Table I. Properties of Streptovaricin

Component	R_f[a]	Mp, °C	$[\alpha]D$ ($CHCl_3$), deg	Mol wt (mass spec)	Molecular formula	Found C	Found H	Found N	Found O	Found C-CH_3 (Kuhn-Roth)	Found O-CH_3	Found OAc (Zeisel)
A[b]	0.37	194–196°	+610	827	$C_{42}H_{53}NO_{16}$	60.94	6.65	1.64	30.68	16.29	3.97	9.49
B[b]	0.67	185–187	+576	811	$C_{42}H_{53}NO_{15}$	62.25	6.55	1.62	29.15	16.54	3.97	9.60
C	0.79	189–191	+602	771	$C_{40}H_{53}NO_{14}$	62.17	6.58	1.88	28.60	16.95	4.01	5.45
D	0.96	167–170	+436	813	$C_{42}H_{55}NO_{15}$	62.16	6.53	1.68	28.95	16.34	...	11.75
E	1.00	...	...	757	$[C_{40}H_{55}NO_{13}]$[c]	...	...	...	...	...	...	...
G	0.65	190–192	+473	785	$C_{40}H_{51}NO_{15}$	61.55	6.64	1.84	30.01	16..11	3.91	5.72

[a] Paper chromatography in benzene–methanol–water (2:1:1), a system originally employed for the streptovaricins in ref 3b. [b] Crystalline. [c] The amount of pure streptovaricin E isolated did not allow elemental analyses. The formula is inferred from the mass spectral molecular weight.

high vacuum to negative chlorine analysis.[6] Results thus obtained agreed with the indicated mass spectral molecular weights, obtained by the direct inlet technique.[7]

The molecular formulas derived, as well as the C-methyl and O-methyl determinations (Table I), all suggest a common carbon skeleton for streptovaricins A–D and G, with varying degrees of oxygenation and acetate functionality, a conclusion in agreement with nmr spectral data.

Since the streptovaricins C-methyl counts (9 or 10) parallel their acetate numbers (1 or 2), a like number of C-methyl groups other than acetate is indicated for all these components and is confirmed by their nmr spectra. However, the chemical shifts and multiplicities of the aliphatic C-methyl groups are not identical for individual components. The nmr spectra of more highly oxygenated streptovaricins (A and G) contain additional O-C-CH_3 singlets (at τ 8.61 and 8.53, respectively), while spectra of less highly oxygenated streptovaricins (B–D) contain additional C-CH-CH_3 methyl doublets (at τ 8.91, 8.80, and 8.90, respectively). The methine protons of the latter groups are allylic, as shown by spin decoupling of the methyl absorption of streptovaricin C. The position of the extra oxygen atom of streptovaricins A and G is located by the observation that they consume 2 moles of sodium periodate, to give prestreptovarone ($C_{29}H_{29}NO_9$), while streptovaricins B and C consume only 1 mole of periodate, without giving prestreptovarone. Prestreptovarone is further oxidized by periodate–osmium tetroxide to streptovarone ($C_{24}H_{23}NO_9$), and this same compound is also formed from treatment with the same reagent of all streptovaricins studied.

The electronic spectra of prestreptovarone and streptovarone are very similar to those of the streptovaricins, identifying them as the central unit of these antibiotics. In the accompanying communication the structures of these oxidative degradation products are assigned.

Acknowledgment. This investigation was supported in part by Public Health Service Research Grants No. AI-01278 and AI-04769 from the National Institute of Allergy and Infectious Diseases. We also thank The Upjohn Co. for generous samples of streptovaricin.

(8) Holder of Union Carbide Co., University of Illinois, and Standard Oil of California Fellowships, and Koppers Co. and U. S. Rubber Co. Summer Fellowships.

(9) Holder of University of Illinois and E. I. du Pont Teaching Fellowships and a National Science Foundation Summer Fellowship.

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Chemistry of the Streptovaricins. II. Streptovarone and Prestreptovarone[1]

Sir:

In the accompanying communication[1] it was reported that oxidation with periodate–osmium tetroxide of all streptovaricins studied (A–C and G) gives streptovarone, while oxidation of streptovaricins A and G with periodate gives prestreptovarone, convertible to streptovarone by periodate–osmium tetroxide oxidation. Both of these orange compounds contain the visible chromophore of the streptovaricins. In the present report their structures are assigned.

