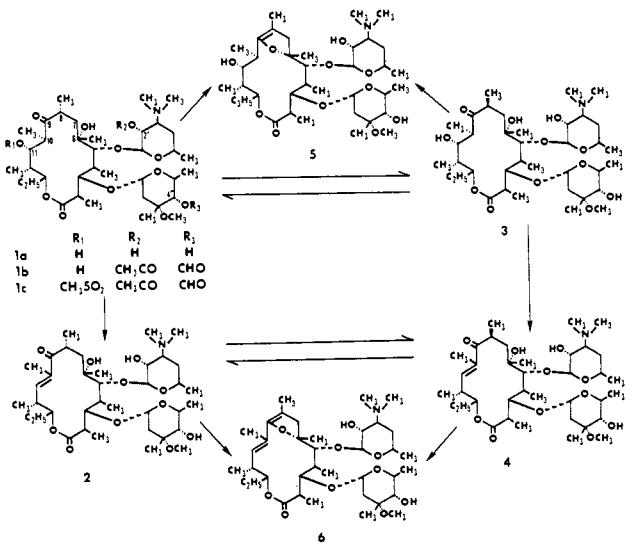
both of the C_8 epimeric 3,5-di-*O*-acetyl-10,11-anhydroerythronolides B by acid-catalyzed degradation of 3,5,11-tri-*O*-acetylerythronolide B. The conditions of Perun are not applicable to modification of the intact antibiotics, however, due to the extreme lability of the nitrogen-free sugar. The recent report[3] of the interconversions of erythromycin B (**1a**) and erythromycin B enol ether (**5**) suggested that acid-catalyzed C_8 epimerization of erythromycins might be effected by equilibration in aqueous acetic acid. We now report the preparation of 10,11-anhydroerythromycin B (**2**), and the C_8 epimerizations of both **1a** and **2**.

The preparation of 10,11-anhydroerythromycin B (**2**) was accomplished by conversion of 2′-*O*-acetyl-4″-*O*-formylerythromycin B (**1b**)[6] to the 11-methanesulfonate **1c** with methanesulfonic anhydride[7] in pyridine, followed by elimination of the elements of methanesulfonic acid with 1,5-diazabicyclo[5.4.0]undecene-5 (DBU)[8] in benzene, either under reflux for 0.5 hr or at 5° for 18 hr. Methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups and purification of the product by chromatography on Sephadex LH-20 with methanol followed by crystallization from ether gave **2** (40%), mp 112–116°; $[\alpha]^{24}D$ −51°.[9]



Treatment of **2** with 1:1 acetic acid–water (v/v) for 48 hr at room temperature led to a mixture containing 8-*epi*-10,11-anhydroerythromycin B (**4**) and 10,11-anhydroerythromycin B (**2**) in a ratio of about 10:1.[10] The former (**4**) was isolated as a white foam, $[\alpha]^{26}D$ −54°, by chromatography on triethylamine-treated silica gel by elution with increasing concentrations of methanol in chloroform.

Treatment of erythromycin B with 1:1 acetic acid–water at room temperature for 5 days led to the isolation[11] of 35% of 8-*epi*-erythromycin B (**3**), which crystallized and recrystallized from methanol–water: mp 169–171°; $[\alpha]^{24}D$ −95°.

To provide chemical evidence that **3** and **4** differed from the parent compounds **1a** and **2** only in their configurations at C_8, **3** was converted in glacial acetic acid to the enol ether **5** identical with that prepared[3] from **1a**.[12] Treatment of both of the C_8 epimeric 10,11-anhydroerythromycins B with glacial acetic acid yielded the dienol ether **6**. In addition, **8**-*epi*-erythromycin B (**3**) was converted to 8-*epi*-10,11-anhydroerythromycin B (**4**) by the same sequence of reactions used to convert erythromycin B (**1a**) to 10,11-anhydroerythromycin B (**2**).

Comparison of the 220-MHz nmr spectra of 8-*epi*-erythromycin B (**3**) and erythromycin B (**1a**) showed essentially no difference in the lactone ring conformations. Since the coupling constant ($J_{10,11}$ = 1 Hz) of **3** is the same as that of **1a**, the configurations at C_{10} of **3** and **1a** are identical.

