Some Chemical and Stereochemical Modifications of the Erythromycin Lactone Rings[1]

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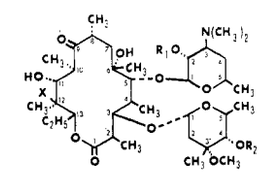
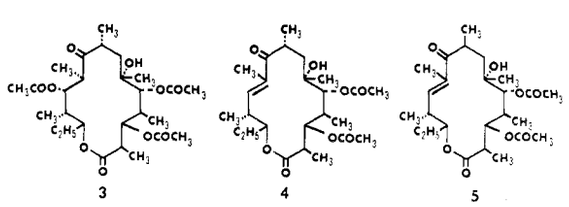
The preparation of 10,11-anhydroerythromycin B (**10**) from 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin B (**7a**) is described. C-8 epimerization of both erythromycin B and **10** was effected in aqueous acetic acid. Base-catalyzed elimination of the elements of methanesulfonic acid from 11-*O*-methanesulfonylerythromycin A (**6a**) may be controlled to lead selectively to either 10,11-anhydroerythromycin A (**13**) or 11,12-epoxyerythromycin A (**14**). Methods for effecting C-8 epimerization of **13** and **14** are described. The C-8 epimeric 11,12-epoxyerythromycins A (**14** and **16**) were readily rearranged to the corresponding C-8 epimeric 10,11-anhydroerythromycins A (**13** and **15**). 8,9-Anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (**18**) was prepared and shown not to be an intermediate in the C-8 epimerization of 11,12-epoxyerythromycin A (**14**) effected by glacial acetic acid. Compound **18** was converted to a mixture of **14** and **16** in aqueous acetic acid.

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

The extreme sensitivity of erythromycins to both acidic and basic conditions presents a challenge with regard to effecting both chemical and stereochemical modifications. Previous studies[2] established that the erythromycins A (**1a**) and B (**2a**) are readily and irreversibly degraded by



	X	R_1	R_2
1a	OH	H	H
1b	OH	$COCH_3$	CHO
2a	H	H	H
2b	H	$COCH_3$	CHO



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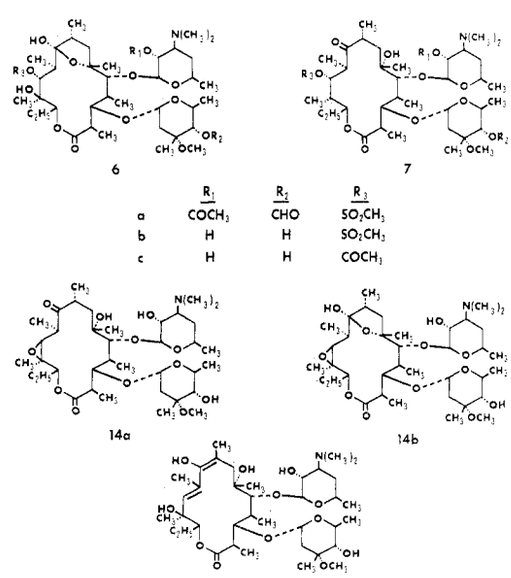
both dilute aqueous alkali and dilute mineral acid. The object of our current work is the development of methodology for chemical and stereochemical modification of the erythromycin lactone rings. Our general approach is based on the selective introduction into the erythromycin lactone rings of functionalizable sites of unsaturation. Our interest in 8-*epi*-erythromycins was stimulated by the postulate of Celmer[3] concerning the importance of the stereochemistry at C-8 to antibacterial activity.

The β-hydroxy ketone functionality present in the erythromycin lactone rings suggested the introduction of a 10,11 double bond. Although the C-8 epimeric 3,5-di-*O*-acetyl-10,11-anhydroerythronolides B (**4** and **5**) were prepared by Perun by acid-catalyzed degradation of 3,5,11-tri-*O*-acetylerythronolide B (**3**),[4] the sensitivity to acid and base of the intact erythromycins precluded direct acid- or base-catalyzed dehydration of the parent antibiotics. It was thus hoped that conversion of the 11-hydroxyl groups of the erythromycins to good leaving groups, followed by treatment of the resulting derivatives with a strong, nonnucleophilic base, would lead to the desired 10,11-anhydroerythromycins. A likely route involved preparation of the 11-*O*-methanesulfonylerythromycins.

11-*O*-Methanesulfonylerythromycins. Selective methanesulfonation of the 11-hydroxyl groups of the erythromycins required protection of the two secondary hydroxyl groups present in the desosamine and cladinose moieties. The technique for protecting the sugar hydroxyl groups was developed by Jones, *et al.*,[5] who prepared the 2′-*O*-acetyl-4″-*O*-formylerythromycins A and B, (**1b** and **2b**) and found that the parent erythromycins were readily regenerated from these diesters by mild basic hydrolysis. Treatment of the 2′-*O*-acetyl-4″-*O*-formylerythromycins A and B with methanesulfonic anhydride[6] in pyridine gave rise to the corresponding 11-*O*-methanesulfonylerythromycins A and B (**6a** and **7a**). These labile products were characterized by their nmr spectra and used in preparative reactions without purification. Methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups of **6a** and **7a** gave the 11-*O*-meth-



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	R_1	R_2	R_3
a	$COCH_3$	CHO	SO_2CH_3
b	H	H	SO_2CH_3
c	H	H	$COCH_3$

14a 14b

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Table I
Antibacterial Activity of Selected Erythromycins

Structure	Minimum inhibitory concentrations, g/ml[a]						
	Staphylococcus aureus 9144	*Staphylococcus aureus* Smith ER[b]	*Streptococcus faecalis* 10541	*Klebsiella pneumoniae* 10031	*Shigella sonnei* 9290	*Mycobacterium gallisepticum* S6	*Haemophilus influenzae* Patterson
1a	0.2	>100	0.05	3.1	12	0.2	1.56
2a	0.39	>100	0.05	6.2	25	0.05	
10	6.2	>100	1.6	25	>100	100	100
13	6.2	>100	1.6	12	>100	0.5	50
7b	3.1	>100	0.2	25	100	0.5	12.5
6b	50	>100	6.2	50	>100	50	>100
14	>100	>100	25	25	>100	1	>100
11	25	100	3.1	100	>100	5	>100
20c	0.39	>100	0.05	6.2	12.5	0.05	1.56
9	12.5	>100	1.56	25	>100	0.1	>100
15	12.5	>100	0.78	12.5	100	1.0	50

[a] Determined by an agar dilution method. [b] Erythromycin resistant.

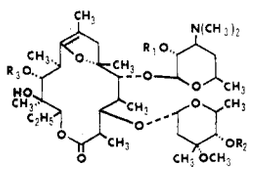
anesulfonylerythromycins A and B (**6b** and **7b**), which were isolated in about 90% purity by column chromatography and characterized spectroscopically.

