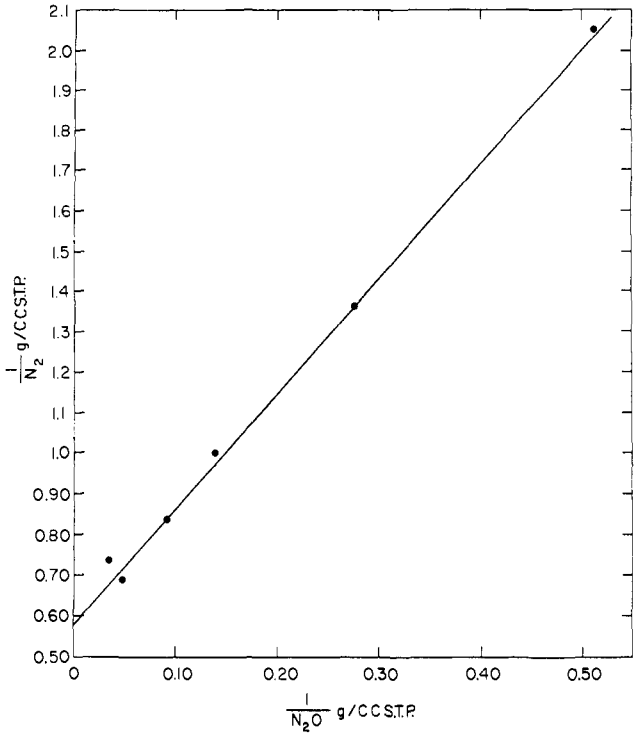

Figure 2. Data of Figure 1 plotted according to eq 6.

been found to be independent of intensity in the range 6.6×10^2 to 9.8×10^6 rads/hr.

It is possible that the additional reactions

$$(O^-) +_S [N_2O]_S \longrightarrow [O_2^-]_S + N_2 \quad (8)$$

$$[O_2^-]_S + \oplus \longrightarrow O_2 \quad (9)$$

are occurring. Our present results suggest that reaction 8 is either absent or very fast in which case $G_e = 1.35$, $k_2/k_1 = 1.5 \times 10^{-2}$, and $k_2'/k_1 = 0.14$ μmole/m^2.

The apparent energy transfer can be equally well explained by migration of excitons which either react with adsorbed N_2O or are annihilated by the surface. At the moment, the electron hypothesis is preferred because N_2O is known to be an electron scavenger in the liquid and gas phases. Also an electron-transfer mechanism has been proposed to explain the catalytic decomposition of N_2O on semiconductor surfaces.[10]

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The Dehydrotetracyclines. I. Epimerization at C-6

Sir:

In 1958 McCormick and co-workers[1] reported the isolation of 7-chloro-5a(11a)-dehydrotetracycline (I) which was accumulated by *Streptomyces aureofaciens* Duggar mutant S-1308, descended from the original 7-chlorotetracycline-producing A-377 soil isolate of Duggar. Its structure was established by spectral and elemental analysis as well as by catalytic reduction to an equimolar mixture of tetracycline and 5a-epitetracycline. Biological reduction[2,3] gave only 7-chlorotetracycline, thus showing conclusively[2] that I is a precursor of 7-chlorotetracycline and that the last step in 7-chlorotetracycline biosynthesis is the stereospecific reduction of the double bond. Miller and co-workers[4] have shown that 5a(11a)-dehydrotetracycline is the common intermediate for the biosynthesis of tetracycline and oxytetracycline and Mitscher and co-workers[5] have used this study to biologically hydroxylate and reduce I to give 7-chloro-5-hydroxytetracycline. Photooxidation of anhydrochlorotetracycline gives the 6-hydroperoxide of I.[6]

The position of the double bond in I has been the subject of some discussion,[6,7] and two tautomers have been isolated.[7] However, the only reported reactions involving I (besides reduction) are acid-catalyzed rearrangements with water[8] and alcohols[7] to give 5-hydroxy- or alkoxyanhydrotetracyclines.

