THE STRUCTURES OF THE *m*-CHLOROPERBENZOIC ACID OXIDATION PRODUCTS OF 8,9-ANHYDROERYTHROMYCINS A- AND B-6,9-HEMIACETAL AND OF (8S)-8-HYDROXYERYTHROMYCIN B

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^{13}C-NMR studies have confirmed the structures of (8S)-8-hydroxyerythromycins A- and B-6,9;9,11-acetal proposed by KROWICKI and ZAMOJSKI[2,3] for the products of the *m*-chloroperbenzoic acid oxidation of 8,9-anhydroerythromycins A- and B-6,9-hemiacetal. The preparations of (8S)-8-methylthiomethoxy- and (8S)-8-methoxyerythromycin B-6,9;9,11-acetals are described. The latter are stable in aqueous acetic acid under conditions which convert (8S)-8-hydroxyerythromycin B-6,9;9,11-acetal into (8S)-8-hydroxyerythromycin B.

In a paper describing the preparation of the C_8-epimeric 8-hydroxyerythromycins B, we reported[1] that buffered *m*-chloroperbenzoic acid oxidation of 8,9-anhydroerythromycin B-6,9-hemiacetal (**1**), followed by catalytic reduction of the resulting *N*-oxide to the free amine, gave (8S,9S)-8,9-anhydroerythromycin B-6,9-hemiacetal-8,9-epoxide (**2**). Our assignment of structure **2** was based on the expected course of olefin epoxidation with peracids and with apparently compatible spectral properties. In addition, the facile conversion of **2** to (8S)-8-hydroxyerythromycin B (**3**) in aqueous acetic acid was expected for the strained epoxy spiroacetal structure (**2**).

Recently, KROWICKI and ZAMOJSKI[2] reported that *m*-chloroperbenzoic acid oxidation of the enol ether **1**, followed by *N*-oxide reduction, gave (8S)-8-hydroxyerythromycin B-6,9;9,11-acetal (**4a**). The structure of **4a** was assigned[2] on the basis of the following observations. Treatment of **4a** with acetic anhydride in pyridine gave the 2′,4″-di-*O*-acetyl derivative **4b** which established the resistance of the lactone ring hydroxyl group to esterification which is characteristic of a tertiary hydroxyl group. The infrared spectrum of **4b**, determined at high dilution in carbon tetrachloride, showed the presence of only a single band in the OH region at 3618 cm^{-1} characteristic of a tertiary hydroxyl group. A split band at 960 cm^{-1} suggested the presence of an oxetane structure. In addition, the infrared spectrum of the hydrorhodanide of **4a** was very similar to that of a compound the structure of which was assigned as (8S)-8-hydroxyerythromycin A-6,9;9,11-acetal (**4c**)[2,3].

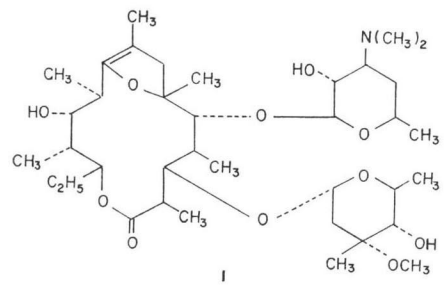
The similar modes of preparation, melting points, and reported NMR parameters of our product[1] and that of KROWICKI and ZAMOJSKI[2] suggested that they were identical. We confirmed the observation that the hydroxyl group attached to the lactone ring was not esterified with acetic anhydride in pyridine, and in addition was not methanesulfonylated with methanesulfonic anhydride in pyridine. However this evidence is more suggestive than definitive. The 11-hydroxyl group of the erythromycins is known[4,5] to esterify slowly and the assignment of discrete infrared bands in such detailed spectra leads to a nonrigorous structural assignment.