It has been established[5] that while 11-*O*-acetylerythromycin B (**7c**) exists as the hydroxy ketone tautomer, 11-*O*-acetylerythromycin A exists as the hemiacetal, **6c.** Similarly nmr and ir spectra provide evidence that 11-*O*-methanesulfonylerythromycin B exists as the hydroxy ketone **7b,** while 11-*O*-methanesulfonylerythromycin A exists as the hemiacetal **6b.** The infrared spectrum of the hydroxy ketone **7b** shows carbonyl absorptions of both lactone (1727 cm^{-1}) and ketone (1704 cm^{-1}) carbonyls, while the infrared spectrum of the hemiacetal **6b** shows only a sharp symmetrical lactone carbonyl (1727 cm^{-1}). In addition, the C-10 proton resonances ($CDCl_3$) of the 11-*O*-acetyl- and 11-*O*-methanesulfonylerythromycins A (**6c** and **6b**) occur at higher field (δ 2.21 and 2.59, respectively) than those of the corresponding B derivatives, **7c** and **7b** (δ 2.99 and 3.16, respectively). This upfield shift of the C-10 proton resonances of the A derivatives relative to the B is presumably the consequence of the absence of the C-9 keto carbonyls in the hemiacetals.

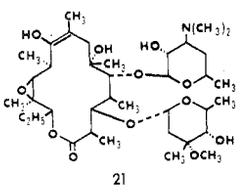
It is of interest that the 11-esters of erythromycin A, which exist as hemiacetals, have little or no antibacterial activity, while the antibacterial activities of the 11-esters of erythromycin B, which exist as hydroxy ketones, is appreciable (Table I).

The C-8 Epimeric Erythromycins B and the C-8 Epimeric 10,11-Anhydroerythromycins B. Kurath, *et al.*,[7] recently established that the erythromycins A (**1a**) and B (**2a**) are dehydrated to the corresponding 8,9-anhydroerythromycin 6,9-hemiacetals **8a** and **8b** in glacial acetic acid. It was also found[7] that the enol ether **8b** is readily hydrated in dilute aqueous mineral acid to regenerate erythromycin B (**2a**) (Scheme I). Since the C-8 carbon of **8b** is no longer an asymmetric center, the interconversion of **2a** and **8b** suggested that under suitable conditions an acid-catalyzed equilibration might be established *via* the enol ether **8b** leading to formation of 8-*epi*-erythromycin B (**9**). Treatment of erythromycin B (**2a**) with 1:1 (v/v) acetic acid–water at room temperature for 96 hr gave a mixture from which were isolated 35% of 8-*epi*-erythromycin B (**9**) and 30% of erythromycin B (**2a**). To provide chemical evidence that **9** differed from **2a** only in its configuration at C-8, it was converted to the enol ether, **8b,** in glacial acetic acid.

Comparison of the 220-MHz nmr spectra of erythromycin B and 8-*epi*-erythromycin B showed that both have essentially the same lactone ring conformations. The aglycone ring vicinal coupling constants and chemical shifts of both compounds involving H-2, -3, -11, -12, and -13 are very nearly identical. This indicates a close conformational



	R_1	R_2	R_3
8a	H	H	H
20a	$COCH_3$	CHO	H
20b	$COCH_3$	CHO	SO_2CH_3
20c	H	H	SO_2CH_3



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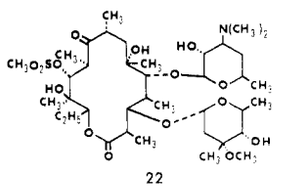

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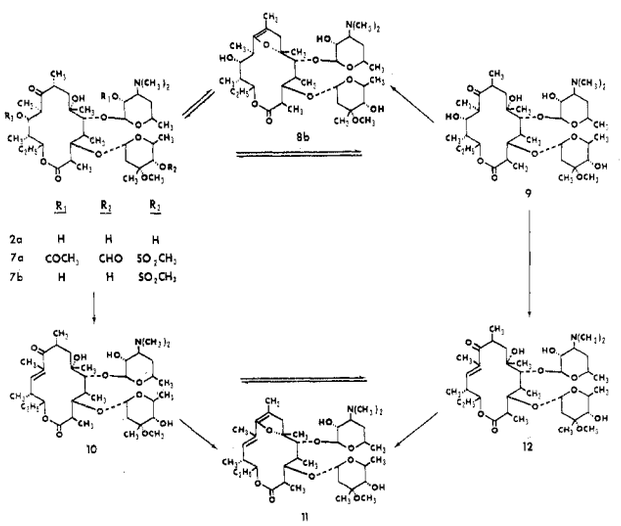
Scheme I



	R_1	R_2	R_3
2a	H	H	H
7a	$COCH_3$	CHO	SO_2CH_3
7b	H	H	SO_2CH_3

similarity of the ring segments containing these protons. Somewhat more substantial differences are observed in the chemical shifts of H-4, -7a, -7e, -8, and -10 and the $J_{4,5}$ and C-7 methylene proton coupling constants. These differences closely parallel those found when the spectra of 8-*epi*-erythronolide B and erythronolide B were compared[8] and are attributable to the same conformational reorganization involving the C-6 to C-9 ring segment as discussed in detail elsewhere.[9] The near identity of the coupling con-

stants, $J_{10,11}$, of erythromycin B (~1 Hz) and 8-*epi*-erythromycin B (~1 Hz) (Table II) established that both had the same configuration at C-10.

Since the C-10 protons and the C-11 hydroxyl groups of the erythromycins A and B (**1a** and **2a**) are antiperiplanar, it was hoped that the corresponding 11-methanesulfonates would undergo facile, base-catalyzed trans elimination to form the 10,11-anhydroerythromycins (**13** and **10**). Treatment of 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin B (**7a**) with 1,5-diazabicyclo[4.3.0]undecene-5 (DBU)[10] either under reflux for 0.5 hr or at 5° for 18 hr smoothly effected elimination of the elements of methanesulfonic acid. Methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups gave 10,11-anhydroerythromycin B (**10**), which was characterized by its infrared and ultraviolet spectra and by its conversion in glacial acetic acid to 8,9:10,11-dianhydroerythromycin B 6,9-hemiacetal (**11**).

Equilibration of **10** in 1:1 glacial acetic acid–water for 48 hr at room temperature gave a mixture containing 8-*epi*-10,11-anhydroerythromycin B (**12**) and 10,11-anhydroerythromycin B (**10**) in a ratio of about 10:1 as estimated from the relative areas of the corresponding C-10 methyl peaks in the nmr spectrum. Pure **12** was isolated by column chromatography.

To prove that **12** differed from **10** only in its configuration at C-8, it was converted to the enol ether **11** in glacial acetic acid. In addition, 8-*epi*-erythromycin B was converted to **12** by the same sequence of reactions used to convert erythromycin B (**2a**) to 10,11-anhydroerythromycin B (**10**).

