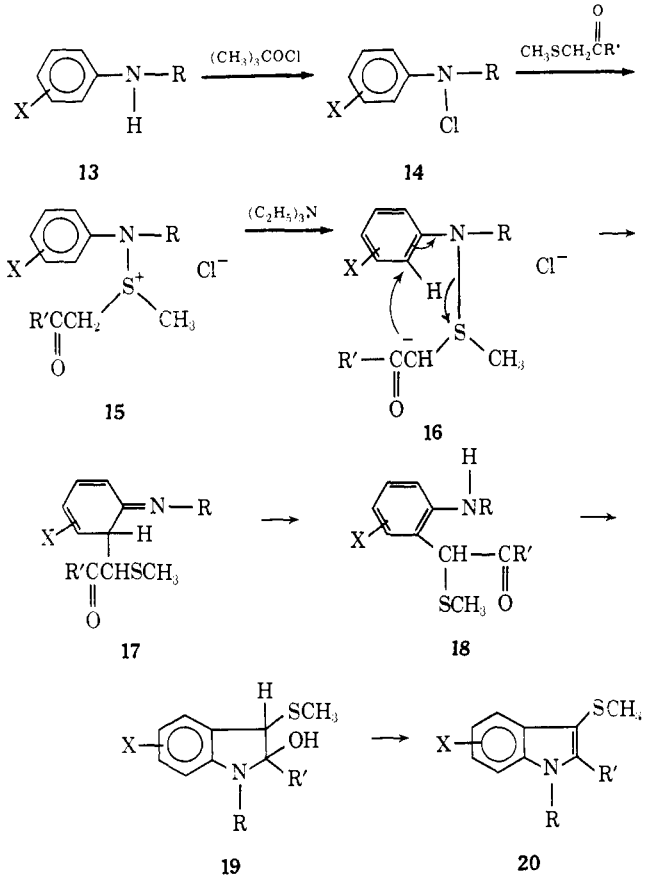
Scheme III



tert-butyl hypochlorite, or with a variety of other hypohalites, to produce *N*-chloroanilines (**14**). *N*-Chloroanilines react readily with sulfides to yield azasulfonium salts (**15**).[6] The azasulfonium salts have fairly acidic hydrogens on the carbons adjacent to the sulfur due to the inductive effect of the positive sulfur. Thus, triethylamine is a strong enough base to abstract a proton from the activated adjacent methylenes.[7] Since the one methylene is also activated by the carbonyl function, it is more acidic and gives up a proton to yield the ylide **16**. Intramolecular attack of the nucleophilic end of the ylide in a Sommelet–Hauser type[5,6,8,9] rearrangement then produces **17**. Proton transfer and rearomatization leads to **18**. In the case where the ketal, **9**, was used instead of a ketone or an aldehyde, the intermediate at this stage was the isolable ketal as illustrated by the characterization of **10**. Intramolecular addition of the free amine to the carbonyl function would be expected to yield the α-amino alcohol **19** after proton transfer. Dehydration would then give the observed polysubstituted indole **20**.

An indication of the scope of the synthesis of indoles by our method can be obtained with reference to the mechanistic scheme presented above (Scheme III). For the substituent on the aromatic ring, X has varied in electronic character from methyl to nitro. Anilines where R has been either hydrogen or methyl[1] have been used successfully. In relation to the sulfide, the indole synthesis has been shown to work well when R′ was hydrogen, methyl,[1] and phenyl.[1] In principle, X, R, and R′ should be able to vary greatly. We are continuing to investigate the various applications of our reaction scheme.

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(10) Fellow of the Netherlands Organization for the Advancement of Pure Research (Z.W.O.), 1972–1973.

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C_8 Epimerizations of Erythromycin B and 10,11-Anhydroerythromycin B[1]

Sir:

The lactone rings of the macrolide antibiotics provide important and interesting substrates for fundamental studies of the chemistry of large ring alicyclic compounds.[2] Knowledge of their chemistry is of practical significance with respect to the goal of preparing chemically modified macrolides with improved antibacterial activities, and should prove useful for contemplated total syntheses of these complex molecules.