CMR spectroscopy offers a clear opportunity to differentiate between structures **2** and **4**. The key lies in the presence of a strained 3-membered epoxide ring in **2** *versus* a 4-membered oxetane ring in **4**. STOTHERS[6] reported the chemical shifts of the carbons adjacent to oxygen in 4- and 5-membered saturated hetero-rings as 72.8 and 68.6 ppm while the same carbons in a strained 3-membered epoxide ring show a substantial upfield shift to 39.7 ppm.

A number of strain-free erythromycin spiroacetal model compounds have been examined by CMR. The C-9 chemical shifts of erythromycin A-6,9;9,12-acetal (**5**) and erythralosamine (**6**) are 116.4 and 120.1 ppm respectively.[7] The methyl acetal of 8-hydroxyerythromycin A (**7**) has a C-9 chemical shift of 106.7 ppm (Table 1). Incorporation of C-9 into a 3-membered ring as in **2** would be expected to result in a chemical shift of approximately 80~90 ppm while the presence of a 4-membered ring as in **4** would result in a chemical shift of approximately 110~120 ppm. As shown in Table 1 the measured C-9 chemical shifts of the erythromycin A and B derivatives are 117.8 and 115.4 ppm thereby clearly supporting structure **4**.

With the thought of providing additional positive evidence to distinguish between the structures **2** and **4a**, it was hoped that alkylation of the hydroxyl group of the lactone ring might strengthen the chemical-spectroscopic proof of structure. Treatment of the oxidation product **2** or **4a** with acetic anhydride in dimethylsulfoxide gave the 4″-oxo-methylthiomethyl ether **8** or **9** which was reduced with sodium borohydride to the methylthiomethyl ether **10** or **11**[8]. RANEY nickel reduction of **8** or **9** gave the methyl ether **12** or **13**.

In the case of structures **10** and **12** a C-11 hydroxyl would be derivatized and a downfield β-shift of C-11 and an upfield γ-shift for C-10 and C-12 would be anticipated. An 8-hydroxyl group would be alkylated in structures **11** and **13** and therefore C-8 would be shifted downfield while C-7 and C-9 undergo upfield shifts. This analysis is not dependent on total and unambiguous carbon assignments (even though they are available) as the off-resonance single frequency decoupling (ORSFD) multipli-



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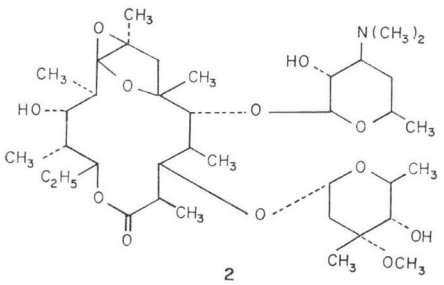

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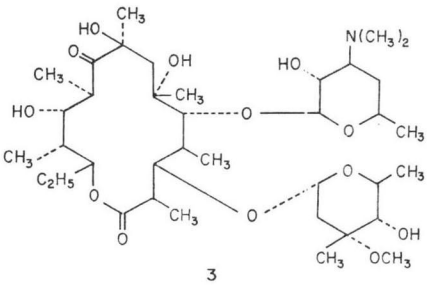

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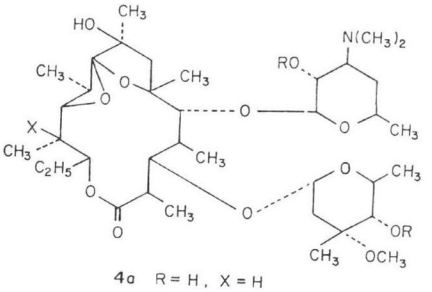
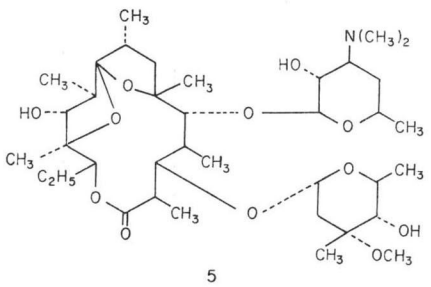


