TABLE I

DESCRIPTION OF E.S.R. SPECTRA OF SOME RADICAL-ANIONS IN DIMETHYL SULFOXIDE(80)–*t*-BUTYL ALCOHOL(20)

System	No. of observed lines	Observed line width (gauss)[a]	Hyperfine structure
	17	29.3	A_N = 5.2, A_H = 1.5 gauss[b]
9,9′-Bifluorene–Δ-9,9′-bifluorene	19	13.4	Main quintet
Hydroazobenzene–azobenzene	41	38.2	Complex
Furoin–furil[c]	27	9.3	Main quintet
Fluorene-9-ol–fluoren-9-one	25	12.6	Main quintet
Xanthen-9-ol–xanthen-9-one	15	17.8	5 sets of 3
$Ph_2CHCH{=}CHCHPh_2$ + $Ph_2C{=}CHCH{=}CPh_2$	28	10.9	Complex

[a] Distance from first resolved maximum to last resolved minimum measured by comparison with *p*-benzosemiquinone (E. W. Stone and A. H. Maki, *J. Chem. Phys.*, **36**, 1944 (1962)). [b] Two equivalent nitrogen atoms and four equivalent hydrogen atoms. [c] In the presence of potassium hydroxide in ethanol.

However, for 1,1,2,2-tetraphenylethane and 1,4-dihydronaphthalene (a) rather than (b) must be occurring since under the reaction conditions electron transfer between the dihydro and unsaturated molecules cannot be observed.

Electron transfer may often involve the formation of an intermediate dimeric species.[9b]

$$\pi^- + \pi \rightleftharpoons {}^-\pi - \pi^- \rightleftharpoons 2\pi\cdot^-$$

Subjecting compounds of the type H–π–π–H to highly basic conditions often leads to the radical anions. In the case of the pinacol of fluoren-9-one in pyridine(80%)–*t*-butyl alcohol (20%) in the presence of excess potassium *t*-butoxide, the fluorenyl ketyl is produced in high yield.[12]

Our results suggest a widespread occurrence of radical-anions as intermediates in reactions occurring in basic solution. In the future we will report on our studies utilizing unsaturated compounds in the presence of good monoanion donors in the carbanion, nitranion, and mercaptide ion categories.

(12) The cleavage by base of pinacols to ketyls is well known. See W. E. Bachmann, *ibid.*, **55**, 355 (1933); W. Schlenk and A. Thal, *Ber.*, **46**, 2840 (1913).

(13) Alfred P. Sloan Foundation Fellow.

(14) National Institutes of Health Predoctoral Fellow, 1962–1963.

DEPARTMENT OF CHEMISTRY
IOWA STATE UNIVERSITY
AMES, IOWA

GLEN A. RUSSELL[13]
EDWARD G. JANZEN
E. THOMAS STROM[14]

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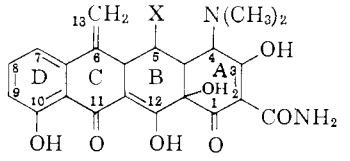
6-METHYLENETETRACYCLINES. II. MERCAPTAN ADDUCTS

Sir:

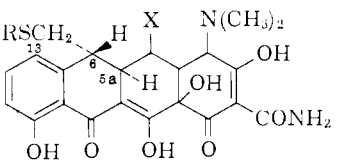
6-Methylenetetracyclines[1] (**1**) have been found to react with mercaptans to produce adducts of structure **2**. The reaction is general, and the



1

1a, X = H
1b, X = OH

(1) R. K. Blackwood, J. J. Beereboom, H. H. Rennhard, M. Schach von Wittenau and C. R. Stephens, *J. Am. Chem. Soc.*, **83**, 2773 (1961).



