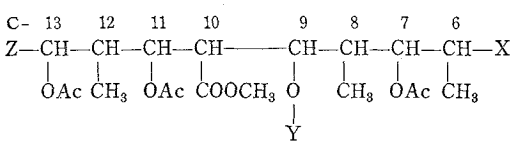
CHEMISTRY OF THE STREPTOVARICINS. VII
REVISED STRUCTURES FOR STREPTOVARONE AND STREPTOVARICIN C[1]

Sir:

In the accompanying communication[1] we noted that newly isolated oxidation products of streptovaricin C and its derivatives require revision of the structure previously assigned[2] to that important ansamycin antibiotic. In the present report we assign structure **1** to streptovaricin C.

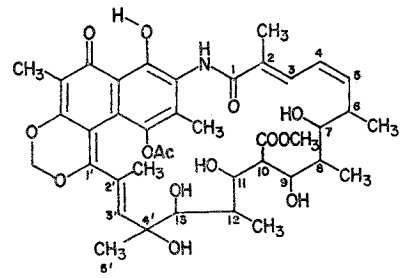
Of the oxidation products discussed in the accompanying report[1] the most significant for present purposes are **2**, which contains the substituents on carbon atoms C-3 through C-13 of the streptovaricin C side chain, and **3**, which contains two carbon atoms of the side chain of streptovarone as well as C-5 through C-13 of streptovaricin C.



2 X=-CH=CHCHO ; Y and Z absent (joined)
3 X=-$COOCH_3$; Y=-Ac ; Z=CH_3CO-

Compound **2** ($C_{22}H_{32}O_{10}$)[1] and streptovarone ($C_{24}H_{23}NO_9$), whose structure we now assign as **4**, account for all the carbon, hydrogen and nitrogen atoms of streptovaricinal C triacetate ($C_{46}H_{55}NO_{17}$)[1], with two additional oxygen atoms having been introduced by the oxidant, osmium tetroxide. The point of attachment of **2** to streptovarone (**4**) in streptovaricinal triacetate must have been the aldehyde carbon (streptovaricin C-3) of **2**, and the pyruvamide ketone carbon (streptovaricin C-2) of **4**. Prior to oxidation by osmium tetroxide followed by periodate these two atoms constituted the C-2, C-3 double bond in the side chain of streptovaricin C, a linkage also assigned by earlier spin decoupling studies on streptovaricin C and its triacetate[2].

Structure **3** requires that C-13 of the side chain of streptovaricin C be attached to a



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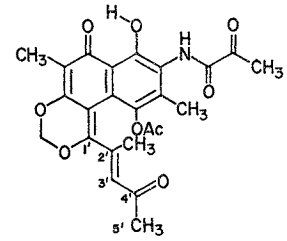

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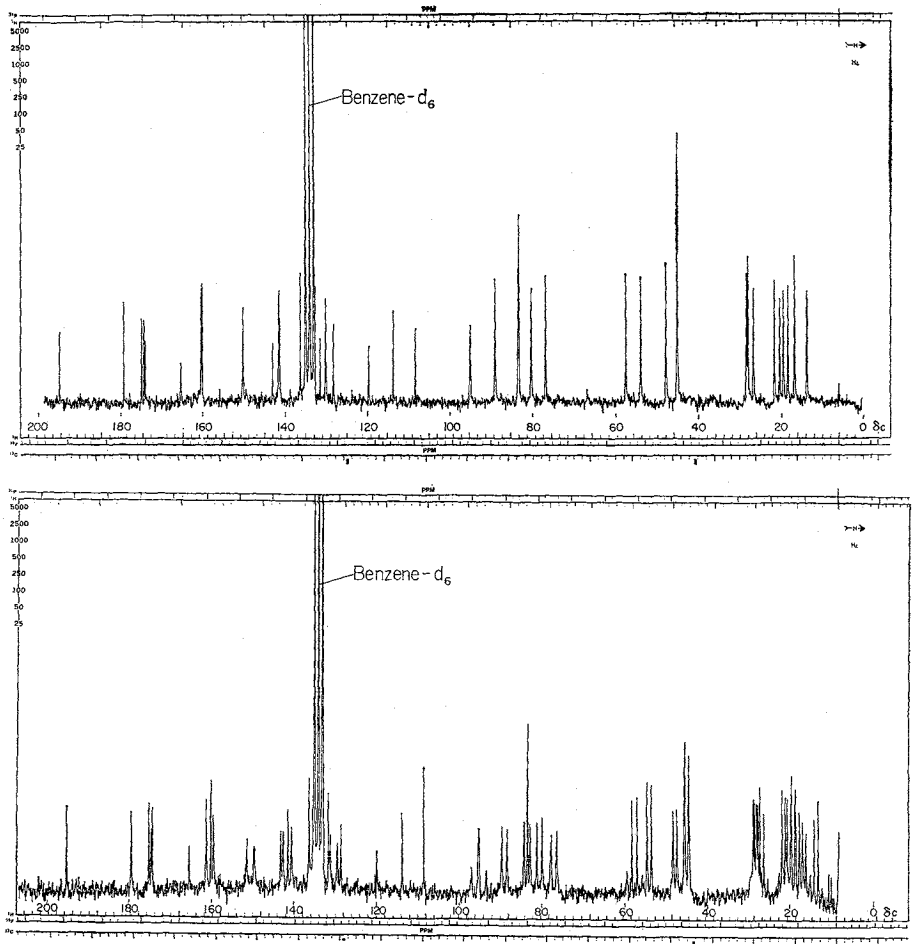
methyl-bearing carbon which must come from the atoms making up the side-chain of streptovarone. The structure of streptovarone was previously assigned as **5**[3]. The carbon skeleton and oxygenation pattern of the side chain (C-1′ to C-5′) of streptovarone are secure[3], based on known degradation products, and the position of the methylenedioxy group has been confirmed by the structure assigned to photostreptovarone[4]. Accordingly, an attempt was first made to locate the terminal acetyl group of **3** in terms of structure **5**, in which only C-2′ or C-4′ could be linked to C-13 to give an acetyl group on oxidation.

