of one of the atropisomers of the *p*-bromobenzeneboronate ester of streptovaricin C triaceate has been determined and many of the features that determine the molecular geometry and capability for interaction of this member of the streptovaricin class have been described and compared with those pertaining in other ansamycins. The influence of the atropisomerism displayed by this derivative of streptovaricin has also been discussed.

Acknowledgment. We wish to thank Professor K. L. Rinehart, Jr., for suggesting the problem and for the benefit of his advice throughout the course of the study. We also thank Dr. F. J. Antosz for providing the crystals. Dr. Kwo-Tsair Wei and Miss Mary K. Greensley assisted in the preparation of the manuscript. We are grateful to Dr. D. Duchamp of the Upjohn Co. for permission to include data from unpublished work on geldanamycin. Financial support was provided by NIH GM 19336.

Supplementary Material Available: listing of observed and calculated structure factors, the complete bond lengths and angles, and some intermolecular contacts of the crystal of the solvate of **3** (21 pages). Ordering information is given on any current masthead page.

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Model Dehydrogenase Reactions. Zinc Ion Catalyzed Reduction of Chelating Aldehydes by *N*-Propyl-1,4-dihydronicotinamides and Borohydride

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Abstract: Zinc ion catalyzes the reduction of 1,10-phenanthroline-2-carboxaldehyde by *N*-propyl-1,4-dihydronicotinamide in acetonitrile. This nonenzymic model reaction for alcohol dehydrogenase supports the view that the catalytic function of the zinc ion at the active site of alcohol dehydrogenase is to polarize the carbonyl group of the aldehyde substrates and to facilitate the deprotonation of the hydroxyl group of alcohol substrates. The model reaction proceeds by direct hydrogen transfer, is absolutely dependent on zinc ion, and is insensitive to free-radical quenching agents such as dihydroquinone. The disparity between the kinetic isotope effects and the isotopic partitioning ratio indicates that an intermediate forms during the course of the reaction. The zinc ion catalyzed reduction of 2- and 4-pyridinecarboxaldehyde by tetraethylammonium borohydride is consistent with coordination or proximity of the metal ion to the carbonyl group being primarily responsible for the absolute dependence on metal ion observed in the dihydronicotinamide reduction of 1,10-phenanthroline-2-carboxaldehyde. The metal ion complex of 2-pyridinecarboxaldehyde is reduced at least 700 000 times faster than the free aldehyde whereas the zinc complex of 4-pyridinecarboxaldehyde is reduced only 100 times faster than the corresponding free aldehyde. The rate of borohydride reduction of the zinc complex of the 2-isomer is independent of borohydride concentration but that of the 4-isomer is not. The mechanistic implications of this observation are discussed.

The NAD^+-dependent alcohol dehydrogenase from horse liver contains one catalytically essential zinc ion at each of its two active sites.[2,3] Solution studies using bipyridine as a probe for interactions taking place at the active site zinc ion have indicated that the metal ion is at or near the substrate binding site and in close proximity to the binding site of the nicotinamide moiety of the coenzyme.[2b] X-Ray crystallographic studies have supported this location of the zinc ion within the active site.[4,5]

These results are consistent with the view that an essential feature of the enzymic catalysis is direct coordination of the enzyme-bound zinc ion by the carbonyl and hydroxyl groups of the aldehyde and alcohol substrates. Such interactions could promote hydrogen transfer between coenzyme and substrate by polarizing the carbonyl group of the aldehyde substrates and by facilitating deprotonation of the hydroxyl group of alcohol substrates.[6-8] In a previous communication, we reported that zinc ion catalyzed the reduction of 1,10-phenanthroline-2-carboxaldehyde (I) to 1,10-phenanthroline-2-carbinol (II) by *N*-propyl-1,4-dihydronicotinamide (III) in anhydrous acetonitrile (eq 1).[9] These studies provided the first chemical precedent for metal ion activation of a carbonyl group for reduction by a dihydronicotinamide and therefore supported the suggested function of the zinc ion at the active site of alcohol dehydrogenase. Subsequently the metal ion catalyzed reduction of pyridoxal phosphate and its derivatives by the Hantzsch ester, 2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydropyridine, was reported in aqueous solution.[10] These studies also demonstrated that dihydropyridine reductions of aldehydes are facilitated by general acid catalysis.[10]

In the present communication, we wish to present further experimental and mechanistic details of the reaction summarized in eq 1. We also report kinetic studies on the zinc