We have now found that I undergoes stereospecific inversion at C-6 in liquid hydrogen fluoride containing 2 equiv of H_2O to give 7-chloro-6-epi-5a(11a)-dehydrotetracycline (II) in 20–25% yield; $[\alpha]^{25}D$ +40.5 ± 6° (*c* 0.493, 0.1 *N* HCl); λ_{max}^{KBr} 5.85 μ; $\lambda_{max}^{0.1\ N\ HCl}$ 253, 319, 385 mμ (log ϵ 4.43, 3.79, 3.99); $\lambda_{max}^{0.1\ N\ NaOH}$ 243, 341, 419 mμ (log ϵ 4.31, 3.88, 3.88).

Anal. Calcd for $C_{22}H_{21}N_2O_8Cl \cdot 0.5H_2O$: C, 54.38; H, 4.56; N, 5.77; Cl, 7.30; H_2O, 1.9; mol wt, 476.-0985. Found: C, 54.69; H, 4.66; N, 5.24; Cl, 7.15; H_2O, 2.1 (glpc); mol wt (mass spectroscopy), 476.0989).

Although the ultraviolet and infrared spectra of II are very similar to those of I, the nmr spectrum clearly is distinct. Whereas the C-methyl absorption of I in deuteriodimethyl sulfoxide is at 109 Hz, the absorption of II is at 85 Hz (both are unsplit singlets). This observation is in agreement with that of Schach von Wittenau and Blackwood[9] wherein the absorption of the C-6 methyl group in β-6-deoxyoxytetracycline is 42 Hz upfield from that of the α-6-deoxy derivative. In these latter cases inversion of a C-6 methyl group in tetracycline or oxytetracycline has taken place upon catalytic hydrogenolysis of the C-6 hydroxyl to give the C-6 β methyl group.[10]

Final proof of the structure of II involved catalytic hydrogenation to give 6-epitetracycline (III) and 5a-epi-6-epitetracycline (IV), both of which were converted to 5a(6)-anhydrotetracycline (Va). 6-Epitetracycline (III) $[[\alpha]^{25}D$ −100 ± 6° (*c* 0.448, 0.1 *N* HCl); $\lambda_{max}^{0.1\ N\ HCl}$ 268, 349 mμ (log ϵ 4.17, 4.07); $\lambda_{max}^{0.1\ N\ NaOH}$ 250 (sh) (log

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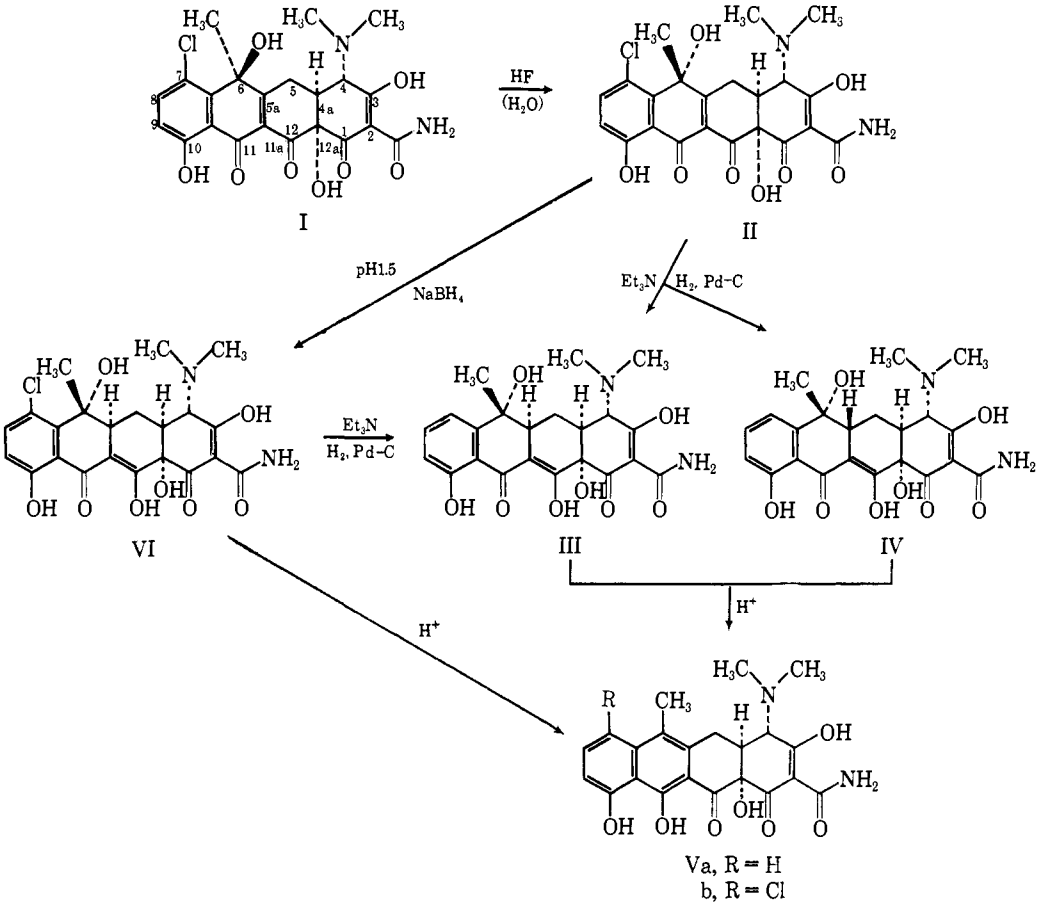