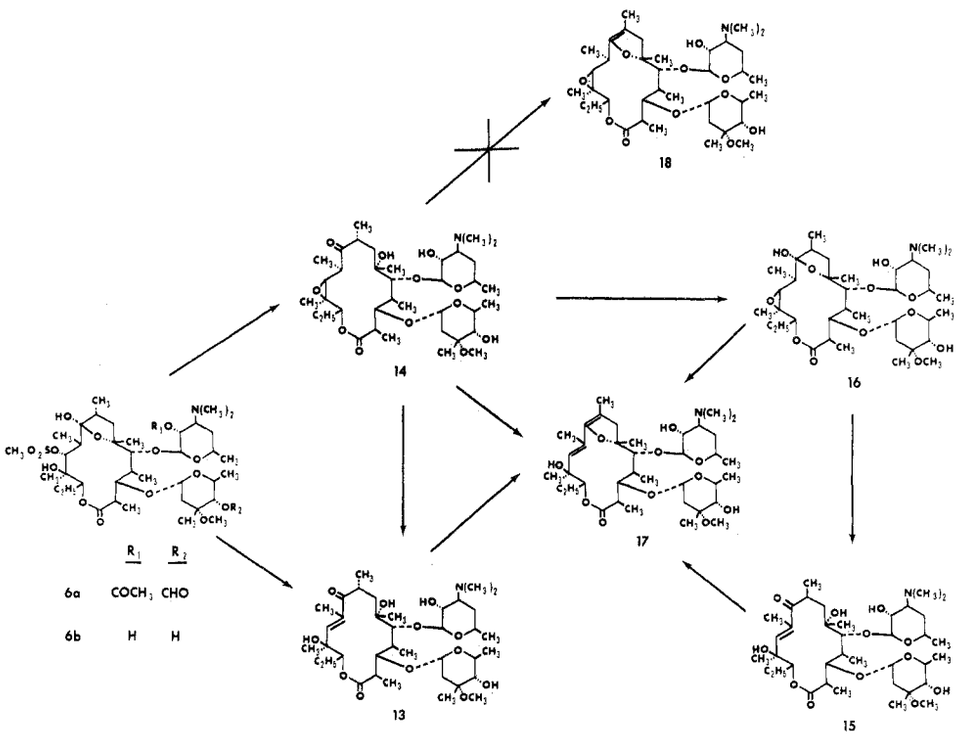
Table II
A Nuclear Magnetic Resonance Comparison of Erythromycin B (2a) and 8-*epi*-Erythromycin B (9)[a]

	Chemical shifts, ppm			Coupling constants, Hz	
	2a	**9**		**2a**	**9**
H-2	2.87	2.89	$J_{2,3}$	8.3	9.1
H-3	4.07	4.05	$J_{3,4}$	1	1
H-4	2.10	2.25	$J_{4,5}$	7.0	9.1
H-5	3.60	3.59	$J_{7a,7e}$	15.0	14.2
H-7a	2.00	2.06	$J_{7a,8}$	10.0	7.2
H-7e	1.6	1.93	$J_{7e,8}$	3.0	2.8
H-8	2.76	2.9	$J_{10,11}$	1	1
H-10	2.98	2.83	$J_{11,12}$	9.8	10.0
H-11	3.83	3.84	$J_{12,13}$	1	1.2
H-12	1.75	1.7	$J_{13,14a}$	9.0	9.1
H-13	5.35	5.31	$J_{13,14e}$	5.5	4.8
H-14a			$J_{14a,14e}$		
H-14e					
H-1′	4.43	4.32	$J_{1',2'}$	7.0	7.1
H-2′	3.21	3.24	$J_{2',3'}$	10.2	10.0
H-3′	2.47	2.53	$J_{3',4a'}$	12.0	12.1
H-4a′			$J_{3',4e'}$	3.5	3.8
H-4e′			$J_{4a',4e'}$		
H-5′	3.52	3.52	$J_{4a',5'}$	10.5	10.6
H-1″	4.89	4.87	$J_{4e',5'}$	1.8	1.6
H-2a″	1.58	1.58	$J_{1'',2a''}$	4.5	4.2
H-2e″	2.37	2.40	$J_{1'',2e''}$	1.5	<1
H-4″	3.00	3.01	$J_{2a'',2e''}$	15.5	15.1
H-5″	4.05	4.02	$J_{4'',5''}$	9.0	9.5

[a] All parameters were measured from 220-MHz spectra obtained at 55° in $CDCl_3$ solution.

The C-8 Epimeric 10,11-Anhydroerythromycins A and the C-8 Epimeric 11,12-Epoxyerythromycins A. DBU-catalyzed elimination of the elements of methanesulfonic acid from 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A (**6a**) (Scheme II) may be controlled to lead selectively to 10,11-anhydroerythromycin A (**13**) or 11,12-epoxyerythromycin A (**14**). Treatment of **6a** with DBU in refluxing benzene for 0.5 hr followed by methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups of the products led to isolation of 35% of 10,11-anhydroerythromycin A (**13**) and 15% of 11,12-epoxyerythromycin A (**14**). In contrast, when the DBU-catalyzed elimination was carried out at 5° for 18 hr complete elimination of the elements of methanesulfonic acid was effected, as indicated by the nmr spectrum of the crude product, but the ir spectrum showed the absence of any α,β-unsaturated ketone. After methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups 11,12-epoxyerythromycin A (**14**) was isolated in 45% yield by column chromatography. A purified sample of 11-*O*-methanesulfonylerythromycin A (**6b**) was smoothly converted to **14** by DBU in benzene at 5° for 18 hr.

Scheme II



Prolonged reflux of 10,11-anhydroerythromycin A (**13**) with DBU in benzene in the presence of methanesulfonic acid effected considerable C-8 epimerization. A reaction time of 96 hr gave a mixture containing 8-*epi*-10,11-anhydroerythromycin A (**15**) and 10,11-anhydroerythromycin A in a ratio of about 3:1 as estimated from the characteristic C-10 methyl peaks in the nmr spectrum. Pure **15** was isolated by column chromatography, and both C-8 epimers, **13** and **15**, were converted to 8,9:10,11-dianhydroerythromycin A 6,9-hemiacetal (**17**) in glacial acetic acid.

Although the erythromycin enol ethers **8b** and **11** are probable intermediates in the C-8 epimerizations of erythromycin B and 10,11-anhydroerythromycin B which are effected by aqueous acetic acid, a control experiment established that the enol ether **17** is not an intermediate in the C-8 epimerization of **13** to **15** effected by DBU and methanesulfonic acid in benzene. Treatment of **17** with DBU and methanesulfonic acid in benzene under reflux for 96 hr in the presence of 1 equiv of water gave only recovered starting material. This suggests that the intermediate involved in the epimerization of **13** to **15** under these conditions is the 8,10-dien-9-ol **19**, or the corresponding dienolate anion.

An attempt to characterize 11,12-epoxyerythromycin A (**14**) by its conversion in glacial acetic acid to 8,9-anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (**18**) was unsuccessful. Instead, treatment of **14** with glacial acetic acid at room temperature for 1 hr gave 8-*epi*-11,12-epoxyerythromycin A (58%) which was found to exist as the hemiacetal **16**. The same product **16** was isolated (48%) after treatment of **14** with 1:1 acetic acid–water at room temperature for 24 hr. Both **14** and **16** were converted to 8,9:10,11-dianhydroerythromycin A 6,9-hemiacetal (**17**) in glacial acetic acid at room temperature for 46 hr. Conversion of **14** and **16** to the corresponding C-8 epimeric 10,11-anhydroerythromycins A (**13** and **15**) was effected with DBU in refluxing benzene in the presence of methanesulfonic acid for 3 hr.

The C-8 epimerization of 11,12-epoxyerythromycin A (**14**), which occurs in glacial acetic acid, is in marked contrast to the behavior of other erythromycin derivatives which are converted to 8,9-anhydroerythromycin 6,9-hemiacetals under similar conditions. To provide some insight into the mechanism of C-8 epimerization of **14** to **16**, and to add to the evidence for their structures, the preparation of 8,9-anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (**18**) was desired, and was accomplished by epoxide formation from 8,9-anhydro-11-*O*-methanesulfonylerythromycin A 6,9-hemiacetal (**20c**). The behavior of **18** in both glacial acetic acid and 1:1 acetic acid–water was investigated.