We believe these data constitute a rigorous chemical–spectroscopic proof of the structures of 10,11-anhydroerythromycin B (**2**), 8-*epi*-10,11-anhydroerythromycin B (**4**), and 8-*epi*-erythromycin B (**6**).

Circular dichroism correlations have confirmed the previous configurational assignments[5] to the C_8 epimeric 3,5-di-*O*-acetyl-10,11-anhydroerythronolides B. The 10,11-anhydro ketones with the natural configuration at C_8, **2** and 3,5-di-*O*-acetylerythronolide B, have negative n → π* bands: $[\theta]_{327}$ −2185 and $[\theta]_{335}$ −2130, respectively. In contrast, the 8-*epi*-10,11-anhydro ketones, **4** and 8-*epi*-3,5-di-*O*-acetylerythronolide B, have positive n → π* bands: $[\theta]_{320}$ +1940 and $[\theta]_{304}$ +1620. The relationship of the CD curves of the C_8 epimeric 3,5-di-*O*-acetyl 10,11-anhydroerythronolides B to that of 10,11-anhydrooleandomycin diacetate has been discussed by Celmer.[2a]

Although antibacterial activities of all new products will be reported in a complete paper, it should be noted that the activity of 8-*epi*-erythromycin B *vs. Staph. aureus* 9144 was only 3.0% that of erythromycin B as determined by a tube dilution assay.

Acknowledgment. The authors wish to thank Drs. L. A. Mitscher, G. W. Clark, and T. J. Perun for the CD data on the C_8 epimeric 3,5-di-*O*-acetyl-10,11-anhydroerythronolides B. Drs. Mitscher and Clark are also to be thanked for determining and interpreting the CD curves of the C_8 epimeric 10,11-anhydroerythromycins B.

(6) P. H. Jones, T. J. Perun, E. K. Rowley, and E. J. Baker, *J. Med. Chem.*, 15, 631 (1972).

(7) The authors are grateful to Dr. T. J. Perun for suggesting the use of this reagent.

(8) DBU is extremely caustic and should be used with care. Tests with rabbits have shown it to be instantly destructive of eye tissue.

(9) Spectroscopic data and elemental analyses of all new compounds were compatible with the assigned structures and will be reported in a complete paper. Optical rotations were determined with 1% solutions in methanol. CD curves were determined with ethanol solutions.

(10) Determined from the relative areas of the characteristic C_{10} methyl peaks in the 100-MHz nmr spectrum.

(11) Unless otherwise specified, products were isolated by the partition column chromatography procedure of N. L. Oleinick and J. W. Corcoran, *J. Biol. Chem.*, 244, 727 (1969).

(12) A qualitative rate comparison (tlc) showed that 8-*epi*-erythromycin B was converted to the enol ether much more slowly than erythromycin B. For the preparative conversion, a reaction time of 19 hr was employed.

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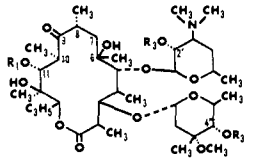
C_8 Epimeric 10,11-Anhydroerythromycins A and the C_8 Epimeric 11,12-Epoxyerythromycins A

Sir:

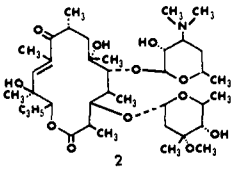
The present report concerns the DBU-catalyzed eliminations of methanesulfonic acid from 11-*O*-meth-

anesulfonyl-2′-*O*-acetyl-4′′-*O*-formylerythromycin A (**1b**) which may be controlled to lead selectively to 10,11-anhydroerythromycin A (**2**) or to 11,12-epoxyerythromycin A (**3** = **3a** + **3b**). The C_8 epimerizations of both products have been accomplished, and the rearrangements of the C_8 epimeric 11,12-epoxyerythromycins A to the corresponding C_8 epimeric 10,11-anhydroerythromycins A are described.