4a R = H, X = H
4b R = $COCH_3$, X = H
4c R = H, X = OH

cities of the affected resonances are diagnostic, *i.e.* in the case of **10** and **12** three doublets are involved whereas in **11** and **13** a triplet and 2 singlets are involved. The measured chemical shifts (Table 1) reveal substantial C-8 downfield and C-7 upfield shifts and confirm the assignment of structures **11** and **13** to these derivatives and of structure **4a** to the starting material. The C-9 chemical shift change is modest and downfield which is a likely consequence of an unfavorable spatial relationship between this carbon and the 8-hydroxyl substituent[9] and does not weaken the assignment of structure **4a**.

The involvement of a hydroxyl group in the course of the epoxidation of an olefin to give larger cyclic ethers is unusual, but not without precedent. WILSON and SHAW[10] obtained large amounts of 5-and 6-membered epoxides from the epoxidation of (−)-α-terpineol. To our knowledge the



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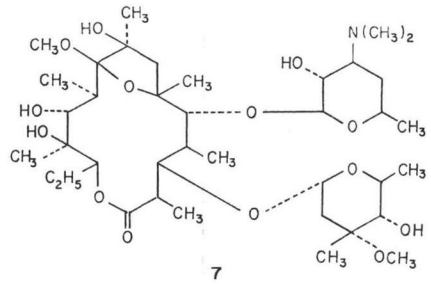

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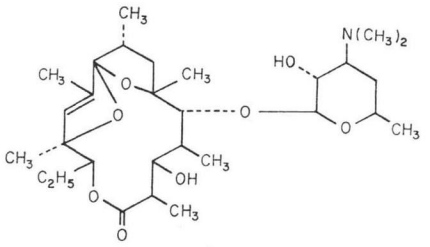

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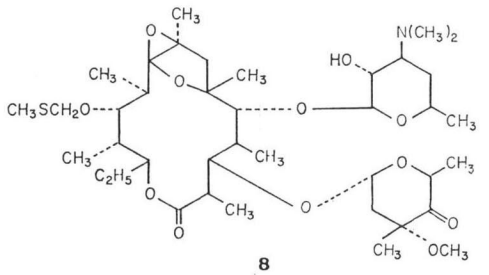

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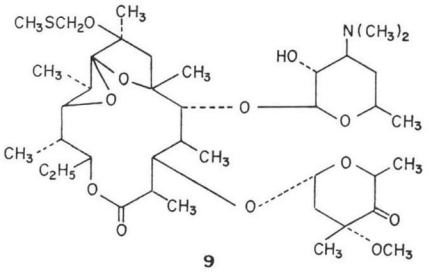

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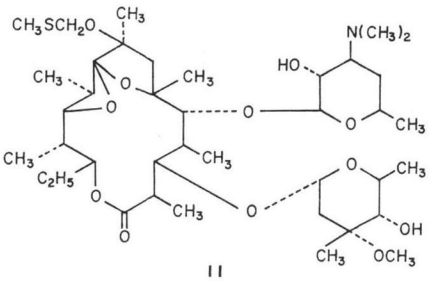

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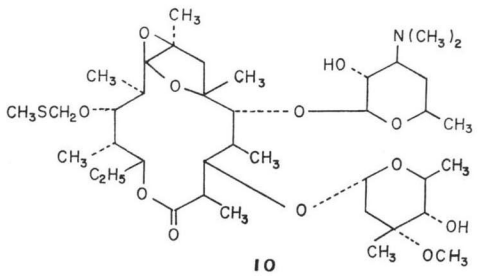

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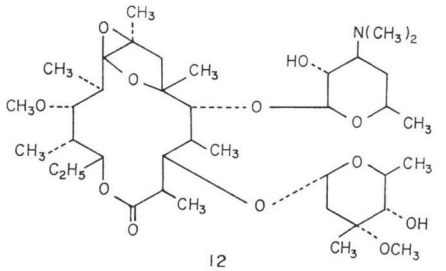

