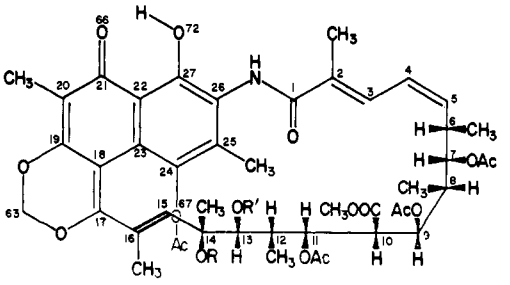
## Chemistry of the Streptovaricins. IX. X-Ray Crystallographic Structure of a Streptovaricin C Derivative[1]

*Sir:*

In the immediately preceding communication,[1] which culminated extensive chemical studies,[2] we assigned structures to streptovaricins A–G, ansamycin antibiotics[3] with potentially important antiviral[4] and antitumor[5] activities. It was recognized early that an X-ray structural determination would be a desirable route to structure elucidation of these compounds, but the prospects for such a study were long frustrated by the difficulty of obtaining a suitably crystalline derivative of one of the antibiotics.

One feature of the newly assigned structures (except that for streptovaricin D) is a vicinal glycol group which is readily cleaved by periodate.[1,2] In accord with this proposed group, when streptovaricin C triacetate (**1**)[2,6,7]



**1**, R = R′ = H
**2**, R = H; R′ = –B(OH)$C_6H_5$
**3**, R + R′ = >B$C_6H_5$
**4**, R = H; R′ = –B(OH)$C_6H_4$Br(*p*)
**5**, R + R′ = >B$C_6H_4$Br(*p*)

A relatively small but untwinned crystal of the solvate of **5** was found to give some data out to $2\theta = 110°$. A total of 2148 nonzero reflections was measured on a Picker FACS-1 diffractometer using Cu K$\alpha$ radiation.

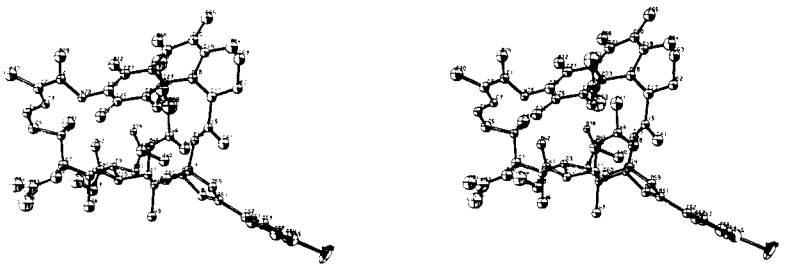


Figure 1. Stereoscopic view of a molecule of the cyclic *p*-bromophenyl boronate (**5**) of streptovaricin C triacetate.

was treated with phenylboronic acid it gave acyclic and cyclic boronate esters (**2**, 12% yield, $C_{52}H_{62}BNO_{18}$,[9a] mp 212–215°, and **3**, 9%, $C_{52}H_{60}BNO_{17}$,[9a,b] mp 210–213°, respectively). Similar treatment of **1** with *p*-bromophenylboronic acid yielded **4** and **5**, the para-bromo analogs of **2** and **3** (**4**, 16%, $C_{52}H_{61}BBrNO_{18}$,[9a] mp 215–220°; **5**, 14%, $C_{52}H_{59}BBrNO_{17}$,[9a,b] mp 214–217°). The latter compound, **5**, crystallized from methylene chloride–ether to give a methylene chloride solvate, $C_{52}H_{59}BBrNO_{17}\cdot CH_2Cl_2$,[9a] mp 275–278°, which, while not ideal for X-ray studies, did diffract to a sufficient extent that a structure determination was possible: 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$^3$, $\rho_{measd}$ = 1.31 g cm$^{-3}$, $Z$ = 4, $\rho_{calcd}$ = 1.35 g cm$^{-3}$, $F(000)$ = 2384, space group $P2_12_12_1$.