2′-*O*-Acetyl-4′′-*O*-formylerythromycin A (**1a**)[1] was converted to the 11-methanesulfonate **1b** with methanesulfonic anhydride in pyridine. Treatment of **1b** with DBU in benzene under reflux for 0.5 hr, followed by methanolysis of the 2′-*O*-acetyl and 4′′-*O*-formyl groups, led to the isolation of 35% of 10,11-anhydroerythromycin A (**2**) ($[\alpha]^{24}D$ −58°; $[\theta]_{340}$ −870) and 15% of 11,12-epoxyerythromycin A (**3**) as a 1.2:1 mixture of hydroxy ketone **3a** and hemiacetal **3b** tautomers, $[\alpha]^{24}D$ −90°. Treatment of **1b** with 1,5-diazabicyclo-[5.4.0]undecene-5 (DBU) in benzene at 5° for 18 hr led to complete elimination of the elements of methanesulfonic acid, as indicated by nmr, but ir showed the absence of any α,β-unsaturated ketone. Methanolysis of the 2′-*O*-acetyl and 4′′-*O*-formyl groups of the product led to the isolation of 45% of 11,12-epoxyerythromycin A (**3**).



	R_1	R_2	R_3
1a	H	CH_3CO_2	CHO
1b	CH_3SO_2	H	H



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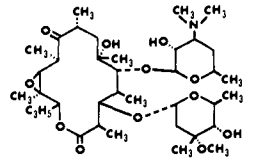
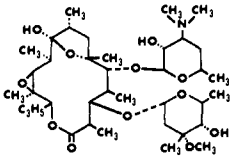
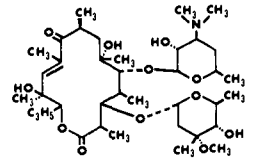


3a



3b



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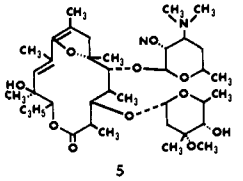


5

Prolonged reflux of 10,11-anhydroerythromycin A with DBU in benzene in the presence of 1 equiv of methanesulfonic acid effects considerable C_8 epimerization. A reaction time of 96 hr gave a mixture containing 8-*epi*-10,11-anhydroerythromycin A (**4**) ($[\alpha]^{26}D$ −59°; $[\theta]_{310}$ +1100) and 10,11-anhydroerythromycin A (**2**) in a ratio of about 3:1. Treatment of both **2** and **4** with glacial acetic acid at room temperature for 4 hr gave the dienol ether **5**.

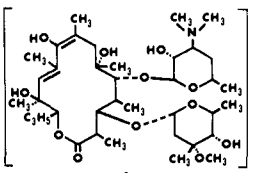
Although the erythromycin enol ethers are probably intermediates in the C_8 epimerizations of the erythromycin B derivatives effected by equilibration in aqueous acetic acid,[2] a control experiment established that 10,11-anhydroerythromycin A enol ether **5** is not the intermediate in the C_8 epimerization of **2** to **4** effected by DBU and methanesulfonic acid in benzene. It seems likely that under the latter conditions the intermediate involved is the 8,10-dien-9-ol **6** or the corresponding dienolate anion.

Treatment of 11,12-epoxyerythromycin A (**3**) with glacial acetic acid at room temperature for 1 hr gave 8-*epi*-11,12-epoxyerythromycin A (**7**, 58%) as a white foam $[\alpha]^{26}D$ −68°. The same product was isolated (48%) after treatment of **3** with 1:1 acetic acid–water at room temperature for 24 hr. Both **3** and **7** were converted to the dienol ether **5** on treatment with glacial acetic acid at room temperature for 46 hr.

Treatment of the C_8 epimeric 11,12-epoxyerythromycins A, **3** and **7**, with DBU and 1 equiv of methanesulfonic acid in refluxing benzene for 3 hr converted them to the corresponding C_8 epimeric 10,11-anhydroerythromycins A, **2** and **4**, respectively.

Evidence based on nmr and ir studies, to be presented in a complete paper, establishes that 11,12-epoxyerythromycin A (**3**) is isolated as a mixture of interconvertible hydroxy ketone **3a** and hemiacetal **3b** tautomers with a relatively high energy barrier to their interconversion. The pure hemiacetal **3b** was isolated (70% recovery) by crystallization from ether, mp 158–162°. In contrast, 8-*epi*-11,12-epoxyerythromycin A (**7**) exists exclusively as the hemiacetal.

The C_8 epimerization of 11,12-epoxyerythromycin A **3** which occurs in glacial acetic acid is in marked contrast to the behavior of other erythromycin derivatives which are converted to the corresponding enol ethers under similar conditions.[2,3] To provide some insight into the mechanism of epimerization of **3** to **7**, and to add to the evidence for their structures, 11,12-epoxyerythromycin A enol ether (**8**) was prepared and its behavior in both glacial acetic acid and aqueous acetic acid was investigated.