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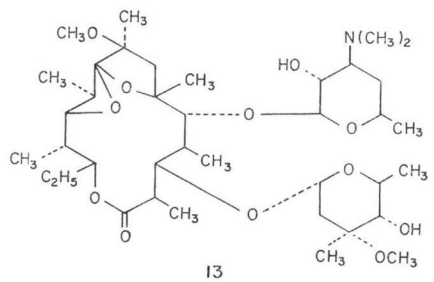
Table 1. CMR Chemical shifts

	Erythromycin A	7	4c	Erythromycin B	3	4a	11	13
C-1	175.8	177.9	117.2	176.1	175.9	178.1	177.9	178.0
C-2	45.1	44.9	43.3	44.9	45.4	43.9	43.9	43.9
C-3	80.0	80.7	77.1	80.4	80.5	76.5	76.6	76.7
C-4	39.5	40.8	42.6	40.0	39.8	42.6	42.6	42.6
C-5	83.6	83.5	80.9	83.8	86.4	81.3	81.6	81.7
C-6	75.1	82.4	87.7	75.3	75.0	86.6	86.8	86.3
C-7	38.6	52.4	44.0	38.2	42.8	43.6	37.7	35.8
C-8	44.9	84.3	80.3	44.7	78.8	80.8	86.5	85.6
C-9	221.8	106.7	117.8	220.0	217.7	115.4	115.9	115.9
C-10	38.0	35.6	37.4	39.2	39.8	36.5	36.7	36.5
C-11	69.0	66.9	81.6	69.4	69.0	77.4	78.7	78.5
C-12	74.7	76.0	74.8	39.5	39.7	36.1	36.3	36.3
C-13	77.0	79.6	82.7	75.0	74.9	79.4	79.3	79.4
C-14	21.2	20.9	23.3	25.7	25.2	20.0	20.1	20.1
C-1″	96.4	97.6	94.7	96.6	97.0	94.4	94.5	94.5
C-2″	35.0	35.3	34.6	35.1	35.1	34.8	34.9	35.0
C-3″	72.6	72.6	73.2	72.7	72.6	73.1	73.2	73.2
C-4″	78.3	78.0	78.1	78.1	78.0	77.9	78.4	78.5
C-5″	65.6	65.4	65.3	65.5	65.1	65.3	65.3	65.4
C-6″	18.7	17.8	18.1	18.5	18.5	18.3	18.4	18.3
OCH_3	49.5	49.3	49.5	49.5	49.4	49.6	49.6	49.6
3″-CH_3	21.4	21.2	21.4	21.4	21.3	21.4	21.4	21.4
C-1′	103.3	104.1	102.4	103.3	103.6	103.0	103.1	103.1
C-2′	71.0	70.5	70.8	71.0	70.9	70.7	70.8	70.9
C-3′	65.6	65.6	65.8	65.6	65.7	65.9	66.0	66.0
C-4′	28.8	28.6	28.6	28.8	28.8	28.7	28.8	28.8
C-5′	69.0	69.1	68.6	68.9	69.1	68.8	68.8	68.8
C-6′	21.5	21.5	21.6	21.4	21.4	21.7	21.7	21.7
$N(CH_3)_2$	40.3	40.2	40.3	40.3	40.3	40.3	40.4	40.3
2-CH_3	15.9	17.6	11.3	15.6	16.1	12.6	12.7	12.6
4-CH_3	9.2	8.3	9.3	9.3	9.7	9.0	8.9	9.0
6-CH_3	27.0	31.5	28.1	27.3	28.5	28.0	27.5	27.0
8-CH_3	18.3	24.8	23.6	18.7	28.7	23.1	17.7	17.0
10-CH_3	12.0	11.0	11.6	9.3	9.1	12.8	12.8	12.8
12-CH_3	16.2	15.2	20.8	9.3	9.7	8.8	8.7	8.7
14-CH_3	10.7	10.8	10.4	10.4	10.4	11.1	11.2	11.1
9-OCH_3	—	50.7	—	—	—	—	—	—
O-CH_2-S	—	—	—	—	—	—	66.5	—
S-CH_3	—	—	—	—	—	—	14.4	—
8-OCH_3	—	—	—	—	—	—	—	49.0



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oxidation of the erythromycin enol ether is the first example of such an oxidation giving an oxetane as the only major product.