The structure was solved by the heavy atom method and has been refined by full-matrix least-squares methods on positional and anisotropic thermal parameters for the bromine atom and the three nonhydrogen atoms of the methylene chloride molecule and on positional and isotropic parameters for all the other nonhydrogen atoms, to an $R$ factor of 0.105. A stereoscopic view of the molecule is shown in Figure 1.[7]

The structure derived from X-ray crystallography substantiates the gross structure assigned streptovaricin C from chemical evidence. Its complete stereochemical detail also confirms those isolated points of stereochemistry assigned earlier: the geometry about the $\Delta^{2,3}$, $\Delta^{4,5}$, and $\Delta^{15,16}$ double bonds (trans, cis, and trans, respectively)[1,6,7] and the relative configurations at C(9), C(10), C(11), and C(12).[8] The bond lengths and angles are consistent with structure **5** within the limits of error of the analysis (*e.g.*, C–C, ±0.03 Å, C–C–C, ±2°). The exocyclic lengths C(21)–O(66) [1.22 (3) Å], and C(17)–C(18) [1.37 (3) Å], support the quinoid structure shown in **5**, with C(27)–O(72) being a phenolic bond [1.37 (3) Å].[7] There was no ambiguity in assigning the oxygen and carbon atoms of the acetate groups in the molecule. The C(15)–C(16) and C(17)–C(18) double bonds are in a cisoid arrangement with a 35° torsion angle between the double bonds. The C(18)–C(23) ring is significantly nonplanar (maximum deviation 0.15 Å). The large torsion angle between conjugated double bonds and the nonplanar quinone ring presumably arise from overcrowding between the substituents on C(16) and C(24); C(15) and O(67) cannot both occupy the same space. The alkylidenedioxacyclohexene ring is markedly nonplanar, with the methylene carbon

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(2) K. L. Rinehart, Jr., and F. J. Antosz, *J. Antibiot.*, in press.
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(6) K. L. Rinehart, Jr., H. H. Mathur, K. Sasaki, P. K. Martin, and C. E. Coverdale, *J. Amer. Chem. Soc.*, **90**, 6241 (1968).
(7) The numbering employed (see formulas **1**–**5** and Figure 1) is designed to assign a unique number to every atom (except hydrogen) in the molecule. The numbering in the preceding communications[1,2,8] was somewhat different. Neither numbering system corresponds to any established chemical convention.
(8) K. Sasaki, K. L. Rinehart, Jr., and F. J. Antosz, *J. Antibiot.*, in press.
(9) In agreement with the molecular formula assigned are (a) microanalyses, (b) low-resolution mass spectral data.

atom, C(63), being 0.78 Å out of the best plane through the other five atoms. C(63) has a large isotropic thermal parameter and this may indicate a freedom to "pass" through the plane of the ring in the isolated molecule. Such behavior would be consistent with the observed broadening of the signal from the two protons on this carbon atom in the nmr spectrum of streptovarone.[10]

The methylene chloride molecules occupy well-defined positions surrounded by several antibiotic molecules. The solvent molecule is so oriented that there is a C···O distance of 3.09 Å and Cl—C···O angles of 115 and 122°, indicating a C—H···O (amide) hydrogen bond. Such C—H···O hydrogen bonds have been noted to occur with chloroform and dichlorobromomethane.[11]

Since coupling constants and chemical shifts of the other streptovaricins are nearly identical[1] with that of streptovaricin C, we assume their stereochemistry is like that in derivative **5**.