ϵ 4.08), 388 mμ (log ϵ 4.12); $\nu_{max}^{(D_3C)_2SO}$ 59 Hz (C-methyl) (tetracycline C-6 methyl is at 93 Hz). *Anal.* Calcd for $C_{22}H_{24}N_2O_8$: mol wt, 444.1531. Found: 444.1535 (mass spectroscopy)] was formed in 30% yield, separated from its 5a epimer by liquid–liquid partition chromatography on neutral (acid-washed) diatomaceous earth, and converted to anhydrotetracycline (Va) in 30% yield with great difficulty. Only by heating in methanesulfonic acid for 3.5 hr at 50° was reaction complete. The stereochemical assignments are based on the fact that 5a-epitetracycline (H and OH *cis*) is converted to Va more difficultly than is tetracycline[1] (H and OH *trans*).

5a-Epi-6-epitetracycline (IV), formed in 5% yield [$[\alpha]^{25}D$ $-130 \pm 6°$ (*c* 0.5, 0.1 *N* MeOH–HCl), $\lambda_{max}^{0.1\,N\,HCl}$ 267, 352 mμ (log ϵ 4.21, 4.06); $\lambda_{max}^{0.1\,N\,NaOH}$ 245, 262, 385 mμ (log ϵ 4.13, 4.13, 4.17); $\nu_{max}^{(D_3C)_2SO}$ 64 Hz (C–CH_3). *Anal.* Calcd for $C_{22}H_{24}N_2O_8$: mol wt, 444.1531. Found: mol wt, 444.1531 (mass spectroscopy)], was converted to Va in 30% yield merely by heating in concentrated hydrochloric acid for 5 min at 60°.

Miller[11] has shown that I gives 7-chloro-5a-epitetracycline upon reduction with sodium borohydride at pH 1.5. When II is subjected to these conditions, a single product was isolated by partition chromatography which was identified as 7-chloro-6-epitetracycline (VI), in contrast to the finding of Miller [$\lambda_{max}^{0.1\,N\,HCl}$ 263, 360 mμ (log ϵ 4.16, 3.52); $\lambda_{max}^{0.1\,N\,NaOH}$ 245, 395 mμ (log ϵ 4.15, 3.80). *Anal.* Calcd for $C_{22}H_{23}N_2O_8Cl$: mol wt, 478. Found: mol wt, 478 (mass spectroscopy)] and which was converted to anhydrochlorotetracycline (Vb) as well as to III.

(11) Dr. P. A. Miller (Chemotherapy Research Section, Lederle Laboratories), private communication. The authors are indebted to Dr. Miller for permission to publish his results here.

Although I and 5a-epitetracycline are biologically inactive,[1] II has *in vitro* activity against *Staphylococcus aureus* 209P of 1.5 times that of tetracycline and an *in vivo* activity orally in mice against *Staphylococcus aureus* strain Smith of 0.5 times that of tetracycline. In addition III and IV have *in vitro* activities of 60 and 40% that of tetracycline.

We shall report the results of further investigations into the chemistry of these interesting compounds as well as more detailed correlations of biological activity in a full paper.

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Formation of Aliphatic Semidiones under Conditions of the Acyloin Condensation[1]

Sir:

Numerous dibasic acid esters yield cyclic semidiones when treated with sodium–potassium alloy in dimeth-

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