Streptovarone, mp 206–208°, optically inactive [$C_{24}H_{23}NO_9$. *Anal.* Found: C, 61.16; H, 5.21; N, 2.96; C-CH_3, 17.03; O-Ac, 9.41; mol wt, 469 (mass spectroscopy)], is hydrolyzed at room temperature by 4 *N* methanolic hydrochloric acid to dapmavarone, mp 194–197° [$C_{18}H_{16}O_7$. *Anal.* Found: C, 62.56; H, 5.09; C-CH_3, 16.85; mol wt, 344 (mass spectroscopy)], which in turn is oxidized by 0.6% hydrogen peroxide in 0.8% sodium hydroxide at room temperature to 2-methyl-4-oxo-2-pentenoic acid (I), identified by comparison with a synthetic sample,[2] and 2,5,6,8-tetrahydroxy-3,7-dimethylnaphthoquinone (IIa). The red quinone IIa, sublimes at 235° [$C_{12}H_{10}O_6$. *Anal.* Found: C, 57.51; H, 4.03; C-CH_3, 11.47; mol wt, 250 (mass spectroscopy)], was identified as a quinone by its reversible reduction with basic sodium hydrosulfite to a *leuco* derivative, as a tetrahydroxynaphthoquinone by comparison of the ultraviolet spectrum of its 2,6-dimethyl ether (IIb), formed from reaction of the more acidic hydroxyl groups of IIa with diazomethane,

(6) We are indebted to Mr. J. Nemeth for special efforts in microanalyses.

(7) Mass spectra were obtained on an Atlas CH4 mass spectrometer, employing a TO4 ion source and vacuum lock.

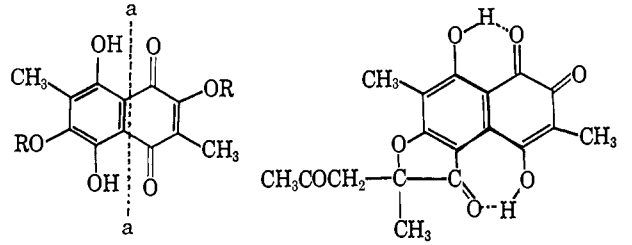
(1) Paper I in this series: K. L. Rinehart, Jr., P. K. Martin, and C. E. Coverdale, *J. Am. Chem. Soc.*, **88**, 3149 (1966).

(2) C. Armengaud, G. Wermuth, and J. Schreiber, *Compt. Rend.*, **254**, 2181 (1962).

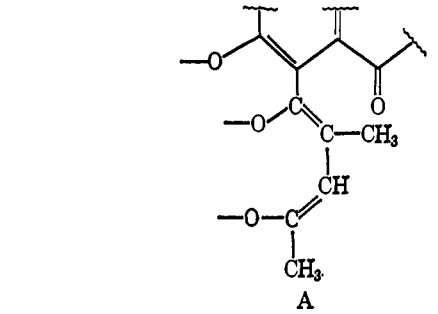
with that of the known 2,6-dimethoxy-5,8-dihydroxynaphthoquinone,[3] and by the nmr spectrum ($CDCl_3$) of IIb, which contains both Ar–CH_3 groups at τ 7.87 (eliminating *peri*-methyl groups from consideration),[4] both O–CH_3 groups at τ 5.95, and *both* O–H protons at τ −3.10 (eliminating the alternative 3,6-dimethyl-2,5,7,8-tetrahydroxynaphthoquinone possibility).[3] The alternative formulation of a 2,3-dimethyl-5,6,7,8-tetrahydroxynaphthoquinone is eliminated by the mass spectrum of IIa, which shows successive fragmentations from one of the two equivalent rings to give, ultimately, a peak at *m/e* 138 corresponding to fragmentation along line a · · · · a.[5]