2′-*O*-Acetyl-4″-*O*-formylerythromycin A (**1b**) was converted to the enol ether **20a** in glacial acetic acid. **20a** was

Experimental Section

Products were isolated by either benzene or chloroform extraction. The reaction mixtures were shaken with mixtures of excess 5% aqueous sodium bicarbonate and the organic solvent. The aqueous phase was separated and washed several times with the organic solvent. The organic solutions were washed with water and combined. Solvents were evaporated under reduced pressure. Any residual pyridine was removed by co-distillation with benzene under reduced pressure.

Optical rotations were determined with 1% solutions in methanol with a Rüger and Watts polarimeter. Ir spectra were determined with deuteriochloroform solutions using a Perkin-Elmer Model 521 grating spectrometer. The cd determinations were made with samples dissolved in spectral grade methanol using a Durrum-Jasco Model CRD/UV-5 instrument equipped with a cd attachment and operating at ambient temperatures. Nmr spectra were determined at 100 MHz, unless otherwise specified, with a Varian HA-100 spectrometer with deuteriochloroform solutions. Chemical shifts are reported in ppm from internal tetramethylsilane (Cb) and coupling constants are reported in Hz. Partition column chromatographies were carried out by the method of Gleinick and Corcoran[11] using silica gel (Merck, Darmstadt).

11-*O*-Methanesulfonylerythromycin A (6b). --- A suspension prepared from 14.4 g of 2′-*O*-acetyl-4″-*O*-formylerythromycin A[5] (1b), 7.3 g of methanesulfonic anhydride, and 108 ml of pyridine was stirred at room temperature for 19 hr. The product, 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A (6a, 15.1 g) was isolated as a brown foam by chloroform extraction: nmr: δ 8.23 (OCOH), 3.33 (OMe), 3.02 (OSO_2Me), 2.28 (NMe_2), 2.06 (OCOMe).

A solution of 2.1 g of 6a in 50 ml of methanol was allowed to stand at room temperature for four days. The major portion of the methanol was evaporated under reduced pressure. Chloroform extraction gave 1.54 g of an orange glass. Pure (~90%) 11-*O*-methanesulfonylerythromycin A (6b, 686 mg) was isolated by partition column chromatography as a white glass: ir 3587, 3400–3350, 1727 cm^{-1}; nmr δ 3.29 (OMe), 3.09 (OSO_2Me), 2.32 (NMe_2), 1.54 (C-6 Me).

11-*O*-Methanesulfonylerythromycin B (7b). --- A suspension prepared from 7.5 g of 2′-*O*-acetyl-4″-*O*-formylerythromycin B[5] (2b), 3.6 g of methanesulfonic anhydride and 53 ml of pyridine was stirred at room temperature for 17 hr. The product, 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin B (7a, 7.8 g) was isolated as a brown foam by chloroform extraction: nmr δ 8.23 (OCOH), 3.36 (OMe), 3.12 (OSO_2Me), 2.29 (NMe_2), 2.06 (OCOMe). A solution of 13 g of 7a, prepared as described above, in 350 ml of methanol was allowed to stand at room temperature for four days. The methanol solution was treated with Darco G-60 and filtered through a celite mat. The major portion of the methanol was evaporated under reduced pressure. Chloroform extraction gave 10.9 g of a light-orange glass. Partition column chromatography of 3.0 g gave 320 mg of pure (~90%) 11-*O*-methanesulfonylerythromycin B (7b) as a white glass: ir 3595, 3540 3470–3400, 1727 and 1704 cm^{-1}; nmr δ 3.31 (OMe), 3.09 (OSO_2Me), 2.29 (NMe_2).

8,9-Anhydro-11-*O*-methanesulfonylerythromycin A 6,9-hemiacetal (20c). --- A solution of 15.5 g of 2′-*O*-acetyl-4″-*O*-formylerythromycin A[5] and 170 ml of glacial acetic acid was allowed to stand at room temperature for 4 hr. The major portion of the acetic acid was evaporated under reduced pressure and the product, 2′-*O*-acetyl-4″-*O*-formyl-8,9-anhydroerythromycin A 6,9-hemiacetal (20a, 14 g) was isolated by chloroform extraction: nmr δ 8.20 (OCOH), 3.37 (OMe), 2.28 (NMe_2), 2.04 (OCOMe), 1.55 (C-8 Me).

A suspension of 2.0 g of 20a, 1.0 g of methanesulfonic anhydride and 20 ml of pyridine was stirred at room temperature for 4 hr. The product, 8,9-anhydro-11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A 6,9-hemiacetal (20b, 2.0 g) was isolated by chloroform extraction.

A suspension of 2.0 g of 20b, 50 ml of methanol and 5 ml of 5% aqueous $NaHCO_3$ was stirred at room temperature for 64 hr during which time a clear solution resulted. Chloroform extraction gave 1.8 g of orange glass. The product, 11-*O*-methanesulfonyl-8,9-anhydroerythromycin A 6,9-hemiacetal (20c) was isolated as a white crystalline solid by partition column chromatography: mp 122–132°, $[\alpha]_D^{23}$ - 38°; ir 3562, 3500–3400, 1735 cm^{-1}, nmr δ 3.34 (OMe); 3.17 (OSO_2Me), 2.28 (NMe_2), 1.58 (C-8 Me); 1.38 (C-6 Me).

Anal. Calcd for $C_{38}H_{69}O_{14}NS$: C, 57.48; H, 8.51; N, 1.76; S 4.04. Found: C, 58.48; H, 8.95; N, 1.69; S, 4.34.

10,11-Anhydroerythromycin B (10). --- A solution of 7.5 g of 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin B (7a), 3.4 g of 1,5-diazabicyclo[5.4.0]undecene-5, and 50 ml of benzene was heated under reflux for 0.5 hr. The reaction mixture was cooled to room temperature and diluted with 50 ml of benzene. Water (50 ml) was added, and the resulting mixture was stirred at room temperature for one hour. Benzene extraction gave 5.48 g of an orange foam.

A solution of 10.7 g of product, prepared as described above, in 260 ml of methanol was allowed to stand at room temperature for three days. The resulting solution was treated with Darco G-60 and filtered through a celite mat. The major portion of the methanol was evaporated under reduced pressure and the product (9.1 g of white foam) was isolated by chloroform extraction. Chromatography of the latter (3.1 g) on Sephadex LH-20, followed by crystallization from ether, gave 2.42 g of 10,11-anhydroerythromycin B: mp 118–130°; $[\alpha]_D^{24}$ -31°; λ max 231nm (ε 10,640); ir 3610, 3575-3400, 1725, 1667 cm^{-1}; nmr δ 6.42 (C-11 H), 3.32 (OMe), 2.30 (NMe_2), 1.77 (C-10 Me).

Anal. Calcd for $C_{37}H_{65}O_{11}N$: C, 63.49; H, 9.36; N, 2.00. Found: C, 63.40; H, 9.63; N, 1.92.

Similar results were obtained when the reaction of 6a with DBU in benzene was carried out at 5° for 18 hr.

10,11-Anhydroerythromycin A (13) and 11,12-Epoxyerythromycin A (14). --- a.) A solution of 13.0 g of 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A (6a), 7.0 g of DBU and 100 ml of benzene was heated under reflux for 0.5 hr. The resulting mixture was cooled to room temperature and diluted with 100 ml of benzene. Water (100 ml) was added, and the resulting mixture was stirred at room temperature for 40 min. Benzene extraction gave 12.0 g of an orange glass. Treatment of this product with 300 ml of methanol for 90 hr followed by chloroform extraction gave 10.7 g of yellow glass. Partition column chromatography of 2.54 g of this product yieldsd, in the earlier fractions, 276 mg of 11,12-epoxyerythromycin A (14 + 16a + 16b) as a white glass from chloroform solution: ir 3600–3350, 1729, 1708 cm^{-1}.