Treatment of either the methylthiomethyl ether **11** or the methyl ether **13** with aqueous acetic acid under conditions sufficient to effect complete conversion of **4a** to (8S)-8-hydroxyerythromycin B (**3**) gave, in both cases, essentially complete recovery of starting material. This suggests facilitation of the acid catalyzed hydrolysis of the spiroacetal system by the neighboring C_8-hydroxyl. Facilitation of epoxy ring openings by neighboring hydroxyl groups has recently been reported by BARTON[11].

The CMR data obtained for (8S)-8-hydroxyerythromycin B (**3**) offer additional support for its assigned structure[1,2]. Most significant are the chemical shift changes localized in the C-7 through C-9 ring segment and the lack of chemical shift effects elsewhere (Table 1). These observations, plus the previously reported PMR results[1], with particular emphasis on the magnitudes of $J_{10,11}$ and $J_{11,12}$ which are unchanged in comparison with those of erythromycin B, offer strong evidence that the configuration at C-11 is unchanged in this compound. The CD molar amplitudes of **3** and erythromycin B, calculated from published molecular rotations[1], are $-117.3°$ and $-131.9°$, respectively. The erythromycin B value is in reasonable agreement with the reported by KROWICKI and ZAMOJSKI[2]. The value for **3**, however, does not show their reported large decrease in amplitude and therefore does not support C-11 epimerization which was suggested by KROWICKI and ZAMOJSKI[2]. Taken together the spectroscopic data support the structure of (8S)-8-hydroxyerythromycin B (**3**).

Experimental

General Procedures

Optical rotations were measured with methanol solutions with a Hilger and Watts polarimeter. IR spectra were determined with deuteriochloroform solutions using a Perkin-Elmer Model 521 grating spectrometer. Mass spectra were recorded with an A.E.I. MS-902 mass spectrometer with an ionizing energy of 70 eV; samples were introduced into the source by a direct inlet system. PMR spectra were determined at 100 Hz using a Varian HA-100 spectrometer with deuteriochloroform solutions. CMR spectra were measured using a Varian XL-100-15/Transform Technology TT-100 spectrometer system. Chemical shifts were measured in deuteriochloroform solution and are reported in ppm downfield from internal TMS.

Assignment of Resonances

The CMR spectra of the erythromycins have been reported by ROBERTS[7] and others[12,13]. Complete assignments have been made by extensive use of model compounds and specific frequency spin decoupling experiments (SFD). In the cases of compounds **3**, **4a**, **4c**, **7**, **11**, and **13**, the CMR spectra of which were not previously reported, signals were first assigned to the sugar carbons since these are expected to show the least variation in chemical shift. As anticipated, with the exception of the anomeric carbons which suffer conformational effects, all sugar carbons have consistent chemical shifts throughout the series and show less than ± 0.5 ppm variation. These carbon assignments are made by direct comparison with the erythromycins. Some ambiguity may remain on the particular assignment for pairs of carbons with close chemical shifts (*i.e.* C-3′, C-5″ or 3″-CH_3, 6′-CH_3) but these assignments have no structural significance in relation to the present discussion.

Aglycone carbon assignments are made by comparison with known models and the use of substituent effects. Substitution of an hydroxyl group at C-8 in **3** results in a large downfield α-shift for C-8 and a smaller downfield β-shift at C-7 as expected. The γ-effect at C-6 is unusually small as are the β- and γ-effects at C-9 and C-10; however, ring carbon assignments can be made with confidence.