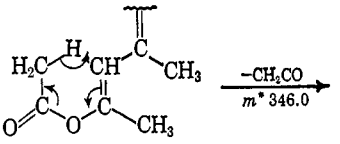
Comparison of the molecular formulas of I and IIa with that of dapmavarone and consideration of their mode of formation from dapmavarone (Dakin reaction)[6] indicates the latter compound to be an acyl-3,7-dimethylnaphthoquinone, most reasonably an acyltrihydroxynaphthoquinone. However, the nmr spectrum of dapmavarone contains peaks at τ 6.68 (2 H, singlet) and 8.51 (3 H, singlet) which must be due to the unit $CH_3COCH_2C(CH_3)(CO–)O–$. Therefore, C-2 of the pentenoic acid unit is linked *via* an ether bridge to the aromatic nucleus, requiring attachment of the acyl group at the naphthoquinone C-5 or C-6 position.[7] A decision in favor of C-5 is rendered by the position of the aromatic ketone's carbonyl absorption in the infrared spectrum of dapmavarone—below 1635 cm^{-1}, indicating hydrogen bonding from a proximate hydroxyl. Dapmavarone is then assigned structure III. In accord with its formulation as an *o*-quinone are the infrared carbonyl absorption noted as well as its purple color and its complex ultraviolet spectrum.

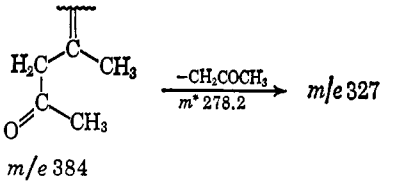
Conversion of streptovarone ($C_{24}H_{23}NO_9$) to III ($C_{18}H_{16}O_6$) is accompanied by loss ($-C_2H_2O$) of an enol acetate [infrared bands at 1770 and 1200 cm^{-1}, nmr singlet at τ 7.80 (3 H)], by loss ($-C_3H_3NO$) of a pyruvamide group [nmr singlet at τ 7.46 (3 H), identified, after hydrolysis, as methyl pyruvate dinitrophenylhydrazone], by loss (−C) of a methylenedioxy group [τ 4.5 (2 H), identified, after hydrolysis, as the dimedone derivative of formaldehyde], and by loss ($-H_2$) of 2 hydrogen atoms through autoxidation.

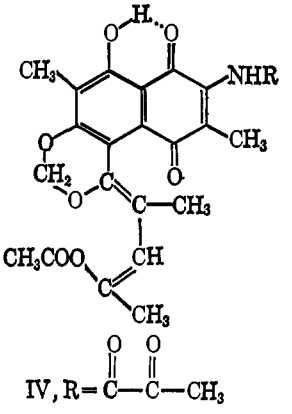


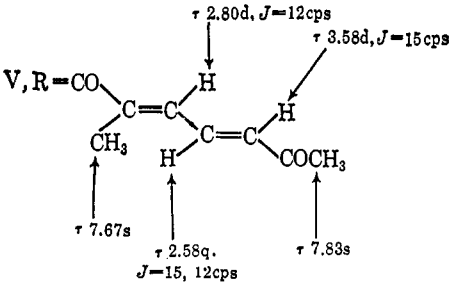
Streptovarone is a naphthoquinone (by its color, reversible reduction, and conversion to dapmavarone) with a *peri*-hydroxyl group, identified by comparison with corresponding properties of juglone (5-hydroxynaphthoquinone) of its positive boric acid–acetic anhydride test,[8] its proton at low field (τ −4.15), and its high pK_a, 10.3 (50% ethanol). The facile loss of pyruvamide in both acid and base[9] allows its placement at C-2.[10,11] The remaining groups (methylene and acetyl) must be attached to the oxygen atoms of the











(3) C. W. J. Chang, R. E. Moore, and P. J. Scheuer, *J. Am. Chem. Soc.*, **86**, 2959 (1964).

(4) (a) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and G. A. Pier, "Varian N. M. R. Spectra Catalog," Vol. 1, The National Press, Palo Alto, Calif., 1963, Spectrum 650; (b) J. Comin, O. Goncalves de Lima, H. N. Grant, L. M. Jackman, W. Keller-Schierlein, and V. Prelog, *Helv. Chim. Acta*, **46**, 409 (1963).

