fied by the fact that both the absolute and relative absorption intensities vary with time and with the concentration of sulfur and sulfur trioxide. For the 30% oleum solutions mentioned above, the intensity ratio of (II)/(I) increased with time and with decreasing concentration of sulfur. Similar two-line spectra were displayed by a mixture of sulfur, anhydrous aluminum chloride, and carbon tetrachloride.

The present data are insufficient to permit a conclusive interpretation of the behavior of sulfur in oleum but, if it is assumed that all the non-solvent sulfur is contained in paramagnetic molecules, then the data indicates that species (I) contains more sulfur than species (II). The similarity of the g-values for the paramagnetic resonance spectra of ultramarine (2.028),[5] liquid sulfur (2.024),[6] and the system S_8–SO_3–H_2O is discussed elsewhere.[6]

(5) D. M. Gardner and G. K. Fraenkel, THIS JOURNAL, **77**, 6399 (1955).

(6) D. M. Gardner and G. K. Fraenkel, *ibid.*, **78**, 3279 (1956).

DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY DONALD M. GARDNER
NEW YORK 27, NEW YORK GEORGE K. FRAENKEL

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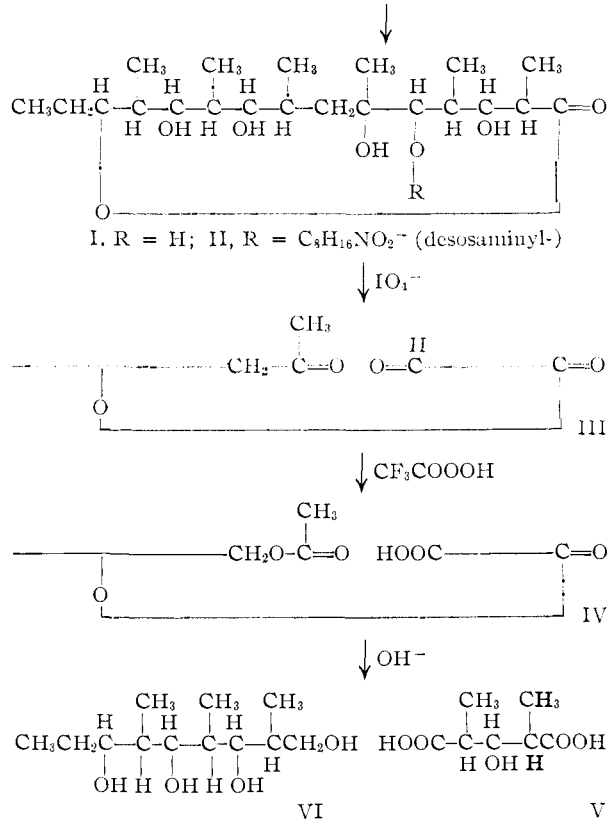
ERYTHROMYCIN. IX.[1] DEGRADATIVE STUDIES OF ERYTHROMYCIN B.

Sir:

A previous report[2] from this laboratory described the isolation and characterization of a second crystalline antibiotic, erythromycin B, from a culture of *Streptomyces erythreus*. The molecular formula $C_{37}N_{71}NO_{12}$ has been proposed,[3] and the presence of the sugars, desosamine[4] and cladinose,[5] has been demonstrated.[3] Erythromycin B and erythromycin[6] have very similar properties,[2,3,6] the principal difference being a greater acid stability of the former.

Degradative studies described below lead to structure I for dihydroerythronolide B,[7] the aglycone of dihydroerythromycin B.

Analytical data of purified erythromycin B, m.p. 198°, are consistent with the molecular formula $C_{37}H_{67}NO_{12}$ [Found: C, 62.09, 62.07; H, 9.46, 9.67; N, 1.99, 1.97; C-CH_3, 14.6; O-CH_3, 4.8; mol. wt., 730 (electrometric titration); pK_a' 8.8[8]], and the infrared (bands at 5.8 μ and at 5.9 μ) and ultraviolet (λ_{max} 289 mμ, ϵ = 36) spectra are consistent with the presence of a ketone and a lactone function. Erythromycin B N-oxide,[9] [Found: C, 60.79, 60.60; H, 9.44, 9.42; N, 1.98; pK_a' 5.4], prepared from the antibiotic and hydrogen peroxide, was stable in the presence of sodium metaperiodate.



Mild acid hydrolysis of erythromycin B N-oxide gave, in addition to cladinose ($C_8H_{16}O_4$), x-O-desosaminyl erythronolide B N-oxide,[7] m.p. 169–173° [Found: C, 60.63; H, 9.39; N, 2.59], also prepared from x-O-desosaminyl erythronolide B,[10] $C_{29}H_{53}NO_9$, m.p. 78–83° [Found: C, 62.26; H, 9.56. N, 2.33; mol. wt., 582; pK_a' 8.3], the product of mild acid hydrolysis of erythromycin B. This N-oxide still contains the ketone function (maximum at 285 mμ, ϵ = 37). It follows that the facile, acid-catalyzed spiro-ketal formation observed with erythromycin[11] does not occur with erythromycin B.