Aglycone ring carbons C-3, 5, 10, 11 and 13 in the oxetanes **4a** and **4c** were assigned by SFD experiments and the same carbons in **11** and **13** were assigned by analogy. Substantial downfield shifts are observed for C-6 and C-11 as a consequence of their involvement in the spiroacetal group. A comparison of the remaining aglycone ring chemical shifts with those of **3** reveals a general $\pm 2 \sim 3$ ppm variance, presumably a consequence of aglycone conformational changes. The quaternary carbons C-6 and C-8 were differentiated by the downfield β-shift exhibited by the latter in the substituted derivatives **11** and **13**. In every case the important assignment of C-7 was confirmed by ORSFD multiplicity. Firm differentiation between C-2 and C-4 as well as many aglycone methyl carbons are not possible but neither are they structurally significant.

(8S)-8-Methylthiomethoxy-4″-oxoerythromycin B-6,9;9,11-acetal (**9**)

A solution prepared from 2.02 g of (8S)-8-hydroxyerythromycin B-6,9;9,11-acetal (**4a**), 12.8 ml of acetic anhydride and 19 ml of dimethylsulfoxide was allowed to stand at room temperature for 50 hours. The resulting solution was added dropwise to a magnetically stirred solution of 8 g of sodium carbonate in 80 ml of water. Water (80 ml) was added and excess solid sodium bicarbonate was added portionwise to the stirred suspension. The mixture was shaken with a mixture of 200 ml of water and 400 ml of chloroform. The chloroform solution was separated and washed with two 400-ml portions of water. The aqueous solutions were washed in series with three 200-ml portions of chloroform. The chloroform solutions were combined and evaporated under reduced pressure. Residual dimethylsulfoxide was removed by codistillation with benzene under reduced pressure. The residue was dissolved in a solution prepared from 5 ml of 5% aqueous sodium bicarbonate and 50 ml of methanol, and the solution was stirred at room temperature for 18 hours. The product (2.13 g of white glass) was isolated by chloroform extraction. The product crystallized on standing to give large flat prisms, mp 165~168°C, $[\alpha]_D^{22.5}$ −34.6° (*c* 0.94); IR 1718, 1737 cm^{-1}; M^+ 773.4398, Calcd. for $C_{39}H_{67}NO_{12}S$ 773.4384; C, 60.52; H, 8.72; N, 1.81%; Found C, 60.22; H, 8.65; N, 1.77%. PMR 2.18 (s, 3H, CH_3S); 2.31 (s, 6H, $(CH_3)_2N$–); 3.34 (s, 3H, CH_3O–); 4.47 (2H, OCH_2S–).

(8S)-8-Methylthiomethoxyerythromycin B-6,9;9,11-acetal (**11**)

A stirred, ice-bath cooled solution of 4.0 g of (8S)-8-methylthiomethoxy-4″-oxoerythromycin B-6,9;9,11-acetal (**9**) in 80 ml of methanol was treated with a freshly prepared solution of 2.64 g of sodium borohydride in 7.2 ml of water. After being stirred for 4 hours the solution was poured into 750 ml of water and extracted with chloroform. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated to leave 3.84 g of (8S)-8-methylthiomethoxyerythromycin B-6,9;9,11-acetal (**11**) as a foam: $[\alpha]_D^{23}$ −33.3° (*c* 1.03); IR 3425, 3359, and 1717 cm^{-1}; M^+ 775.4522, Calcd. for $C_{39}H_{69}NO_{12}S$ 775.4540; PMR 2.17 (s, 3H, CH_3S); 2.28 (s, 6H, $(CH_3)_2N$–); 3.36 (s, 3H, CH_3O–); 4.45 (2H, OCH_2S–).