(5) The mass spectrum of the model compound phthiocol (2-hydroxymethylnaphthoquinone) contains a corresponding peak at *m/e* 76; the 2,3-dimethyl alternative to IIa should give a peak at *m/e* 134.

(6) H. D. Dakin, "Organic Syntheses," Coll. Vol. I, H. Gilman and A. H. Blatt, Ed., 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1941, p 149.

(7) The presence of only two free hydroxyl groups in dapmavarone is confirmed by methylation to give two di-O-methyldapmavarones, *ortho* and *para* isomers.

(8) O. Dimroth and T. Faust, *Ber.*, **54**, 3020 (1921).

(9) P. K. Martin, Ph.D. Thesis, University of Illinois, 1965.

(10) V. Prelog, *Pure Appl. Chem.*, 7, 551 (1963).

(11) B. R. Baker, T. H. Davis, L. McElroy, and G. H. Carlson, *J. Am. Chem. Soc.*, **64**, 1096 (1942).

partial structure A. In this unit the olefinic proton is found at τ 3.45 and the methyl groups at τ 7.85 and 8.06. A decision in favor of placing the acetyl group at the terminal oxygen of the unit A is reached from consideration of the mass spectrum of streptovarone, which shows the fragmentation sequence indicated. The structure of streptovarone is then assigned as IV.

The nmr spectrum of prestreptovarone, mp 194–197° [$C_{29}H_{29}NO_9$. *Anal.* Found: C, 65.07; H, 5.55; N, 2.65; mol wt, 535 (mass spectroscopy)], indicates that it has structure V and, in particular, that it differs from streptovarone in having the amide side chain shown in V in place of the pyruvamide group.

Future reports in this series will deal with the side chains and structures of the individual streptovaricin components, as well as their obvious relationship to rifamycin S.[9]

Acknowledgment. This investigation was supported in part by Public Health Service Research Grants No. AI-01278 and AI-04769 from the National Institute of Allergy and Infectious Diseases. We also thank The Upjohn Co. for generous samples of streptovaricin.

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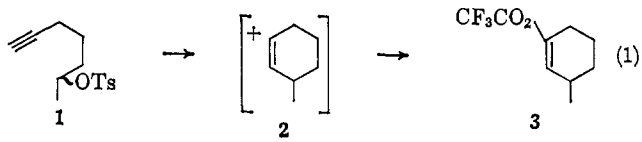
Triple Bond Participation and a Bent Vinyl Cation in the Trifluoroacetolysis of 6-Heptyn-2-yl *p*-Toluenesulfonate[1]

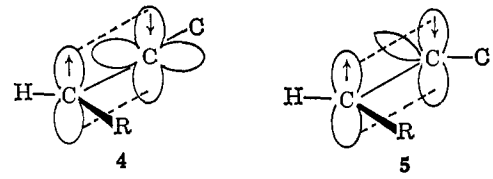
Sir:

We wish to report that the solvolysis of 6-heptyn-2-yl tosylate (**1**) in trifluoroacetic acid (eq 1) occurs with triple bond participation to give predominantly the cyclic product 3-methylcyclohexenyl trifluoroacetate (**3**).[2] In addition to the synthetic interest attached to



1 2 3 (1)

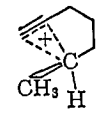
this new cyclization reaction there are novel mechanistic implications concerning the hybridization of the cationic intermediate or transition state. In general, vinyl cations obtained by addition of a positive R group to a terminal triple bond might retain the hybridization and linear geometry of the alkyne at C-2 (cation **4**, below)[3] or might undergo rehybridization to sp^2 at



4 5

C-2 to give a bent cation, **5**. The ion **4** is favored, based on the considerations of maximum bond strength and maximum s character for the occupied orbitals which also lead to the familiar prediction of a planar structure for carbonium ions of the type R_3C^+.