2

2a, R = C_6H_5, X = H
2b, R = C_6H_5, X = OH
2c, R = $C_6H_5CH_2$, X = H
2d, R = $C_6H_5CH_2$, X = OH
2e, R = $HOCH_2CH_2$, X = OH
2f, R = CH_3CO, X = H
2g, R = CH_3CO, X = OH

sulfides themselves are reactive intermediates. Thus a new route is provided for broad structural variation at a position amply demonstrated[1,5,6] to be outside the area of the tetracycline molecule intimately associated with antimicrobial activity.[2]

Exemplary of the 13-alkyl, aryl, aralkyl and acyl-α-6-deoxytetracyclines prepared are compounds **2a–2g**.[3] (Table I). The reaction is a typical free radical addition of mercaptan to olefinic double bond,[4] being catalyzed by oxygen, peroxides, or, as preferred in practice, 2,2′-azo-bis-(2-methylpropionitrile). Solvent is not critical, the mercaptan itself being used where suitable. That the products arise from addition across the double bond is evident from analyses, ultraviolet spectra (there is no longer the extended BCD-ring chromophore of the methylenetetracyclines[1]) and acid stability which is typical of the 6-deoxytetracyclines.[5,6] That the direction of addition is anti-Markownikow is shown by C-methyl analyses and n.m.r. spectra, which indicate lack of C-methyl groups. Stereochemistry at C.6 is assigned on the basis of Raney nickel desulfurization to the α-6-deoxytetracyclines (**3**),[6] for which independent stereochemical arguments have been presented.[6,7]

(2) Biological aspects of the sulfur derivatives will be reported.

(3) Other mercaptans successfully employed include R = CH_3, *n*-C_4H_9, $HOOCCH_2$, $C_2H_5OOCCH_2$, $H_2NCH_2CH_2$ and $HOOCCH(NH_2)CH_2$.

(4) See C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 313–326, for a discussion of this reaction.

(5) (a) C. R. Stephens, K. Murai, H. H. Rennhard, L. H. Conover and K. J. Brunings, *J. Am. Chem. Soc.*, **80**, 5324 (1958); (b) J. R. D. McCormick, E. R. Jensen, P. A. Miller and A. P. Doerschuk, *ibid.*, **82**, 3381 (1960).

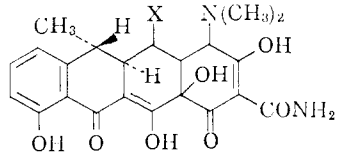
(6) M. Schach von Wittenau, J. J. Beereboom, R. K. Blackwood and C. R. Stephens, *ibid.*, **84**, 2645 (1962).

(7) H. Muxfeldt, *Angew. Chem. Internat. Edit.*, **1**, 372 (1962).

TABLE I

	α-6-Deoxytetracycline	λ_{max}^{MeOH} 0.01 *N* HCl, mμ	Log ε	Composition	C	H	N	S
2a	13-Phenylmercapto	256 356	4.41 4.13	$C_{28}H_{28}N_2O_7S \cdot C_7H_8O_3S$[a]	58.8	5.2	3.7	9.4
2b	13-Phenylmercapto-5-hydroxy	259 347	4.41 4.07	$C_{28}H_{28}N_2O_8S$	61.0	5.1	4.7	5.8
2c	13-Benzylmercapto	267 358	4.27 4.14	$C_{29}H_{30}N_2O_7S \cdot C_7H_8O_3S$[a]	59.8	5.5	3.5	8.9
2d	13-Benzylmercapto-5-hydroxy	266 348	4.30 4.06	$C_{29}H_{30}N_2O_8S$	61.7	5.4	4.7	6.0
2e	13-(2-Hydroxyethylmercapto)-5-hydroxy	264 347	4.31 4.06	$C_{24}H_{28}N_2O_9S \cdot C_7H_8O_3S$[a] $\cdot H_2O$[b]	52.5	5.2	3.8	9.0
2f	13-Acetylmercapto[g]	268 355	4.30 4.16	$C_{24}H_{26}N_2O_8S \cdot C_7H_8O_3S$[a]	55.0	5.0	4.0	9.3
2g	13-Acetylmercapto-5-hydroxy[h]	268 317 348	4.30 4.06 4.11	$C_{24}H_{26}N_2O_9S \cdot C_7H_8O_6S$[c]	51.0	4.5	3.5	8.6
4a	13-Phenylmercapto S-oxide	257 355	4.32 4.17	$C_{28}H_{28}N_2O_8S \cdot C_7H_8O_3S$[a]	58.5	4.9	3.7	9.0
4b	13-Benzylmercapto S-oxide	267 352	4.28 4.17	$C_{29}H_{30}N_2O_8S \cdot C_7H_8O_3S$[a]	58.8	5.1	3.5	8.4
5	13-Mercapto-5-hydroxy	267 317 350	4.29 4.03 4.11	$C_{22}H_{24}N_2O_8S \cdot C_7H_6O_6S \cdot 2H_2O$[d]	47.3	5.0	3.7	8.7
6	11a,13-Epithio[i]	262 346	4.30 3.70	$C_{22}H_{22}N_2O_7S \cdot HCl$[e]	53.1	4.5	5.2	6.6
7	7,13-Epithio[j]	251 337 420	4.38 4.08 3.64	$C_{22}H_{22}N_2O_7S \cdot HCl \cdot H_2O$[f]	51.4	4.9	5.2	6.2