Reduction of erythromycin B with sodium borohydride followed by mild acid hydrolysis of the intermediate dihydroerythromycin B yielded 5(?)-O-desosaminyl dihydroerythronolide B (II), $C_{29}H_{55}NO_9$, m.p. 207–208° [Found: C, 62.21; H, 9.76; N, 2.62; C-CH_3, 18.0; mol. wt., 548; pK_a' 8.2; $\alpha^{25}D$ −1.7° (c, 1 in methanol)]. This lactone (II) formed the corresponding N-oxide,[9] m.p. 170–173° [Found: C, 59.45; H, 9.36; N, 2.46; pK_a' 5.2], which consumed no periodate.

Hydrolysis of II with 1 *N* hydrochloric acid in a two phase system with toluene gave, in addition to

(1) Previous paper in this series: Erythromycin. VIII, THIS JOURNAL, **78**, 6396 (1956).

(2) C. W. Pettinga, W. M. Stark and F. R. Van Abeele, *ibid.*, **76**, 570 (1954).

(3) R. K. Clark, Jr., and M. Taterka, *Antibiotics and Chemotherapy*, **5**, 206 (1955).

(4) R. K. Clark, Jr., *ibid.*, **3**, 663 (1953).

(5) P. F. Wiley and Ollidene Weaver, THIS JOURNAL, **78**, 808 (1956).

(6) J. M. McGuire, R. L. Bunch, R. C. Anderson, H. E. Boaz, E. H. Flynn, H. M. Powell and J. W. Smith, *Antibiotics and Chemotherapy*, **2**, 281 (1952). The Eli Lilly and Company trademark for the antibiotic erythromycin is "Ilotycin" (Erythromycin-Lilly).

(7) The names erythronolide B and dihydroerythronolide B are proposed for the aglycone portions of erythromycin B and dihydroerythromycin B, respectively.

(8) The pK_a' values reported herein were determined in 66% dimethylformamide solution.

(9) This N-oxide is isomeric with the corresponding tertiary amine in the erythromycin series.

(10) We have not been able to show the identity of this base with the corresponding base reported by Clark, *et al.* (reference footnote 3) for which the authors propose the molecular formula $C_{29}H_{55}NO_9$.

(11) Paper VI in this series: THIS JOURNAL, **78**, 388 (1956).

desosamine, dihydroerythronolide B (I) $C_{21}H_{40}O_7$, m.p. 182°, [Found: C, 62.69; H, 10.01; C-CH_3, 19.92; mol. wt., 410.3 (ebull. in acetone); $\alpha^{25}D$ +6° (*c*, 1 in methanol)] which consumed one mole of sodium metaperiodate, demonstrating that removal of desosamine ($C_8H_{17}NO_3$) liberates an α-glycol system.

Oxidation of I with periodate yielded the syrupy aldehydo-ester-methyl ketone (III) (increased carbonyl absorption, positive iodoform test), which was oxidized with peroxytrifluoroacetic acid[12] to the semi-solid ester-acetate (IV) (no carbonyl absorption in the ultraviolet). Saponification of (IV) at *p*H 12 gave the known *meso*-α,α′-dimethyl-β-hydroxyglutaric acid[13] (V) and the crystalline C_{12}-tetrol (VI), $C_{12}H_{26}O_4$, m.p. 146–148° [Found: C, 61.64; H, 11.38; C-CH_3, 21.62; mol. wt., 231 (ebull. in acetone); $\alpha^{25}D$ −2° (*c* 1 in methanol)] which was stable toward periodate and did not give an iodoform test.

Isolation of the C_7-dicarboxylic acid (V) and C_{12}-tetrol, and demonstration of a methyl ketone function in III,[14] satisfactorily account for the 21 carbon atoms of I.

On the basis of the above data and in view of the common biogenesis of erythromycin and erythromycin B, we propose structure I[15] for dihydroerythronolide B, which differs from the structure established for dihydroerythronolide[1] merely in the absence of a hydroxyl substituent at the carbon atom (C-12) adjacent to the lactone termination point. The lack of this hydroxyl function in erythromycin B apparently precludes the irreversible, acid-catalyzed formation of a spiro-ketal which, in erythromycin, leads to inactivation of the molecule.

(12) W. D. Emmons and G. B. Lucas, THIS JOURNAL, **77**, 2287 (1955).