The most striking evidence for the planar structure of ordinary carbonium ions is the unreactivity of bridgehead leaving groups, attributable to restraint upon the achievement of planarity. Clearly the ion **2** is constrained to be nonlinear; yet it seems to be formed readily in competition with ordinary substitution and elimination reactions available to **1**. Furthermore the cyclization appears to occur during the rate-determining step, as indicated by the rate constant for solvolysis of **1** at 25.0°, 26.6×10^{-5} sec^{-1}, which is as large as that for solvolysis of 2-heptyl tosylate (24.9×10^{-5}),[4] despite the expected 17.5-fold rate-retarding inductive effect of the triple bond.[5] The postulation of a bridged transition state or intermediate **6** may avoid the neces-



6

sity for bending at the cationic carbon in the rate-determining step, but, in view of the ultimate formation of **3**, a bridged ion postulate merely defers the formation of a transition state resembling **2**.

The apparent formation of the unfavored bent vinyl cation or a similar species in our study is, as an afterthought, not difficult to rationalize. The energetically favored formation of a new C–C σ bond in **2** from a C–C π bond in **1** can be invoked to supply the "driving force." The discovery of a reaction which proceeds *via* the unfavored type of vinyl cation, however, opens the way to many interesting studies, including comparison with alkene cyclizations *where there is no comparable unfavorable geometrical constraint*, comparison of the ease of formation of various ring sizes having *differing extents* of bending in the transition state,[6] and solvolyses in solvents of differing nucleophilicities which may compete to differing extents

(1) This work was supported by the Petroleum Research Fund of the American Chemical Society through Grant No. 790A-4.

(2) From **1** (6.0 g, 0.022 mole), which was allowed to react for 10 hr at 25° in 100 ml of trifluoroacetic acid containing 0.025 mole of sodium trifluoroacetate, 2.8 g of distillate was obtained (60% calculated as **3**). Gas chromatographic analysis of the distillate indicated the presence of 9% 3-methylcyclohexanone, 3% 6-heptyn-2-yl trifluoroacetate, and ~4% incompletely resolved peak, possibly 5-methylcyclohexenyl trifluoroacetate, in addition to **3**. A 150-ft diethylene glycol succinate (LAC) capillary column at 55° was used. Areas based on the uncorrected flame ionization detector response are reported here. Identification of **3** is based on the C and H analyses, infrared and nmr data, and hydrolysis to 3-methylcyclohexanone. In another experiment an 80.5% yield of the crude 2,4-dinitrophenylhydrazone of 3-methylcyclohexanone was obtained, based on the weight of tosylate **1** employed. Under the same conditions authentic 3-methylcyclohexanone gave a 90% yield.

(3) See D. S. Noyce, M. A. Matesich, O. P., M. D. Schiavelli, and P. E. Peterson, *J. Am. Chem. Soc.*, **87**, 2295 (1965), for a reaction proposed to involve an ion of type **4** and for leading references to recent studies of vinyl cations.

(4) P. E. Peterson, R. E. Kelley, Jr., R. Belloli, and K. A. Sipp, *ibid.*, **87**, 5169 (1965).

(5) Our estimate is based on the σ^* value of 1.3 previously used by M. M. Kreevoy, *ibid.*, **81**, 1608 (1959). Using an attenuation factor of 0.65 per methylene group to obtain a σ value for the H—C≡C—CH_2 group in *H—C≡C—CH₂—*$CH_2CH_2C^+HCH_3$, applying the relationship $\sigma 1 = 0.45\sigma^*$, and using a $\rho 1$ value of 3.27 applicable to solvolysis of substituted tosylates proceeding *via* the ion *X—CH₂—*$CH_2CH_2C^+HCH_3$ (P.E. Peterson and D. M. Chevli, unpublished results) gives the factor 17.5. Although the magnitude of this estimate is not very reliable, a very appreciable inductive effect of the remote triple bond may be predicted with confidence, based on our previous extensive studies of the remarkably large substituent effects found in trifluoroacetic acid. *Cf.* P. E. Peterson, C. Casey, E. V. P. Tao, A. Agtarap, and G. Thompson, *ibid.*, **87**, 5163 (1965).

(6) Formolysis of a 3-pentyn-1-yl sulfonate to give products possibly arising *via* triple bond participation has very recently been reported by M. Hanack, J. Haeffner, and I. Herterich, *Tetrahedron Letters*, 875 (1965).