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C,62.08; H, 9.15; N, 1.96. Found: C, 62.14; H, 9.34; N, 1.77.

Crystallization of 1.97 of 16[12] from ether gave 1.23 g of the pure hemiacetal tautomer 16b: mp 158–162°; $[\alpha]_D^{24}$ -90°; ir 3578, 3500-3400, 1727 cm^{-1}.

Further elution of the column gave 923 mg of 10,11-anhydroerythromycin A (13) as a white glass; $[\alpha]_D^{24}$ - 58°; λmax 233nm (ε 9479); ir 3610-3350, 1727, 1665 cm^{-1}; nmr δ 6.48 (C-11 H), 3.32 (OMe), 2.28 (NMe_2), 2.02 (C-10 Me).

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C,62.08; H, 9.15; N, 1.96. Found: C, 61.88; H, 9.43; N, 1.94.

b.) A solution of 15.8 g of 11-*O*-methanesulfonyl-2′-*O*-acetyl-4″-*O*-formylerythromycin A (6a), 8.8 g of DBU, and 98 ml of benzene was stirred at 5° for 18 hr. Benzene (98 ml) and water (98 ml) were added and the resulting mixture was stirred at room temperature for 1 hr. The product (12.9 g), isolated by benzene extraction, showed the absence of α,β-unsaturated ketone absorption in the infrared. A solution of 4.0 g of the product, 88 ml of methanol and 9 ml of 5% aqueous $NaHCO_3$ was stirred at room temperature for 48 hr. Chloroform extraction gave 3.58 g of product which was chromatographed on a partition column to yield 1.5 g of 11,12-epoxyerythromycin A (14) identical in all respects to that described above.

c.) A pre-cooled solution of 2.49 g of DBU in 30 ml of benzene was added to 1.84 g of 11-*O*-methanesulfonylerythromycin A (6b) and the resulting solution was stirred at 5° for 18 hr. Benzene (50 ml) and water (50 ml) were added and the resulting mixture was stirred at room temperature for 1 hr. Benzene extraction yielded 1.72 g of 11,12-epoxyerythromycin A (14) identical with that described above.

d.) *A mixture of 912 mg of 11,12-epoxyerythromycin A (14), 533 mg of DBU, 0.076 ml of methanesulfonic acid and 7.6 ml of benzene was heated under reflux for 3 hour.* The usual workup and benzene extraction gave 687 mg of orange glass. Partition column chromatography of 632 mg gave 357 mg of pure 10,11-anhydroerythromycin A (13).

8-*epi*-Erythromycin B (9). --- A solution of 1.0 g of erythromycin B (2a) in 17 ml of acetic acid and 17 ml of water was allowed to stand at room temperature for 96 hr. The resulting solution was added dropwise to a stirred suspension of excess $NaHCO_3$ in water. The product (719 mg) was isolated by chloroform extraction. Partition column chromatography yielded, in the

converted to 8,9-anhydro-11-*O*-methanesulfonylerythromycin A 6,9-hemiacetal (**20c**) on treatment with methanesulfonic anhydride in pyridine followed by methanolysis of the 2′-*O*-acetyl and 4″-*O*-formyl groups. Treatment of **20c** with DBU in benzene under reflux for 18 hr gave 8,9-anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (**18**) in good yield.

Treatment of **18** with 1:1 acetic acid–water for 0.5 hr at room temperature gave a mixture from which were isolated 11,12-epoxyerythromycin A (**14**, 49%) and 8-*epi*-11,12-epoxyerythromycin A (**16**, 18%). Treatment of **18** with glacial acetic acid at room temperature for 1 hr yielded 20% of starting material, 20% of the enol ether **17**, and only 9% of 8-*epi*-11,12-epoxyerythromycin A (**16**). Since the latter conditions effect essentially complete C-8 epimerization of **14** we believe that this result excludes the enol ether **18** as the intermediate in the C-8 epimerization of **14** effected by glacial acetic acid, and suggests that the epimerization occurs *via* the 8-en-9-ol **21**.

The contrast to the ease of formation of 11,12-epoxyerythromycin A (**14**) from 11-*O*-methanesulfonylerythromycin A (**6b**), effected by DBU in benzene (5°, 18 hr), identical treatment of 8,9-anhydro-11-*O*-methanesulfonylerythromycin A 6,9-hemiacetal (**20c**) led to quantitative recovery of starting material.

Hydroxy Ketone–Hemiacetal Tautomerism of the C-8 Epimeric 11,12-Epoxyerythromycins A (14 and 16). Although 11,12-epoxyerythromycin A (**14**), isolated as a glass by evaporation of chloroform from a chloroform solution, showed a single spot in several tlc systems, the nmr spectrum of a freshly prepared solution in deuteriochloroform at 35° showed **14** to be a mixture of two components in a ratio of 1.2:1, estimated from the heights of the two NMe_2 and two OMe peaks. The major component showed peaks at δ 3.35 (OMe) and 2.31 (NMe_2), while the minor component showed peaks at δ 3.36 (OMe) and 2.29 (NMe_2). A characteristic singlet appeared at δ 1.66 which was associated with the minor component and is tentatively assigned to its C-6 methyl protons. When the deuteriochloroform solution of **14** was heated at 56° for 0.5 hr, the ratio of components changed to 2.4:1 with the original major component predominating. When the solution was cooled to 35° the ratio of components remained at 2.4:1 and little change in the ratio was noted even after several days at room temperature.

Comparison of the infrared spectrum of the freshly prepared deuteriochloroform solution of **14** with that of an aliquot which had been heated at 56° for 0.5 hr showed significant increase, in the heated sample, of the ratio of intensities (log I/I_0) of the ketone carbonyl absorption (1708

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earlier fractions, 8-epi-erythromycin B (145 mg) as a white glass. Crystallization of 485 mg[12] from methanol water gave 322 mg of prisms: mp 169–171° $[\alpha]_D^{24}$ - 95°; ir 3602, 3560–3440, 1710 cm^{-1} ($CDCl_3$); 1733, 1720 cm^{-1} (Et_3N); nmr δ 3.28 (OMe), 2.30 (NMe_2), 1.44 (C-6 Me).

Anal. Calcd for $C_{37}H_{67}O_{12}N$: C, 61.90; H, 9.40; N, 1.95. Found: C, 61.80; H, 9.65; N, 1.94.

Further elution gave 123 mg of erythromycin B.

8-epi-10,11-Anhydroerythromycin B (12). --- a.) A solution prepared from 5.3 g of 10,11-anhydroerythromycin B (10), 10 ml of acetic acid, and 10 ml of water was allowed to stand at room temperature for 49 hr. The resulting solution was added dropwise to a stirred suspension of 150 g of solid $NaHCO_3$ in 800 ml of water. Chloroform extraction gave 5.2 g of white glass containing 8-epi-10,11-anhydroerythromycin B (12) and 10,11-anhydroerythromycin B (10) in a ratio of about 10 to 1 estimated from the characteristic C-10 methyl peaks in the nmr spectrum. Partition column chromatography of 1.82 g of the product gave 883 mg of pure 8-epi-10,11-anhydroerythromycin B (12) as a white glass: $[\alpha]_D^{26}$ - 54°; λ_{max} 230nm (ϵ 10,526); ir 3610 (shoulder), 3520–3400, 1723, 1664 cm^{-2}; nmr δ 6.35 (C-11 H), 3.29 (OMe), 2.29 (NMe_2), 1.83 (C-10 Me).