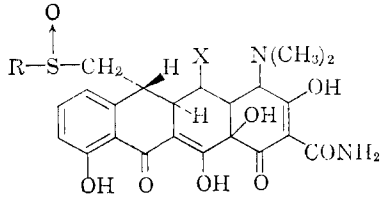
[a] *p*-Toluenesulfonic acid. [b] O, 29.4; H_2O, 2.3. [c] 5-Sulfosalicylic acid. [d] H_2O, 3.8. [e] Cl^-, 6.9. [f] Cl^-, 7.1; H_2O, 3.4. [g] λ_{max}^{KBr} 5.93 μ. [h] λ_{max}^{KBr} 5.95 μ. [i] λ_{max}^{KBr} 5.75 μ. [j] $\lambda_{max}^{MeOH-0.01\ N\ NaOH}$ 248, 392 mμ, log ε 4.18, 4.40.



3

3a, X = H
3b, X = OH

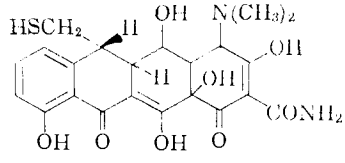
The tetracycline thio compounds undergo reactions typical of sulfur chemistry. Thus, under mild conditions (slight excess of 30% aq. HOOH in CH_3OH) the sulfides are oxidized to the corresponding sulfoxides (*e.g.*, **4a**, **4b**) (Table I). Hydrolysis of acyl compounds is typified by the conversion,



4

4a, X = H, R = C_6H_5
4b, X = H, R = $C_6H_5CH_2$

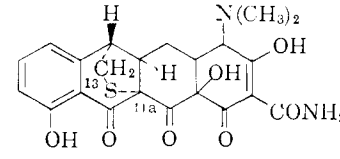
in concentrated hydrochloric acid, of 13-acetyl mercapto-α-6-deoxytetracycline (**2g**) into the mercaptan (**5**). The latter is characterized by its analysis and typical mercaptan color reaction with



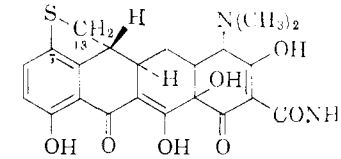
5

sodium nitroprusside.

A reaction not so typical of sulfur chemistry is the conversion, in concentrated hydrochloric acid, of 13-benzylmercapto-α-6-deoxytetracycline S-oxide (**4b**) into two compounds for which we propose structures **6** and **7**. The first of these, which we call 11a,13-epithio-α-6-deoxytetracycline, gives an analysis which clearly shows loss of the benzyl group. It has the typical spectral properties of 11a-blocked tetracycline derivatives retaining the

