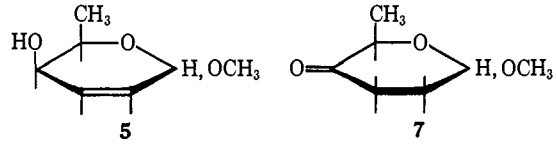
The pyranoside **1** was converted to the *N*-oxides **3** (M^+ 205), chromatography of which gave the α[3] [$C_9H_{19}NO_4$; mp 162–163°; $[\alpha]_D$ +117.3° (MeOH)] and β anomers [$C_9H_{19}NO_4$; mp 178–179°; $[\alpha]_D$ −37.2° (MeOH)]. Treatment of **3**α and **3**β with triethyl phosphite gave methyl α-D-rhodosaminide (**1**α; $[\alpha]_D$ +119.1° (MeOH); ν_{max} (liquid film) 3410, 2770, and 1045 cm^{-1}) and methyl β-D-rhodosaminide (**1**β; $[\alpha]_D$ −58.8° (MeOH); ν_{max} (liquid film) 3440, 2780, and 1070 cm^{-1}), respectively. The nmr of **1**α indicated a secondary methyl (δ 1.34, $J_{5a,6}$ = 7 Hz), a dimethylamino group (δ 2.30), a methoxyl group (δ 3.38), a triplet (H_1, δ 4.80, $J_{1e,2a} = J_{1e,2e}$ = 3 Hz), an octet (H_5, δ 4.07, $J_{5a,6}$ = 7 Hz, $J_{4e,5a}$ = 2.5 Hz), a quartet (H_4, δ 3.71, $J_{4e,5a}$ = 2.5 Hz, $J_{3a,4e}$ = 3 Hz), and an octet (H_3, δ 2.63, $J_{3a,4e}$ = 3 Hz, $J_{2a,3a}$ = 8.5 Hz, $J_{2e,3a}$ = 7.5 Hz). The nmr of **1**β showed a secondary methyl group (δ 1.29, $J_{5a,6}$ = 6.5 Hz), a dimethylamino group (δ 2.31), a methoxyl group (δ 3.39), a quartet (H_1, δ 4.66, $J_{1a,2a}$ = 8 Hz, $J_{1a,2e}$ = 5 Hz), a multiplet (H_{2a}, δ 1.55, $J_{1a,2a}$ = 8 Hz, $J_{2a,2e} = J_{2a,3a}$ = 12.5 Hz), a multiplet (H_{2e}, δ 1.99, $J_{1a,2e}$ = 5 Hz, $J_{2e,2a}$ = 12.5 Hz, $J_{2e,3a}$ = 4 Hz, $J_{2e,4e}$ = 1.5 Hz), an octet (H_5, δ 3.93, $J_{5a,6}$ = 6.5 Hz, $J_{4e,5a}$ = 4.5 Hz), a sextet (H_4, δ 3.54, $J_{4e,5a}$ = 4.5 Hz, $J_{3a,4e}$ = 4 Hz, $J_{2e,4e}$ = 1.5 Hz), and an octet (H_3, δ 2.31, $J_{3a,4e} = J_{2e,3a}$ = 4 Hz, $J_{2a,3a}$ = 12.5 Hz). The 1,3-diequatorial coupling between H_{2e} and H_{4e} lent additional support to the *lyxo* configuration. The mass spectrum of **1** gave a molecular ion at *m/e* 189 and fragment ions at *m/e* 114, 87, and 71, consistent with the proposed structure. The pK_a of 8.8 was in agreement with a β-amino alcohol grouping in **1**. Attempted acid hydrolysis of glycoside **1** caused extensive decomposition even under mild conditions. Acetylation of **1** gave the monoacetate **4** [M^+ 231; pK_a = 7.5; ν_{max} ($CHCl_3$) 1725, 1240 cm^{-1}; δ 1.12 (acetate)], which was identical with the product obtained in high yield on attempted oxidation of **1** with acetic anhydride–DMSO.[4,5] Pfitzner–Moffatt oxidation conditions gave only unreacted starting material **1**. The decrease in the pK_a on acetylation confirmed the presence of the β-amino alcohol sequence in **1**.

A Cope elimination on **3** gave a mixture of the amine **1** and the olefin **5**. When methyl D-rhodosaminide (**1**)



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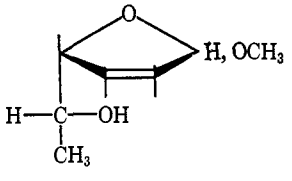

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was quaternized with methyl iodide and heated with sodium hydride, the same olefin [**5**; M^+ 144; ν_{max} 3400, 1055 cm^{-1}; δ 5.83 (multiplet, olefinic protons)] was obtained. The formation of the olefin **5** in the latter reaction, rather than an epoxide, confirmed the *cis* orientation of the dimethylamino and hydroxyl groups at C_3 and C_4, respectively, in D-rhodosamine.