(13) Isolation of the same *meso*- acid (V) from dihydroerythronolide (see reference footnote 1) is evidence of an extensive structural similarity between the aglycones of the cognate antibiotics, erythromycin and erythromycin B. Obviously, desosamine is substituted at the C-5,6 α-glycol system of I; a tentative assignment of substitution at C-5 as shown in II has been made on the basis of analogous substitution of desosamine in erythromycin.

(14) The experimental conditions employed made isolation of acetic acid formed by oxidation of III impractical.

(15) The configurations of the asymmetric carbon atoms in I (and VI), with the exception of carbons C-2 and C-4 have been drawn on arbitrary basis. Carbons C-2 and C-4 in I correspond to the two methyl-substituted carbons in the *meso*-acid (V) and must, therefore, have identical configuration.

KOERT GERZON
ROSEMARIE MONAHAN
LILLY RESEARCH LABORATORIES OLLIDENE WEAVER
INDIANAPOLIS 6, INDIANA MAX V. SIGAL, JR.
PAUL F. WILEY

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THE REACTION BETWEEN TRIETHYL PHOSPHITE AND ALKYL AND ARYL-SULFONYL CHLORIDES

Sir:

We wish to give a preliminary report on a novel reaction of general character, which was observed when triethyl phosphite was treated with alkyl- or arylsulfonyl chlorides. This reaction, which can be represented by the general equation

$$3(C_2H_5O)_3P + RSO_2Cl \longrightarrow (C_2H_5O)_2P(O)SR + C_2H_5Cl + 2(C_2H_5O)_3PO \quad (1)$$
(I) (II)

gives instead of the expected sulfonylphosphonate (III) the corresponding O,O-diethyl S-alkyl (or aryl) phosphate (I) in good yields with the simultaneous formation of two mole equivalents of triethyl phosphate (II). Even in the presence of a large excess of sulfonyl chloride over triethyl phosphite, it was not possible to obtain III; the phosphorus-containing products obtained under a wide variety of conditions were always I and II.

The statement by Kosolapoff[1] that sulfonylphosphonates are apparently unstable is confirmed by our observations, although the references cited in the chapter on the reactions of trialkyl phosphites refer actually to the reactions of dialkyl sodium phosphites with sulfonyl halides.

The I formed from the sulfonyl chlorides might suggest that the first step of the reaction is a reduction to the corresponding sulfenyl chloride which then in turn reacts with triethyl phosphite to yield I according to the general reaction reported by Morrison.[2] This possible reaction route is substantiated somewhat by the fact that aromatic sulfonyl fluorides, which are not affected by reducing agents,[3] were found to be unreactive toward triethyl phosphite. This, however, does not rule out the possibility that the reaction proceeds by a Michaelis–Arbuzov type condensation forming first the unstable intermediate III which is then reduced by triethyl phosphite to I.

The general character of the reaction represented by equation (1) could be demonstrated by the formation of the corresponding thiol phosphates I in good yields from triethyl phosphite and a series of sulfonyl chlorides, RSO_2Cl, where R is CH_3, C_2H_5, Bu, C_6H_5, *o*-MeC_6H_4, *p*-MeC_6H_4, *p*-FC_6H_4, *p*-BrC_6H_4, *m*-$HO_2CC_6H_4$, and 2-$C_{10}H_7$. Substitution of the phenyl ring of benzenesulfonyl chloride in various positions by electron-donating or withdrawing groups was found not to change the generality of the reaction. A detailed study of the effect of different R groups on the yields of I and of the mechanism of the reaction is under way. The results of a typical example each for the reaction of an alkyl- and arylsulfonyl chloride with triethyl phosphite are described briefly in the following paragraph.

The reaction between triethyl phosphite and *n*-butylsulfonyl chloride gave an 87.5% yield of O,O-diethyl S-butyl phosphate, b.p. 94–5° (0.5–0.7 mm.), $n^{25}D$ 1.4550 (calcd. for $C_8H_{19}O_3PS$: C, 42.29; H, 8.43; P, 13.67; S, 14.17: Found: C, 42.6; H, 8.7; P, 14.04; S, 14.23); and 82.5% of slightly impure triethyl phosphate, b.p. 40–42° (0.25–0.30 mm.), $n^{25}D$ 1.4061 (lit.[4]) b.p. 90° (10 mm.), $n^{25}D$ 1.4039 (identified further by comparison of its infrared spectrum with that of an authentic sample); 60% of the theoretical amount of ethyl chloride was collected in an attached cold trap. The reaction between triethyl phosphite and *p*-bromobenzenesulfonyl chloride yielded 87% of

(1) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 197.

(2) D. C. Morrison, THIS JOURNAL, **77**, 181 (1955).

(3) J. H. Simons, "Fluorine Chemistry," Vol. I, Academic Press, Inc., New York, N. Y., 1950, p. 179.

(4) D. P. Evans, W. C. Davies and W. J. Jones, *J. Chem. Soc.*, 1310 (1930).