(8S)-8-Methoxyerythromycin B-6,9;9,11-acetal (**13**)

(8S)-8-Methylthiomethoxyerythromycin B-6,9;9,11-acetal (**11**) (1.56 g) in ethanol (400 ml) was heated together with RANEY nickel (approximately 30 g, W-2 grade, thoroughly prewashed with ethanol) under gentle reflux with occasional agitation for 45 minutes. The mixture was cooled and filtered through a pad of Celite. The filter pad was washed well with ethanol and solvent was removed from the combined filtrate and washings. The residue was extracted exhaustively with benzene and the extracts were filtered and concentrated to a white glass (1.0 g); $[\alpha]_D^{25}$ −25.9° (*c* 0.94); IR 3550, 1708 cm^{-1}; M^+ 729.4653, Calcd. for $C_{38}H_{67}O_{12}N$ 729.4663; PMR 2.30 (s, 6H, $(CH_3)_2N$); 3.15 (s, 3H, CH_3O–); 3.37 (s, 3H, CH_3O–).

Treatment of (8S)-8-Methylthiomethoxyerythromycin B-6,9;9,11-acetal **11** with 1:1 Acetic Acid-Water

A solution of 150.0 mg of **11**, 2.5 ml of acetic acid and 2.5 ml of water was stirred at room temperature for 4 hours. The resulting solution was added dropwise to a magnetically stirred solution of 1 g of Na_2CO_3 in 12 ml of water. Excess solid $NaHCO_3$ was added portionwise. The resulting suspension was shaken with a mixture of 50 ml of $CHCl_3$ and 50 ml of water. The $CHCl_3$ solution was separated and washed with two 50-ml portions of water. The aqueous solutions were washed in series with three 50-ml portions of $CHCl_3$. The $CHCl_3$ solutions were combined and the $CHCl_3$ was evaporated under reduced pressure leaving 149.7 mg of white glass. Identical (PMR and TLC) with starting material **11**.

Treatment of (8S)-8-Methoxyerythromycin B-6,9;9,11-acetal (**13**) with 1:1 Acetic Acid-Water

(8S)-8-Methoxyerythromycin B-6,9;9,11-acetal (**13**) (141.1 mg) was treated with acetic acid (2.5 ml) and water (2.5 ml) under conditions identical to those used above for the treatment of (8S)-8-methylthiomethoxyerythromycin B-6,9;9,11-acetal (**11**), to obtain 139.1 mg of white froth identical (PMR, IR, and TLC) with (8S)-8-methoxyerythromycin B-6,9;9,11-acetal (**13**).

(8S)-8-Hydroxyerythromycin A-6,9;9,11-acetal (**4c**)

(8S)-8-Hydroxyerythromycin A-6,9;9,11-acetal (**4c**) was prepared according to the method of KROWICKI and ZAMOJSKI[3]. Isolation of the N-oxide intermediate was accomplished by chromatography on a column of Sephadex LH-20 from which it was eluted with chloroform - heptane - ethanol (10: 10: 1, v/v/v) after other by-products of the reaction. The reduced product (**4c**) was purified by a similar chromatography in chloroform - hexane (1: 1, v/v) and had the properties described in reference 3 and Table 1.

(8S)-8-Hydroxyerythromycin A-6,9-methylacetal (**7**)

(8S)-8-Hydroxyerythromycin A-6,9-methylacetal (**7**) was prepared by the method of KROWICKI and ZAMOJSKI[14]. The *N*-oxide intermediate was purified by chromatography on Sephadex LH-20 in chloroform - heptane - ethanol (10: 10: 1, v/v/v) as elution solvent prior to crystallization and the reduced product was purified by a similar chromatography using chloroform - hexane (1: 1, v/v) as solvent. Initial fractions yielded a minor by-product presumably epimeric with **7** at C-8 and/or C-9. M^+ 763.4731, Calcd. for $C_{38}H_{69}NO_{14}$ 763.4718; PMR 1.52 (s, 3H, C–CH_3); 2.26 (s, 6H, $(CH_3)_2$–N–); 3.26 (s, 3H) and 3.30 (s, 3H, 2X CH_3O–). Later fractions yielded (8S)-8-hydroxyerythromycin A-6,9-methylacetal **7** having the properties described in reference 14.

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