Communications to the editor

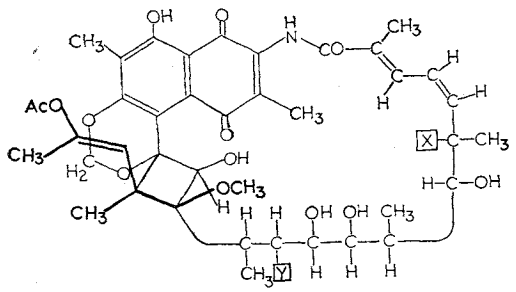
CHEMISTRY OF THE STREPTOVARICINS. VI

OXIDATION PRODUCTS FROM STREPTOVARICIN C*

Sir:

Intense recent interest has been generated in the ansamycins[2] as potential anti-viral agents: rifamycin derivatives[3] and streptovaricins[4] inhibit virus replication, other rifamycin derivatives inhibit DNA polymerase activities of RNA tumor viruses[5], the streptovaricins inhibit mouse leukemia virus[6]. These biological results prompt us to report in this and the accompanying communication our recent structural results with streptovaricin C. In this report we describe oxidative degradation products whose structures necessitate a revision of the structure (**1**) earlier assigned[1] to streptovaricin C [as well as a revision of that assigned then (**1**, but X=OH, Y=OAc) to streptovaricin A]. The accompanying manuscript assigns a revised structure to streptovaricin C[7], related work assigns structures to streptovaricins A, B, D, E, F, and G[8].

Oxidation of streptovaricin C triacetate[1] with osmium tetroxide–sodium periodate for different periods of time gave the dialdehydes **2** [$C_{14}H_{18}O_4$**, $\lambda\lambda_{max}$ 227, 270 nm; $\tilde{\upsilon}$ 2700, 1725, 1690, 1610 cm^{-1}, no OH; *bis*-DNP derivative, $C_{26}H_{26}N_8O_{10}$**, m.p. 189~190°C] and **4** [$C_{18}H_{24}O_6$**, $\lambda\lambda_{max}$ 222, 268 nm; $\tilde{\upsilon}$ 2700, 1735, 1720, 1680, 1620 cm^{-1}], whose nmr spectra are summarized in Fig. 1. Reduction of these compounds with sodium borohydride gave **3** [$C_{14}H_{22}O_4$**, $\lambda\lambda_{max}$ 210 nm (end absorption), 230 nm (inflection); $\tilde{\upsilon}$ 3400–3350, 1710, 1620 cm^{-1}] and **5** [$C_{18}H_{28}O_6$*** λ_{max}^{EtOH} 214, 236 nm (ε 10,200, 7800 inflection); $\tilde{\upsilon}_{CHCl_3}$ 3600~3300, 1725 (broad) cm^{-1}]. Further reduction of **5** with lithium aluminum hydride gave **6** [$C_{15}H_{26}O_4$***, λ_{max}^{EtOH} 232 nm (ε 9300); $\tilde{\upsilon}$ 3500~3100 cm^{-1}]. A related oxidative degradation product(**7**)was obtained in four steps from streptovaricin C, whose treatment with periodate (one mole consumption) gave streptovaricinal C ($C_{40}H_{49}NO_{14}$†, mp 140~143°C), containing the side chain system (C-1' to C-5') common to streptovarone and prestreptovarone[7,8,9]. Acetylation of streptovaricinal C gave its triacetate ($C_{46}H_{55}NO_{17}$†, m.p. 122~124°C), which on oxidation with osmium tetroxide–hydrogen peroxide, followed by oxidation with periodate, gave **7**, a yellow oil ($C_{22}H_{32}O_{10}$***, end absorption <222 nm; $\tilde{\upsilon}$ 1745 cm^{-1}, no OH).

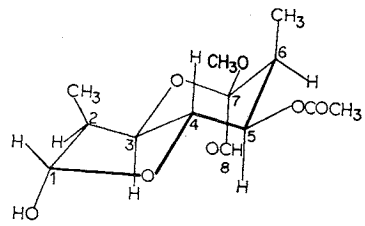


1: X=H, Y=OH
(previously assigned structure)

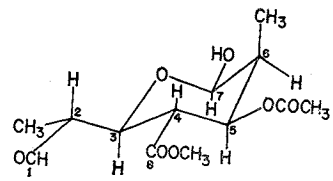
These oxidation products, especially **7**, are all clearly derived from the portion of streptovaricin C related to varicinal A[10]†† formed from two-mole periodate cleavage of streptovaricin A (which contains a C-6 hydroxyl)–between C-6 and C-7 and between C-13 and the streptovarone side chain. However, the carbon chains of **2**, **4** and **7** are extended toward the streptovaricin dienamide system (C-1 to C-5)[1,7] since streptovaricin C contains no C-6 hydroxyl for periodate cleavage[1].

Structures **2**, **4**, and **7** obviously demand a revision of the structure (**1**) previously assigned streptovaricin C since they contain a carbomethoxyl group, while **1** does not†††. This group is required by the infrared

* Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March–April, 1971; Abstracts, ORGN 111.
** Low resolution mass spectral data agree with the molecular formula assigned.
*** Microanalyses and low resolution mass spectral data agree with the molecular formula assigned.
† Microanalyses agree with the molecular formula assigned.
†† The structure formerly assigned to varicinal A (**8a**)[10] can now be revised to **8b**.
††† Structure **1** was based in large measure on the structure (**8a**) earlier assigned to varicinal A, in which the carbomethoxyl group was not detected[10].