The extreme sensitivity of the macrolides to both acidic and basic conditions presents a challenge with regard to effecting both chemical and stereochemical modifications. It is hoped that the studies initiated in these laboratories on the chemistry of the erythromycin lactone rings[3] may have some general applicability to other macrolide antibiotics.

Our approach to the selective chemical modification of the erythromycin lactone rings is based on the introduction of functionalizable sites of unsaturation. Our interest in 8-*epi*-erythromycins derives from the postulate of Celmer concerning the importance of the stereochemistry at C_8 to antibacterial activity.[2a,4]

A detailed study of the chemistry of the erythromycin B aglycone was carried out by Perun,[5] who isolated

(1) The configurational notation of macrolides used in this and the accompanying communication is different from that used previously at positions 3, 6, 10, and 13. This change at the inward directed bonds has been made to conform to the notation used by Celmer.[2a]

(2) For recent reviews of the macrolide antibiotics see: (a) W. D. Celmer in "Symposium on Antibiotics, March 1–3, 1971, St. Marguerite, Quebec, Canada," Butterworths, London, 1971, pp 413–453; *Pure Appl. Chem.*, **28**, No. 4 (1971); (b) R. S. Egan, Ph.D. Thesis, University of Illinois Medical Center, 1971; (c) T. J. Perun in "Drug Action and Drug Resistance in Bacteria. I. Macrolide Antibiotics and Lincomycin," S. Mitsuhashi, Ed., University of Tokyo Press, Tokyo, Japan, 1971, pp 123–152.

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

(4) W. D. Celmer in "Biogenesis of Antibiotic Substances," Z. Vanek and Z. Hošťalek, Ed., Academic Press, New York, N. Y., 1965, Chapter 10.

(5) T. J. Perun, *J. Org. Chem.*, **32**, 2324 (1967).

(6) P. G. Gassman, G. Gruetzmacher, and R. H. Smith, *Tetrahedron Lett.*, 497 (1972); see also R. Appel and W. Büchner, *Chem. Ber.*, **95**, 849, 855 (1962).

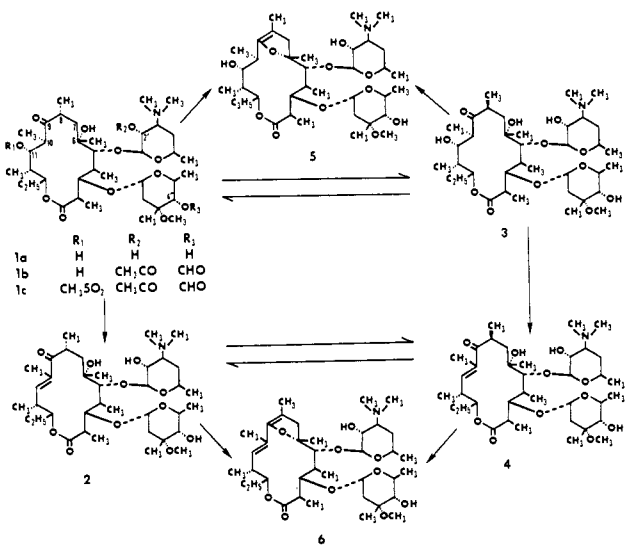
(7) When R was hydrogen, the possibility existed that the proton might be removed from nitrogen to give a sulfilimine. If a sulfilimine was formed, it must have been equilibrated with **16** by the triethylamine.

(8) M. Sommelet, *C. R. Acad. Sci.*, **205**, 56 (1937); G. C. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3572 (1962); G. C. Jones, W. Q. Beard, and C. R. Hauser, *ibid.*, **28**, 199 (1963).

(9) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966); **89**, 4725 (1967); P. Claus, *Monatsh. Chem.*, **102**, 913 (1971); P. Claus, N. Vavra, and P. Schilling, *ibid.*, **102**, 1072 (1971); P. Claus and W. Vycudilik, *ibid.*, **101**, 396, 405, (1970); P. Claus and W. Vycudilik, *Tetrahedron Lett.*, 3607 (1968); U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 3861 (1971).

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.

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(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-