Anal. Calcd for $C_{37}H_{65}O_{11}N$: C, 63.49; H, 9.36; N, 2.00. Found: C, 63.43; H, 9.56; N, 1.89.

b.) A sample of 8-epi-erythromycin B (9, 382 mg) was converted to 2′-O-acetyl-4″-O-formyl-8-epi-erythromycin B (340 mg), by the method of Jones, et al.[5] Treatment of the diester (340 mg) with

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178 mg of methanesulfonic anhydride in pyridine at room temperature for 4 hr followed by chloroform extraction gave 380 mg of crude 11-O-methanesulfonyl-2′-O-acetyl-4″-O-formyl-8-epi-erythromycin B. The latter was treated with 580 mg of DBU in 8.1 ml of benzene at room temperature for 25 hr and then under reflux for 1 hr. Treatment of the product with methanol (10 ml) at room temperature for 90 hr followed by chloroform extraction gave 256 mg of product. Partition column chromatography yielded 68 mg of pure 12, identical with that prepared as described above.

Conversion of 8-epi Erythromycin B (9) to 8,9-Anhydroerythromycin B 6,9-Hemiacetal (8b). --- A solution of 320 mg of 8-epi-erythromycin B (9) in 4 ml of glacial acetic acid was allowed to stand at room temperature for 19 hr. The acetic acid was evaporated under reduced pressure, and a slurry of 5 g of $NaHCO_3$ in 50 ml of water was added to the residue. The product (293 mg) was isolated by chloroform extraction and was identical with a sample of 8,9-anhydroerythromycin B 6,9-hemiacetal (8b) prepared as described by Kurath, et al.[7], by criteria of nmr, ir and tlc.

8,9-10,11-Dianhydroerythromycin B 6,9-Hemiacetal (11). --- a.) A solution of 2.1 g of 10,11-anhydroerythromycin B (10) in 25 ml of glacial acetic acid was allowed to stand at room temperature for 4 hr. The product (2.0 g) was isolated as a white glass by the method employed for the isolation of 8b, above. Partition column chromatography of 800 mg of product gave 725 mg of pure 11 as a white glass after treatment with Darco G-60: $[\alpha]_D^{24}$ - 94°; λ_{max} 262nm (ϵ 2864); ir 3595, 3545, 3500–3400, 1723 cm^{-1}, nmr δ 5.12 (C-11 H), 2.29

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(NMe_2), 1.66 (C-10 Me), 1.59 (C-8 Me), 1.47 (C-6 Me).

Anal. Calcd for $C_{37}H_{63}O_{10}N$: C, 65.17; H, 9.32; N, 2.06. Found: C, 64.92; H, 9.41; N, 1.99.

b.) A solution prepared from 211 mg of 8-epi-10,11-anhydroerythromycin B (12) in 2.5 ml of glacial acetic acid was allowed to stand at room temperature for 4 hr. The product (169 mg) was isolated as described above, and proved identical with the sample of 8,9-10,11-dianhydroerythromycin B 6,9-hemiacetal (11) prepared from 10 as described above.

8-epi-11,12-Epoxyerythromycin A (16). --- a.) A solution of 11,12-epoxyerythromycin A (14) in 26 ml of glacial acetic acid was allowed to stand at room temperature for 1 hr, and then added dropwise to a stirred suspension of 50 g of $NaHCO_3$ and 300 ml of water. Chloroform extraction of the resulting mixture gave 1.92 g of white glass. Partition column chromatography of 1.77 g gave 1.17 g of pure 8-epi-11,12-epoxyerythromycin A (16): $[\alpha]_D^{26}$ - 68°; ir 3600–3550, 3510–3430, 1727 cm^{-1}, nmr δ 3.35 (OMe), 2.72 (C-12 H, $J_{10,11}$ 10.0 Hz), 2.29 (NMe_2), 1.58 (C-6 Me).

Anal. Calcd for $C_{37}H_{65}O_{12}N$: C, 62.08; H, 9.15; N, 1.96 Found:C, 61.95; H, 9.27; N, 1.90.

Later fractions gave 37 mg of 8,9-10,11-dianhydroerythromycin A 6,9-hemiacetal (11) (See below).

b.) A solution of 1.20 g of 11,12-epoxyerythromycin A (14), 20 ml of acetic acid, and 20 ml of water was allowed to stand at room temperature for 24 hr. The product was isolated by chloroform extraction as described above to yield 1.1 g of 8-epi-11,12-

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epoxyerythromycin A (16). Partition column chromatography gave 536 mg of pure 16.

8,9-10,11-Dianhydroerythromycin A 6,9-hemiacetal (17). --- a.) A solution of 1.57 g of 10,11-anhydroerythromycin A (13) in 20 ml of glacial acetic acid was allowed to stand at room temperature for 4 hr. The usual workup and chloroform extraction gave 1.23 g of 17. Repeated partition column chromatography gave 527 mg of analytically pure 17: $[\alpha]_D^{26}$ - 88°; λ_{max} 267nm (ϵ 2628); ir 3605; 3554, 3500–3400, 1727 cm^{-1}, nmr δ 5.26 (C-11 H); 3.32 (OMe), 2.28 (NMe_2), 1.88 (C-10 Me), 1.60 (C-8 Me), 1.46 (C-6 Me).

Anal. Calcd for $C_{37}H_{63}O_{11}N$: C, 63.68; H, 9.10; N, 2.01. Found: C, 63.56; H, 9.29; N, 1.94.

b.) A solution of 1.98 g of 8-epi-10,11-anhydroerythromycin A (15) in 25 ml of glacial acetic acid was allowed to stand at room temperature for 24 hr. The usual workup followed by chloroform extraction gave 1.66 g of 8,9-10,11-dianhydroerythromycin A 6,9-hemiacetal (17).

c.) A solution of 205 mg of 11,12-epoxyerythromycin A (14) in 2.5 ml of glacial acetic acid was allowed to stand at room temperature for 46 hr. The usual workup gave 162 mg of white glass. Partition column chromatography of 120 mg gave 47 mg of pure 17.

d.) A solution of 300 mg of 8-epi-11,12-epoxyerythromycin A (16) in 3.8 ml of glacial acetic acid was allowed to stand at room temperature for 46 hr. The usual workup gave 248 mg of white glass.

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Partition column chromatography gave 133 mg of pure 17.

8-epi-10,11-Anhydroerythromycin A (15). --- a.) A mixture prepared from 6.0 g of 10,11-anhydroerythromycin A (13), 3.9 g of DBU, 0.51 ml of methanesulfonic acid, and 31 ml of benzene was heated under reflux for 96 hr. The usual workup gave 4.82 g of glass, the nmr spectrum of which indicated a 3 to 1 mixture of 8-epi-10,11-anhydroerythromycin A (15) and 10,11-anhydroerythromycin A (13) based on the heights of the corresponding C-10 methyl protons. Pure 15 was isolated by partition column chromatography: $[\alpha]_D^{26}$ -59°; λ_{max} 231nm (ϵ 8801); ir 3604, 3550-3400, 1728, 1664 cm^{-1}, nmr δ 6.45 (C-11 H), 3.28 (OMe), 2.28 (NMe_2), 2.08 (C-10 Me).