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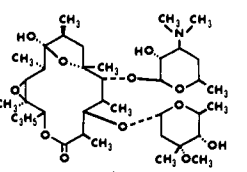

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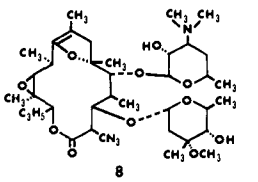
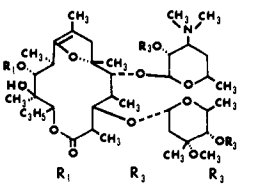
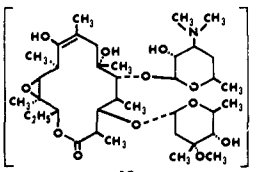


8



	R_1	R_2	R_3
9a	H	CH_3CO	CHO
9b	CH_3SO_3	H	H



10

2′-*O*-Acetyl-4′′-*O*-formylerythromycin A[1] was converted to the enol ether **9a** by the procedure of Kurath,

(1) P. H. Jones, T. J. Perun, E. K. Rowley, and E. J. Baker, *J. Med. Chem.*, **15**, 631 (1972).

(2) J. Tadanier, J. R. Martin, R. S. Egan, A. Goldstein, E. Hirner, and F. Fischer, *J. Amer. Chem. Soc.*, **95**, 592 (1973).

(3) P. Kurath, P. H. Jones, R. S. Egan, and T. J. Perun, *Experientia*, **27**, 362 (1971).

et al.[3] The latter **9a** was converted to 11-*O*-methanesulfonylerythromycin A enol ether **9b**, mp 122–131°, $[\alpha]^{23}D$ −38°, with methanesulfonic anhydride in pyridine followed by methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups. Treatment of **9b** with DBU in refluxing benzene for 18 hr gave 11,12-epoxyerythromycin A enol ether **8** in 80% yield as a white foam, $[\alpha]^{26}D$ −42°.[4]

Treatment of 11,12-epoxyerythromycin A enol ether (**8**) with 1:1 acetic acid–water for 0.5 hr at room temperature gave a mixture from which were isolated 11,12-epoxyerythromycin A (**3**) (49%) and 8-*epi*-11,12-epoxyerythromycin A (**7**) (18%). Treatment of **8** with glacial acetic acid for 1 hr at room temperature yielded 20% of recovered starting material, 20% of the dienol ether **5**, and only 9% of 8-*epi*-11,12-epoxyerythromycin A (**7**). We believe the latter result proves that 11,12-epoxyerythromycin A enol ether **8** is not an intermediate in the C_8 epimerization of 11,12-epoxyerythromycin A (**3**) to 8-*epi*-11,12-epoxyerythromycin A (**7**) effected by glacial acetic acid, and that the epimerization proceeds *via* the 8-en-9-ol **10**.

Acknowledgment. The authors wish to thank Professor L. A. Mitscher and Dr. G. W. Clark for determining and interpreting the CD data reported, and Messrs. J. Leonard and D. Nelson for carrying out many thin-layer chromatographies under the supervision of Dr. R. Hasbrouck. We are especially indebted to Drs. Paul Kurath, Wayne Cole, P. H. Jones, and T. J. Perun of Abbott Laboratories, and to Professor D. S. Tarbell of Vanderbilt University and Professor Peter Beak of the University of Illinois, Urbana, for many helpful and stimulating discussions in regard to this and the accompanying communication.

(4) A discussion of the contrast in the ease of 11,12-epoxide formation from 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A and 11-*O*-methanesulfonylerythromycin A enol ether will be deferred to a complete paper.

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Photodecarboxylation of Esters. Photolysis of α- and β-Naphthyl Derivatives[1]

Sir:

Recent studies of the photochemistry of esters and carboxylic acids have demonstrated the generality of the photodecarboxylation of benzyl- and phenyl-substituted derivatives.[1-6] A study of Meiggs and Miller[2] detailed the photochemistry of phenylacetic acid and methyl phenylacetate for which photodecarboxylation was a major pathway and the intermediacy of benzyl radicals was clearly demonstrated.