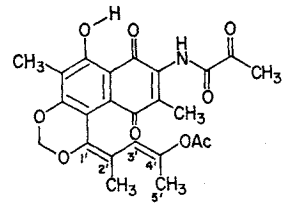
A decision between those two positions can be reached from the ^{13}C-nmr spectrum of streptovaricin C (Fig. 1), in which all forty carbon atoms of the antibiotic are individually displayed. In particular, the relevant quaternary carbon atom (C-2′ or C-4′) is found at 82.9 ppm from tetramethylsilane, in a region appropriate for an oxygen-substituted carbon but inappropriate for a carbon attached only to other carbon atoms[5]. The position of the quaternary methyl singlet in the proton spectrum of streptovaricin C (δ 1.13)[2] is in agreement with this conclusion. Thus, C-13 is linked to C-4′ and the partial structure **a1** emerges as a hypothesis. However, **a1** cannot be

Fig. 1. Fourier transform ^{13}C-nmr spectrum of streptovaricin C (0.1 M solution in benzene-d_6, determined on a Varian XL-100 spectrometer). Above, protons completely decoupled; below, protons partially decoupled.



correct, since no additional methine (-CH-) group is allowed either by the ^{13}C-nmr spectrum (Fig. 1) or the proton nmr spectrum[2]. Since the nmr spectrum of streptovaricin C shows the C-3′ proton to be olefinic, and slightly split by a methyl group, C-2′ and C-3′ are olefinic. Thus C-1′, which cannot bear hydrogen, must also be doubly bonded into the ring, suggesting partial structure **a2**. This, too, can be eliminated, by the presence of an enol acetate band at 1760 cm^{-1} in the infrared spectrum of streptovaricin C[3] which serves to eliminate the tautomer **a1** as well.

The partial structure **a3**, however, admirably meets the requirements imposed: enolic acetate infrared absorption[3], strongly hydrogen-bonded hydroxyl group[3], ready



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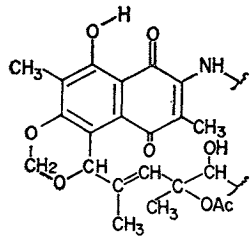
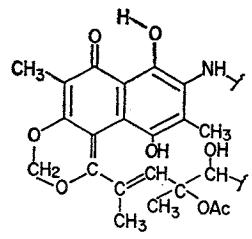
cleavage by periodate.[1,2,3]

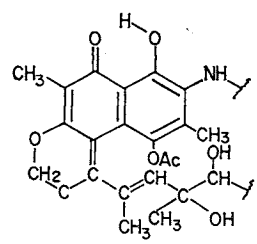
Partial structure **a3** for streptovaricin C is clearly not in accord with the structure (**5**) previously assigned to streptovarone and requires a revision of that structure to **4**. The most obvious new structural feature of **4** is the keto group at C-4′. In accord with structure **4**, when streptovarone was treated with hydroxylamine it gave a dioxime (**6**,



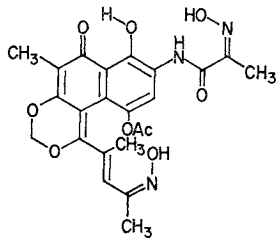
a1



a2



a3



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$C_{24}H_{25}N_3O_9$;* mp 199~201°C decomp.). The only notable changes in chemical shifts in the nmr spectrum (C_5D_5N) of the dioxime *vs* that of **4** were those expected** for structure **6**; in the pyruvamide methyl protons (from δ 2.61 for **4** to $<\delta$ 2.42 for **6**), in the olefinic proton on C-3′ (from δ 6.78 for **4** to δ 7.40 for **6**), and in the C-2′ methyl protons (from δ 2.15 for **4** to δ 1.89 for **6**).

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* In agreement with the molecular formula assigned are (a) microanalyses, (b) low resolution mass spectral data, (c) high resolution mass spectral data.

** The nmr spectrum (C_5D_5N) of mesityl oxide oxime displays similar changes in chemical shifts *vis-à-vis* those of mesityl oxide. from δ 6.03 (=CH) and 2.10 (*cis*-methyl) for mesityl oxide to δ 6.40 and 1.78 for mesityl oxide oxime.

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