Anal. Calcd for $C_{37}N_{65}O_{12}N$: C, 62.08; H, 9.15; N, 1.96. Found: C, 62.15; H, 9.34; N, 1.89.

b.) A mixture of 387 ml of 8-epi-11,12-epoxyerythromycin A (16), 243 mg of DBU, 0.032 ml of methanesulfonic acid and 3.22 ml of benzene was heated under reflux for 3 hr. The usual workup and benzene extraction gave 308 mg of 8-epi-10,11-anhydroerythromycin A (15).

8,9-Anhydro-11,12-epoxyerythromycin A 6,9-Hemiacetal (18). --- A solution of 2.22 g of 11-O-methanesulfonyl-8,9-anhydroerythromycin A, 6,9-hemiacetal (20c), 3.0 g of DBU and 36 ml of benzene was heated under reflux for 18 hr. The usual workup followed by benzene extraction gave 1.74 g of white glass. Partition column chromatography of 1.10 g gave 834 mg of pure 8,9-anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal: $[\alpha]_D^{26}$ -42°, ir 3590 (shoulder), 3550, 3500-3400,

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1727; nmr δ 3.28 (OMe), 2.66 (C-11 H, $J_{10,11}$ = 6.2 Hz), 2.28 (NMe_2), 1.62 (C-8 Me), 1.39 (C-6 Me).

Anal. Calcd for $C_{37}N_{63}O_{11}N$: C, 63.68; H, 9.10; N, 2.01. Found: C, 63.81; H, 9.14; N, 1.90.

Treatment of 8,9-Anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (18) with Glacial Acetic Acid. --- A solution of 184 mg of 18 in 2.2 ml of glacial acetic acid was allowed to stand at room temperature for 1 hr and then added dropwise to a stirred suspension of 8.7 g of $NaHCO_3$ in 87 ml of water. Benzene extraction gave 161 mg of white glass. Partition column chromatography gave 38.4 mg of recovered 18, 39 mg of 8,9-10,11-dianhydroerythromycin A (17) and 17 mg of 8-epi-11,12-epoxyerythromycin A (16).

Treatment of 8,9-Anhydro-11,12-epoxyerythromycin A 6,9-hemiacetal (18), with 1:1 Acetic Acid–Water. --- A solution of 612 mg of 18, 9.6 ml of acetic acid and 9.6 ml of water was allowed to stand at room temperature for 0.5 hr and then added dropwise to a stirred suspension of 30 g of $NaHCO_3$ in 300 ml of water. Chloroform extraction gave 641 mg of white glass. Partition column chromatography gave 297 mg of 11,12-epoxyerythromycin A (14) and 109 mg of 8-epi-11,12-epoxyerythromycin A (16).

Treatment of 8,9-10,11-Dianhydroerythromycin A 6,9-hemiacetal (17) with DBU in Benzene in the Presence of Methanesulfonic Acid and Water. --- A solution of 704 mg of 17, 476 mg of DBU, 0.018 ml of water, 0.065 ml of methanesulfonic acid, and 6 ml of benzene was heated under reflux for 94 hr. The usual workup, and benzene extraction gave 585 mg of recovered 17.

cm^{-1}) to the lactone carbonyl absorption (1729 cm^{-1}) from 0.5 to 0.8. This established that the minor component was the hemiacetal tautomer **14b** which was largely converted to the hydroxy ketone tautomer **14a** on heating in deuteriochloroform.

A preparative attempt to convert the 1.2:1 mixture of **14a** and **14b** to a 2.4:1 mixture by heating a chloroform solution of **14** under reflux for 0.5 hr was unsuccessful. After evaporation of chloroform under reduced pressure and drying of the residue under high vacuum at 56° for 20 hr, the hydroxy ketone to hemiacetal ratio (**14a**:**14b**) was identical with that of the starting material (1.2:1) by criteria of both nmr and ir. This result is interpreted to indicate that the 2.4:1 ratio of **14a** to **14b** in the heated chloroform solution reverted to the original 1.2:1 ratio on evaporation of solvent.

An nmr spectrum of a freshly prepared sample of **14** in methanol-d_4 showed a ratio of hydroxy ketone to hemiacetal of 1.2. On heating at 56° for 0.5 hr, the ratio changed to 0.9 favoring the hemiacetal. The identities of the two components in methanol-d_4 is based on the intensity of the singlet at δ 1.63 attributed to the C-6 methyl of the hemiacetal **14b,** relative to the intensities of the two NMe_2 peaks observed.

A pure sample of the hemiacetal tautomer **14b** was isolated (70% recovery) by crystallization from ether. The tautomeric purity of **14b** was established from the nmr spectrum of a freshly prepared solution in deuteriochloroform. When the nmr spectrum was determined after the solution had remained at room temperature overnight it was found that the sample had reverted to a 2.3:1 mixture of **14a** to **14b.** When the solution was heated at 56° for 0.5 hr the ratio of **14a** to **14b** was found to be 2.4:1.

These data indicate that the tautomers **14a** and **14b** are interconvertible, but have a sufficiently high energy barrier to interconversion to preclude rapid equilibration at room temperature in chloroform solution.

In contrast to 11,12-epoxyerythromycin A, which exists as an interconvertible mixture of tautomers **14a** and **14b,** the following evidence indicates that 8-*epi*-11,12-epoxyerythromycin A exists exclusively as the hemiacetal (**16**).

(1) The nmr spectrum of a freshly prepared solution of **16** in $CDCl_3$ showed only one sharp NMe_2 peak and one sharp OMe peak, and otherwise indicated the presence of a single component. The appearance of the spectrum did not change on prolonged heating of the solution at 56°.

(2) The ir spectra of the pure C-8 epimeric hemiacetals **14b** and **16** (in deuteriochloroform) were virtually identical. Both showed only lactone carbonyl absoprtions at 1727 cm^{-1}. In contrast the 1.2:1 mixture of **14a** and **14b** showed both lactone (1729 cm^{-1}) and ketone (1708 cm^{-1}) absorptions.

(3) The nmr spectra of the hemiacetals **14b** and **16** showed singlet *C*-methyl absorptions at δ 1.66 and 1.57, respectively, tentatively assigned to the C-6 methyl protons. In contrast the hydroxy ketone **14a** shows no such absorption in the region between δ 1.40 and 2.30.

(4) The C-10 proton resonances of the hemiacetals **14b** and **16** appear at δ 2.4 ($J_{10,11}$ = 10.0 Hz) and 2.21 ($J_{10,11}$ = 10.0 Hz), respectively, while the C-10 proton resonance of the hydroxy ketone **14a** appears at δ 3.09 ($J_{10,11}$ = 10.0 Hz). This downfield shift of the C-10 proton resonance of **14a** relative to the hemiacetals is presumably the consequence of the presence in **14a** of the C-9 keto carbonyl.

Examination of Dreiding models of the hydroxy ketone and hemiacetal tautomers of 8-*epi*-11,12-epoxyerythromycin A suggests that relief of steric interaction between the C-6 and C-8 methyl groups, resulting from cyclization to the hemiacetal **16,** may be a major factor responsible for the existence of **16** as the sole observable tautomer. In contrast, no steric interaction between the C-6 and C-8 methyl groups of either the hydroxy ketone **14a** or the hemiacetal **14b** of 11,12-epoxyerythromycin A is apparent.