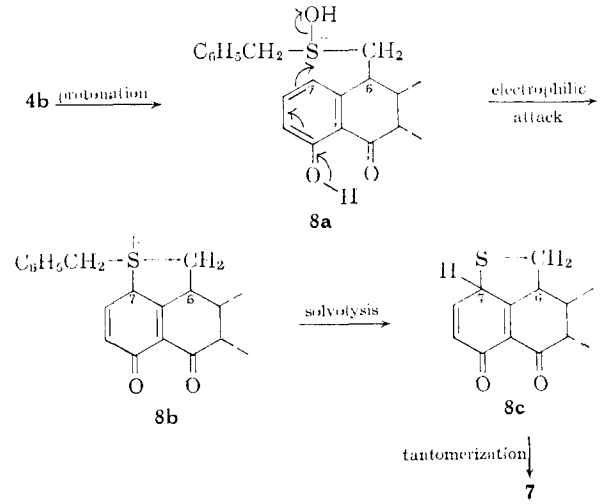


6



7

12-carbonyl. The second compound (**7**), which we call 7,13-epithio-α-6-deoxytetracycline, is similarly indicated to have lost the benzyl group. It shows a negative sodium nitroprusside test, exhibits typical broad spectrum, tetracycline like, antimicrobial activity,[8] and has a typical tetracycline type ultraviolet spectrum in methanolic sodium hydroxide, but a modified one in methanolic hydrochloric acid where the long wave length maximum (associated with the BCD-ring chromophore) is dramatically split.[9] The following mechanism



(8) A. R. English, private communication.

(9) A modified tautomeric form in acid, such as **8c**, which would relieve strain in the 5-membered sulfur ring, could account for these unusual spectral properties.

is proposed for the formation of these compounds Formation of **6** would involve electrophilic attack at the 11a- rather than the 7-position.

Acknowledgment.—The authors are indebted to Professor E. J. Corey and to Professor G. Büchi for stimulating discussions concerning this work.

MEDICAL RESEARCH LABORATORIES
CHAS. PFIZER AND CO., INC. ROBERT K. BLACKWOOD
GROTON, CONNECTICUT CHARLES R. STEPHENS

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GENERAL BASE-GENERAL ACID-CATALYSIS OF ESTER SOLVOLYSIS[1]

Sir:

Facilitation of the alkaline solvolysis of an alicyclic axial acetate by a hydroxyl group bearing a 1,3-diaxial juxtaposition to the acetate is a well-established fact.[2-5] Evidence is presented herewith for the argument that the solvolysis of 1,3-diaxial hydroxyacetates is subject to general base catalysis and that the reaction is therefore an instance of concerted general base-general acid-catalysis of ester solvolysis. Furthermore, in suitably constituted molecules, the solvolysis may be subject to general base and *bifunctional intramolecular* general acid-catalysis.[6]

Acetate esters were methanolyzed in solutions prepared by dissolving each compound in chloroform (10% of the total volume), adding buffer, and diluting to the required volume with 10% aqueous methanol. The rate of production of methyl acetate, the solvolysis product, was determined by direct gas chromatographic analysis of the reaction mixture, using a Wilkens Hy-Fi A600 Gas Chromatograph with a hydrogen flame detector.[7]

RATES OF ESTER SOLVOLYSIS AT IONIC STRENGTH 0.1 AND 3:1 TRIETHYLAMINE:TRIETHYLAMINE ACETATE BUFFER (0.21 *M*) AT 40°

Compound	k obs. (sec.$^{-1}$) (pseudo-first-order)	Ratio of rates
Coprostanol acetate (I)	3.0×10^{-8}	1
Coprostane-3β,5β-diol 3-monoacetate (II)	8.9×10^{-6}	300
Strophanthidin 3-acetate (III)	3.6×10^{-5}	1200
Strophanthidol 3-acetate (IV)	1.4×10^{-5}	470
Strophanthidinic acid methyl ester 3-acetate (V)	9.7×10^{-6}	320

(1) This is part VI of a series entitled "Intramolecular Catalysis"; part V, S. M. Kupchan and M. F. Saettone, *Tetrahedron*, in press.

(2) S. M. Kupchan and W. S. Johnson, *J. Am. Chem. Soc.*, **78**, 3864 (1956).

