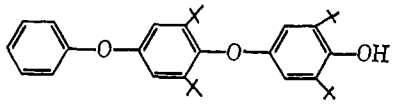
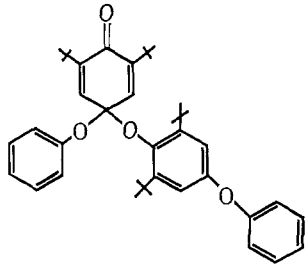
When the red solution of the radical II is reduced with acidic iodide solution and the liberated iodine titrated with sodium thiosulfate solution, the correct titer is obtained for the amount of radical corresponding to the original amount of I. However, the products of this reduction are phenol, 4-phenoxy-2,6-di-*t*-butylphenol, and a trimer to which the structure IV is assigned. The amount of these materials obtained is erratic but the usual ratio is 1:2:1.



IV

The trimer IV is thought to arise from iodide–acid reduction of the quinone ketal V which probably exists in equilibrium with the radical II. The quinone

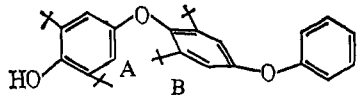


V

ketal V has not yet been isolated.

The trimer IV is difficult to separate from the phenol I. The samples obtained have been collected from the vapor phase chromatograph. Recrystallization from hexane gave white needles, mp 141°. *Anal.* Calcd for $C_{34}H_{46}O_3$: C, 81.3; H, 9.2; mol wt, 502, Found: C, 81.0; H, 9.3; mol wt, 472. The infrared spectrum of the trimer IV is almost identical with that of the phenol I. The chief differences lie in the intensities of various peaks, as might be expected. The nuclear magnetic resonance spectrum offers further support of the structure.

The *t*-butyl groups of the phenol I have a single sharp resonance at τ 8.58 in chloroform. The trimer IV has a sharp resonance at τ 8.80 and a broad resonance at τ 8.60. The peak at higher field is ascribed to the *t*-



IV

butyl groups on the B ring. The broad peak is ascribed to the two *t*-butyl groups on the A ring. One group is under the influence of the B ring and the other is not, as illustrated in IV. The hindrance of the *t*-butyl groups on the B ring prevents the A ring from rotating and prevents the *t*-butyls on the A ring from being equivalent. Preliminary examination of the temperature dependence of the nmr spectrum is in agreement with this interpretation.

In summary, it has been found that there is no evidence for any electron density being able to cross the diaryl ether linkage in the radical 4-phenoxy-2,6-di-*t*-butylphenoxyl (II). Additionally, a 2,6-di-*t*-butylphenyl ether has been prepared which exhibits a marked hindrance to rotation about the aryl ether bond.

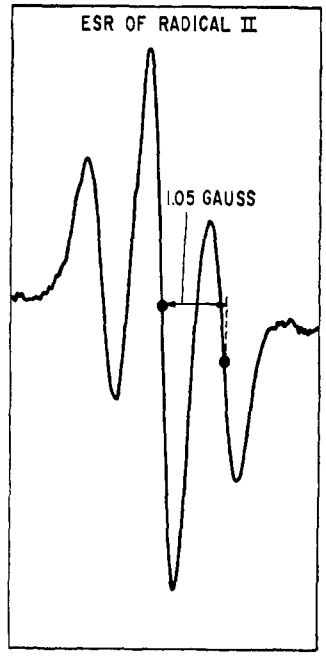


Figure 1.

Acknowledgment. The author wishes to thank Dr. John Lupinski for taking the esr spectrum and Dr. John Bush for taking and helping to interpret the nmr spectra.

Donald A. Bolon
General Electric Research and Development Center
Schenectady, New York
Received April 1, 1966

Chemistry of the Streptovaricins. I. Characterization of Streptovaricins A, B, C, D, E, and G

Sir:

Streptovaricin,[1] an orange antibiotic showing marked *in vivo* activity against *Mycobacterium tuberculosis*,[2] has been shown to be a complex of at least five compounds, partially separable by countercurrent distribution[3] and by partition chromatography.[3b,4] The present report describes the properties of the more abundant components, separated by countercurrent distribution and silica gel chromatography, while the accompanying report[5] assigns the structure of the central chromophore of the antibiotics.

Physical and analytical properties of streptovaricins A–E and G are summarized in Table I. Due to the tendency of the streptovaricins to form strong crystal solvates, meaningful analyses were obtained only after precipitating the component from a chlorinated solvent, grinding to a fine powder, and drying under

(1) (a) P. Siminoff, R. M. Smith, W. T. Sokolski, and G. M. Savage, *Am. Rev. Tuberc. Pulmonary Diseases*, 75, 576 (1957). (b) The tradename of The Upjohn Co. for streptovaricin is Dalacin.

(2) L. E. Rhuland, K. F. Stern, and H. R. Reames, *Am. Rev. Tuberc. Pulmonary Diseases*, 75, 588 (1957).

(3) (a) G. B. Whitfield, E. C. Olson, R. R. Herr, J. A. Fox, M. E. Bergy, and G. A. Boyack, *ibid.*, 75, 584 (1957); (b) R. R. Herr, G. B. Whitfield, G. A. Boyack, B. Bannister, J. A. Fox, E. C. Olson, and M. E. Bergy, 134th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1958; *cf.* Abstracts, p 21-O.

(4) W. T. Sokolski, N. J. Eilers, and P. Siminoff, *Antibiot. Ann.*, 119 (1957–1958).

(5) K. L. Rinehart, Jr., C. E. Coverdale, and P. K. Martin, *J. Am. Chem. Soc.*, 88, 3150 (1966).

Table I. Properties of Streptovaricin

Component	R_f[a]	Mp, °C	$[\alpha]_D$ ($CHCl_3$), deg	Mol wt (mass spec)	Molecular formula	Found C	H	N	O	C-CH_3 (Kuhn-Roth)	O-CH_3	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.

Kenneth L. Rinehart, Jr., Preston K. Martin[8]
Charles E. Coverdale[9]
Department of Chemistry and Chemical Engineering
University of Illinois, Urbana, Illinois

Received May 7, 1966

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).