Circular Dichroism of the 10,11-Anhydroerythromycins. Circular dichroism determinations have shown that the C-8 epimeric 10,11-anhydroerythromycins have quite distinctive n → π^* transitions of the C-9 keto carbonyls. The 10,11-anhydro ketones with the natural configuration at C-8 show circular dichroism minima (**13,** $[\theta]_{340}$ −870; **10,** $[\theta]_{327}$ −2185) while the 8-*epi*-10,11-anhydro ketones show circular dichroism maxima (**15,** $[\theta]_{310}$ +1100; **12,** $[\theta]_{320}$ +1940). The signs of the n → π^* bands of the C-8 epimeric 3,5-di-*O*-acetylerythronolides B (**4,** $[\theta]_{335}$ −2130; **5,** $[\theta]_{304}$ +1620) confirm the assignments of Perun.[4] The relationship of the CD curves of **4** and **5** to that of 10,11-anhydroleandromycin diacetate has been discussed by Celmer.[3a]

Antibacterial Activities. Antimicrobial activities of many of the modified erythromycins described above, against a cross section of bacteria, are shown in Table I. None of the compounds possess *in vitro* antibacterial activity approaching that of the parent erythromycins and most are devoid of activity against many strains except at extreme levels. Earlier reference was made to the predictions of Celmer,[3b] later abandoned,[3a] concerning the possible antibacterial benefit of C-8 epimerization. It should be noted that C-8 epimerization of erythromycin B drastically lowers *in vitro* activity against wild and resistant strains, thus conforming to the current view of Celmer.[3a]

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(10) DBU is extremely caustic and should be used with care. Tests with rabbits have shown it to be instantly destructive of eye tissue.
(11) N. L. Oleinick and J. W. Corcoran, *J. Biol. Chem.*, **244**, 727 (1969).
(12) Obtained from several runs.

Studies on Resin Acids. IX. Synthesis and Stereochemistry of 6-Ketoabietatrienes[1]

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In an effort to explore the stereochemistry of 6-ketoabieta-8,11,13-trienes, 18-nor-5β-abieta-8,11,13-trien-6-one (**8**), 19-nor-5β-abieta-8,11,13-trien-6-one (**14**), 19-norabieta-8,11,13-trien-6-one (**3**), and abieta-8,11,13-trien-6-one (**1**) have been prepared. 19-Norabieta-8,11,13-triene (**7**) was converted to ketone **8** by the sequence oxidation to 18-norabieta-8,11,13-trien-7-one (**5**), reduction to the 7β-ol (**6**), dehydration to 18-norabieta-6,8,11,13-tetraene (**4**), oxidation to a mixture of glycols, and dehydration to **8**. 19-Norabieta-8,11,13-trien-6-one (**3**) was prepared by a similar route using 19-norabieta-8,11,13-trien-7-one (**19**) as starting material and also by isomerization of 19-nor-5β-abieta-8,11,13-trien-6-one (**14**). Ketone **14** was obtained by oxidation of 19-nor-5β-abieta-8,11,13-trien-6β-ol (**15**), which was the principal alcoholic product from the hydroboration–oxidation of 18-norabieta-4,8,11,13-tetraene (**9**). Prolonged treatment of **9** with diborane, followed by oxidation, gave a mixture of 19-nor-5β-abieta-8,11,13-trien-7α- and -7β-ol (**17** and **18**). Abieta-8,11,13-trien-6-one (**1**) was prepared from abieta-8,11,13-triene (**23**) by the method used for the synthesis of ketones **3** and **8**. The mechanism of the anomalous hydroboration of **9** and the conformations of the various 6-ketones are discussed.

Several naturally occurring compounds, among them taxodione[2] and maytenoquinone,[3] have been isolated which contain a keto group in the 6 position of an abietane ring system. In addition to these compounds, and their derivatives, the parent compound abieta-8,11,13-trien-6-one (**1**) has been prepared,[4] as have a few other structurally related ketones.[5] In the compounds of this type in which the stereochemistry about the A–B ring fusion has been discussed, it has been either shown or assumed that the stable ring juncture is trans. However, ketones similar to **1** are essentially 9-methyl-1-decalone systems, in which it is known that there is very little energy difference between the cis and trans isomers,[6] and in the trans isomer of **1** there is also a severe axial–axial interaction between the β-methyl group (C-19) at C-4 and the angular methyl. It would thus appear that for ketones such as **1** the cis isomer should be more stable. In order to explore this apparent stereochemical inconsistency, the synthesis of **1** has been reinvestigated, and the preparation of the 18- and 19-nor ketones (**2** and **3**) and their stereochemical preferences at C-5 studied.

The obvious precursor of the 18-nor ketone (**2**), 18-norabieta-6,8,11,13-tetraene (**4**), was prepared from 18-norabieta-8,11,13-trien-7-one (**5**)[7] by hydride reduction to the 7β-ol (**6**) which gave olefin **4** on dehydration with toluenesulfonic acid in benzene. In order to ensure that no isomerization at C-5 had occurred under the conditions of the dehydration, olefin **4** was reduced to18-norabieta-8,11,13-triene (**7**).[8] The attempted direct conversion of ketone **5** to the olefin by reaction with toluenesulfonylhydrazine, followed by methyllithium,[9] gave a complex mixture containing no hydrocarbon.

Although olefins similar to **4** have been converted to the 6-ketones by various procedures,[4,5a] in our hands these did not prove efficient and an alternative route was chosen, which entailed oxidation of **4** to a stereoisomeric mixture of cis glycols using sodium chlorate–osmium tetroxide,[10] followed by treatment with hot formic acid to give the 6-ketone.

The nmr spectrum of the product ketone shows a secondary methyl signal at δ 0.84 with a coupling constant of 5 Hz, indicating that this group is equatorial,[11] consistent only with a cis A–B ring fusion and a steroidal conformation of these rings.[12] It is thus aparent that the product of this sequence is 18-nor-5β-abieta-8,11,13-trien-6-one (**8**), and that during the reaction with formic acid, isomerization to the more stable cis isomer has occurred.

19-Norabietatrien-6-one (**3**) was initially obtained *via* a fortuitous series of reactions resulting from the investigation of the hydroboration–oxidation of 18-norabieta-4,8,11,13-tetraene (**9**). It has been reported that hydroboration–oxidation of the mixture of olefins obtained by lead tetraacetate decarboxylation of abieta-8,11,13-trien-18-oic acid (dehydroabietic acid) affords, in addition to other products, 19-nor-5β-abieta-8,11,13-trien-7-one (**10**).[7] It was suggested that this ketone was probably derived from olefin **9** *via* 19-nor-5β-abieta-8,11,13-triene (**11**); however, this could not be confirmed. In subsequent work, attempts were made to obtain a homogeneous sample of hydrocarbon **9**; however, a practical method for preparation of this compound by acid-catalyzed isomerization of the mixture of olefins obtained from dehydroabietic acid could not be accomplished.[12b]

Attempted separation of a mixture of **9** and 18-nor-5β-abieta-3,8,11,13-tetraene (**12**)[12] by reaction with bis(3-methyl-2-butyl)borane, which has been utilized to separate trisubstituted from tetrasubstituted olefins, gave residual hydrocarbons with essentially the same composition as the starting mixture.[13] Both olefins apparently react with the reagent at nearly the same rate, and 18-nor-5β-abieta-8,11,13-trien-3α-ol (**13**),[12b] arising from olefin **12**, was isolated from the reaction. When the mixture of olefins from the decarboxylation of dehydroabietic acid[7] was treated