(3) H. B. Henbest and B. J. Lovell, *Chemistry and Industry*, 278 (1956); *J. Chem. Soc.*, 1965 (1957).

(4) S. M. Kupchan, W. S. Johnson and S. Rajagopalan, *Tetrahedron*, **7**, 47 (1959).

(5) S. M. Kupchan and C. R. Narayanan, *J. Am. Chem. Soc.*, **81**, 1913 (1959).

(6) *Cf.* the discussions in (a) S. M. Kupchan, P. Slade, R. J. Young and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962), and (b) B. M. Anderson, E. H. Cordes and W. P. Jencks, *J. Biol. Chem.*, **236**, 455 (1961).

(7) Identification of peaks and calibration of areas were carried out by injecting standard solutions of methyl acetate in the same solvent system. The chromatographic column consisted of 12.6 cm. of 10% Nujol on Fluoropak 80 and 1.5 m. of 20% glycerol on 60/80 mesh Gaschrom A. The column temperature was maintained at 50–55° and the over-all accuracy of the analytical procedure is estimated at ±5%.

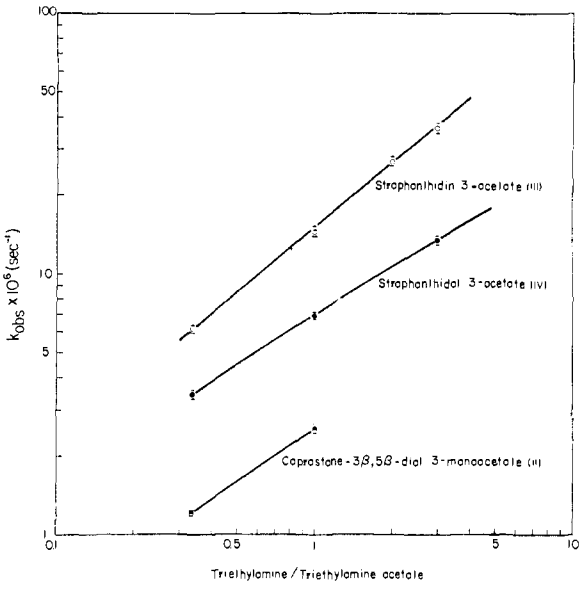
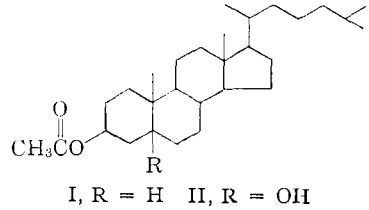
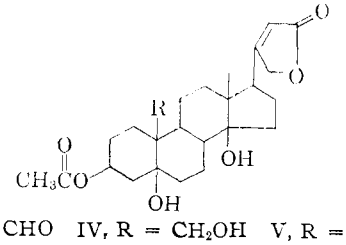


Fig. 1.—Plots of the observed pseudo-first-order rate constants (k_{obs}) for solvolysis at 40° (μ = 0.10 *M*) *vs.* buffer ratio.

The methanolysis reaction is base-catalyzed; a solution of II in the solvents described above in the absence of base shows no perceptible change for at least two months. The buffer ratio–rate profile (Fig. 1) confirmed the postulated basic catalysis of the pseudo-first-order solvolysis of II, III and IV. The basic catalysis of the solvolysis could have involved either general base-catalysis or specific base nucleophilic catalysis. The classic experiment for distinguishing general base catalysis from specific base nucleophilic catalysis involves determination of the reaction rate in a series of buffers of constant buffer ratio but varying absolute buffer concentration, and at constant ionic strength.[8,9] Figure 2 shows the variation of ob-



I, R = H II, R = OH



III, R = CHO IV, R = CH_2OH V, R = $COOCH_3$

served rates of methanolysis of coprostane-3β,5β-diol 3-monoacetate (II) and strophanthidin 3-acetate (III) with increasing concentrations of triethylamine–triethylamine acetate at constant

(8) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960).

(9) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).