Of particular interest is the observation that the relative configuration at every comparable chiral center of **5** is identical with that in rifamycins B[12a] and Y[12b] and tolypomycin,[13] although the geometry of the dienamide unit is reversed (trans, cis for **1–5** *vs.* cis, trans for rifamycins B and Y). This identity of relative configurations and the strong positive rotations of streptovaricin C (+602°)[14] and rifamycin S (+476°)[15] argue for identical absolute configurations[16] as well (*i.e.*, that shown for **5**: 6*S*, 7*S*, 8*R*, 9*R*, 10*S*, 11*S*, 12*R*, 13*S*, 14*R*). The helicity of the *ansa* (bridged) system is P.[17]

**Acknowledgment.** This investigation was supported in part by Public Health Service Research Grant No. AI 01278 from the National Institute of Allergy and Infectious Diseases.

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(18) Alfred P. Sloan Research Fellow, 1968–1970.
(19) Recipient of a National Institutes of Health Postdoctoral Fellowship (AI 43866) from the National Institute of Allergy and Infectious Diseases.

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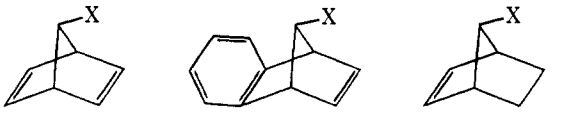
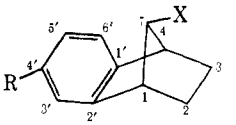
## Enhanced Solvolytic Reactivity in the *exo-syn*-Tricyclo[3.2.1.0$^{2,4}$]oct-6-en-8-yl Series. Evidence for Extensive Steric Acceleration

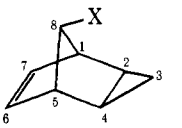
*Sir:*

The additional solvolytic rate enhancement provided by the syn double bond in 7-norbornadienyl and anti 7-benznorbornadienyl derivatives I[1] and II[2] compared to the corresponding anti dihydro systems III[3] and IV[2] may be ascribed to either a ground–transition state effect[4] or to extra charge delocalization into the adjacent nonconjugated $\pi$ center in the transition state, *i.e.*, a homoconjugative reinforcing effect.[1,4] In view of the magnitude of direct edge participation by cyclopropane in the *endo*-tricyclo[3.2.1.0$^{2,4}$]octan-8-yl system[5] it appeared instructive to examine the reactivities of appropriate exo cyclopropanated analogs of I and II for possible homoconjugative reinforcing effects by cyclopropane.[6] Accordingly we have examined the solvolytic reactivity of *exo-syn*-tricyclo[3.2.1.0$^{2,4}$]oct-6-en-8-yl *p*-nitrobenzoate (V-OPNB) and *exo-anti*-5,6-benztricyclo[3.2.1.0$^{2,4}$]octen-8-yl brosylate (VI-OBs) in addition to related systems. We now wish to report that these cyclopropanated esters represent an extreme of solvolytic reactivity in their respective series, although evidence presented below suggests that these rate enhancements should not be ascribed to homoconjugative electron release by cyclopropane.



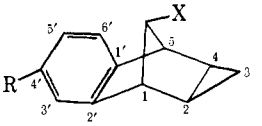

I II III

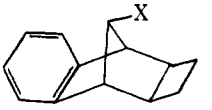



IV, R = H
VIII, R = Br
IX, R = $CH_3$

V




VI, R = H
X, R = Br
XI, R = $CH_3$

VII

As reported earlier by several groups of workers,[7] alcohol V-OH is available as the major component of

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(6) Recent photoelectron spectroscopic examination of *exo*- and *endo*-tricyclo[3.2.1.0$^{2,4}$]oct-6-ene by P. Bischof, E. Heilbronner, H. Prinzbach, and H. D. Martin [*Helv. Chim. Acta*, **54**, 1072 (1971)] has revealed significant homoconjugative interaction between the $\pi$ orbital of the double bond and the symmetric *Walsh* orbital $e_s$ of the cyclopropane ring in the exo isomer. The extent of interaction approaches that found between the $\pi$ orbitals of the two double bonds in norbornadiene. On the other hand only negligible interaction was detected between the double bond and the cyclopropane ring in the endo isomer.
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