In our earlier report on the facile photodecarboxylation of benzyl esters and lactones,[6] we suggested a possible mechanism for these reactions (Scheme I)

Scheme I. Proposed Mechanism for the Photodecarboxylation of Benzyl Esters and Lactones

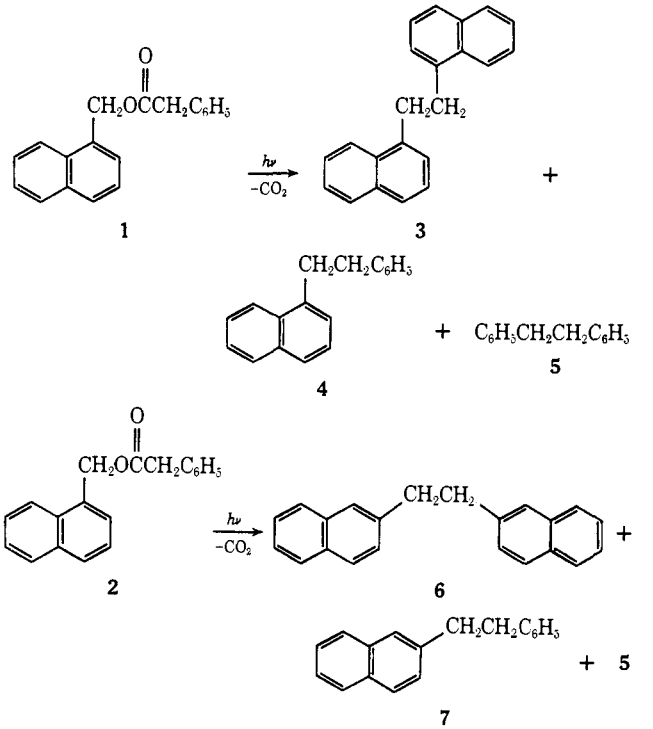
$$C_6H_5CH_2CO_2CH_2C_6H_5 \xrightarrow{h\nu} [C_6H_5CH_2CO_2CH_2C_6H_5]^*$$

$$[C_6H_5CH_2CO_2CH_2C_6H_5]^* \xrightarrow{\text{concerted or stepwise}} C_6H_5CH_2CH_2C_6H_5 + 2C_6H_5CH_2\cdot + CO_2$$

which involved the excitation of the phenyl chromophore, homolytic cleavage of the ether oxygen–carbon bond with expulsion of CO_2 (either simultaneously or stepwise), and generation of a pair of radicals. We now present additional evidence for that mechanism and some interesting comparisons of the reactivity of α- and β-naphthyl esters.

Photodecarboxylation of α-naphthylmethyl phenylacetate (**1**) and β-naphthylmethyl phenylacetate (**2**) proceeded smoothly to yield the three products expected from the coupling of the naphthylmethyl radical and the benzyl radical (**3**, **4**, and **5** and **6**, **7**, and **5**, respectively). Interestingly, the ratios of the coupling products (1:10:1 for both esters) were not statistical but reflected a much higher cross coupling of the radicals. This probably resulted from a cage effect on the initially generated radical pair.[7] In a subsequent study, benzyl α- and β-naphthylacetates (**8** and **9**, respectively) were irradiated under identical conditions with those used for **1** and **2**. After very long reaction times, only a trace of product could be detected from photolysis of either **8** or **9** having a vpc retention time identical with that of the major isomer from irradiation of **1** or **2**, respectively.

Scheme II. Photodecarboxylation of α- and β-Naphthylmethyl Esters **1** and **2**



(7) This large deviation from statistical coupling is currently under investigation.

(1) VIII. For part VII, see R. S. Givens and W. F. Oettle, *J. Org. Chem.*, in press.
(2) T. O. Meiggs and S. I. Miller, *J. Amer. Chem. Soc.*, 94, 1989 (1972), and references therein.
(3) I. S. Krull and D. R. Arnold, *Tetrahedron Lett.*, 1247 (1969), and references therein.
(4) R. Simonaitis and J. N. Pitts, *J. Amer. Chem. Soc.*, 91, 108 (1969), and references therein.
(5) R. A. Finnegan and D. Knutson, *ibid.*, **89**, 1970 (1967), and references therein.
(6) R. S. Givens and W. F. Oettle, *ibid.*, 93, 3301 (1971).