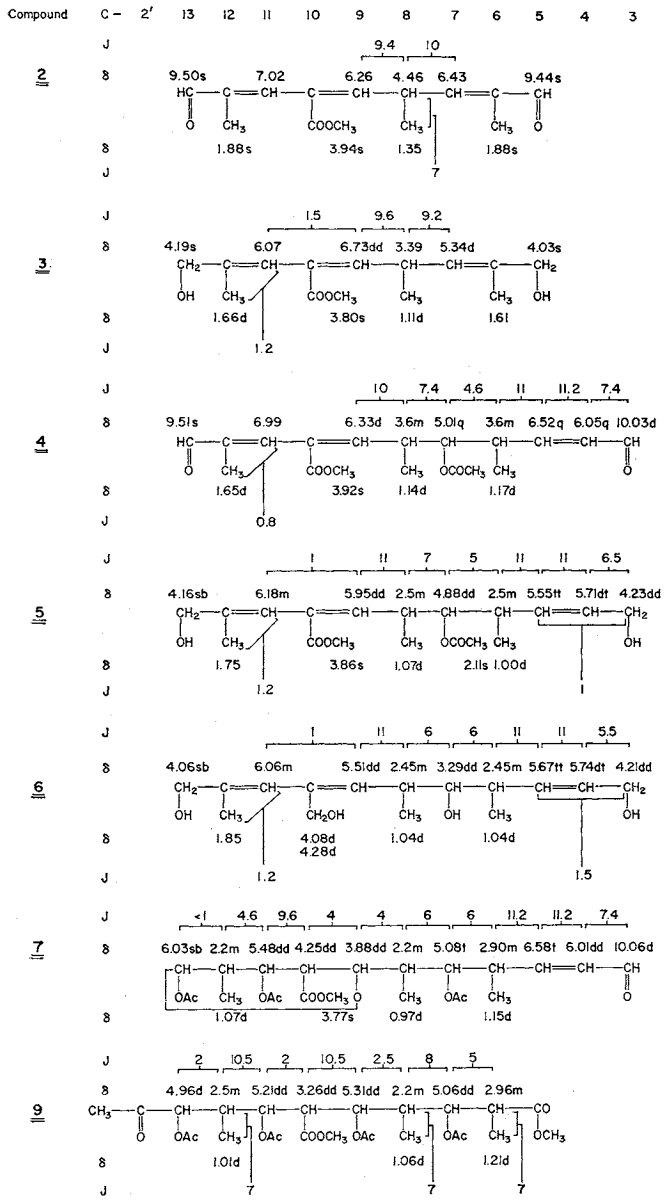
8 a



8 b

Fig. 1. Chemical shifts and multiplicities of protons in nmr spectra ($CDCl_3$) of compounds discussed.

Abbreviations of multiplicities are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad. Funds contributing to the purchase of the HA 220 nmr spectrometer were provided by the National Science Foundation.



carbonyl absorption (1710 cm^{-1}) of **3** and by the ultraviolet unsaturated ester absorption of **5** (214 nm, ε 10,200), lacking in **6**. The carbomethoxyl group is located conclusively from the nmr chemical shift and coupling patterns of **2**~**7**, as well as by the nmr data for streptovaricin C itself[8]. The structure of compound **7** juxtaposes the carbomethoxyl and the other substituents of the side chain. Their positions agree with earlier studies[1,10].

A final important oxidation product is **9**, obtained by oxidation of streptovaricin C tetraacetate [$C_{48}H_{59}NO_{18}$*, m.p. 180~182°C] with ruthenium tetroxide[11] in aqueous acetone at room temperature, followed by methylation of the product with diazomethane. The structure of compound **9** [$C_{25}H_{38}O_{13}$†, colorless oil, bp 180°C (0.05 Torr); end absorption <210 nm, weak λ_{max} 280 nm; $\tilde{\nu}$ 1735, 1715 (sh) cm^{-1}, no hydroxyl absorption; positive 2,4-DNP test] was assigned from its 220 MHz nmr spectrum and from spin decoupling of its 100 MHz spectrum, as summarized in Fig. 1.

The structure assigned (**9**) establishes that C-13 of the aliphatic chain is attached in streptovaricin C to a methyl–

* Microanalyses and low resolution mass spectral data agree with the molecular formula assigned.

† Microanalyses, low resolution mass spectral data, and high resolution mass spectral data agree with the molecular formula assigned.

bearing carbon (in fact, C-4′)[7] in the side chain of streptovarone. The ramifications of that linkage allow the assignment of a structure to streptovaricin C but require a revision of the previously assigned structures of streptovaricin C and streptovarone, as discussed in the accompanying communication[7].

Acknowledgment

This investigation was supported in part by PHS Research Grants AI 01278 and AI 04769 from the National Institute of Allergy and Infectious Diseases and CA 11388 from the National Cancer Institute.

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(Received October 15, 1971)

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* Recipient of an NIH Postdoctoral Fellowship (AI 43866) from the National Institute of Allergy and Infectious Diseases.