Reduction of the olefin **5** gave the pyranoside[6] **6**, which on oxidation with ruthenium tetroxide gave the ketone **7** [M^+ 144; ν_{max} (liquid film) 1730 cm^{-1}], the CD curve of which showed a negative Cotton effect at λ_{max} 298 mμ ($\Delta\epsilon$ = −1.07) (methanol) indicating a D configuration for sugar **1**.[7]

The nmr of the furanoside **2** [$C_9H_{19}NO_3$; M^+ 189; $[\alpha]_D$ +12.4°; pK_a = 7.9; ν_{max} ($CHCl_3$) 3400, 2770, 1035 cm^{-1}] indicated a secondary methyl group (δ 1.21, J = 6 Hz, and δ 1.24, J = 6 Hz), a dimethylamino group (δ 2.23 and 2.29), and a methoxyl group (δ 3.36 and 3.38), while the mass spectrum gave ions at *m/e* 144, 115, 114, and 100 consistent with structure **2**. Acetylation of the furanoside **2** gave a monoacetate (**8**, M^+ 231; $[\alpha]_D$ +46.6°; pK_a = 7.6; ν_{max} ($CHCl_3$) 1730, 1245 cm^{-1}) which was identical with the product obtained on attempted oxidation of **2** with acetic anhydride–DMSO.[4,5] The nmr spectrum in deuteriobenzene showed a secondary methyl group (δ 1.31, J = 6.5 Hz), an acetyl group (δ 1.78), a dimethylamino group (δ 2.03), a methoxyl group (δ 3.18), a triplet (H_1, δ 4.86, $J_{1,2'} = J_{1,2}$ = 4 Hz), a quintet (H_5, δ 5.23, $J_{5,6} = J_{4,5}$ = 6.5 Hz), a quartet (H_4, δ 3.99, $J_{4,5}$ = 6.5 Hz, $J_{3,4}$ = 4.5 Hz), and a multiplet (H_3, δ 3.19). The above assignments were confirmed by spin decoupling.

The furanoside **2** was converted to the *N*-oxides **9**, and the α anomer crystallized [**9**α; mp 129–131°; M^+ 205; $[\alpha]_D$ +94.1°; pK_a = 6.0; δ 3.12, 3.20 (dimethylamino N-oxide)]. A Cope elimination on the *N*-oxide **9**α gave a mixture of the amine **2**α and the olefin **10**α [M^+ 144; $[\alpha]_D$ +147.5°; δ 6.06 (multiplet, olefinic protons)]. Reduction of the olefin **10** gave the furanoside[6] **11** (M^+ 146; $[\alpha]_D$ +38.3°), which on methylation gave the methyl ether **12** (M^+ 160; $[\alpha]_D$ +49.2°). Mercaptolysis of the furanoside **11** with ethanethiol gave the mercaptal (M^+ 238; $[\alpha]_D$ +12.1°).

Acknowledgments. The author wishes to express his thanks to Mr. M. Yudis and his colleagues for providing analytical and spectral services.

(3) Elemental analyses were satisfactory for all new compounds. Unless otherwise stated optical rotations were recorded at 26° in ethanol; nmr spectra were run at 60 MHz in $CDCl_3$ with internal TMS standard; ir spectra were obtained in CCl_4; pK_a values were recorded coulometrically in 66% aqueous DMF; mass spectra were obtained on a Perkin-Elmer RMU-6D instrument.

(4) Y. Ali and A. C. Richardson, *J. Chem. Soc., C*, 320 (1969).

(5) B. A. Dmitriev, A. A. Krost, and N. K. Kochetkov, *Bull. Acad. Sci. USSR, Chem. Ser.*, 903 (1969).

(6) C. L. Stevens, P. Blumbergs, and D. L. Wood, *J. Amer. Chem. Soc.*, **86**, 3592 (1964), reported the corresponding ethyl glycoside.

(7) The CD curve of a cuprammonium solution of methyl D-rhodosaminide (**1**α)[8a] gave a positive band at 570 mμ and a negative band at 290 mμ corresponding to the formation of a *k* chelate[8b] (*i.e.*, a negative dihedral angle between the dimethylamino and hydroxyl groups), thus confirming the D-*lyxo* configuration for **1** and demonstrating that no racemization occurred at C_5 under the mild oxidation conditions used to prepare **7**.

(8) (a) Kindly run by Dr. R. D. Guthrie and Miss S. T. K. Bukhari, University of Sussex, Brighton, England; (b) S. T. K. Bukhari, R. D. Guthrie, A. I. Scott, and A. D. Wrixon, *Chem. Commun.*, 1580 (1968).

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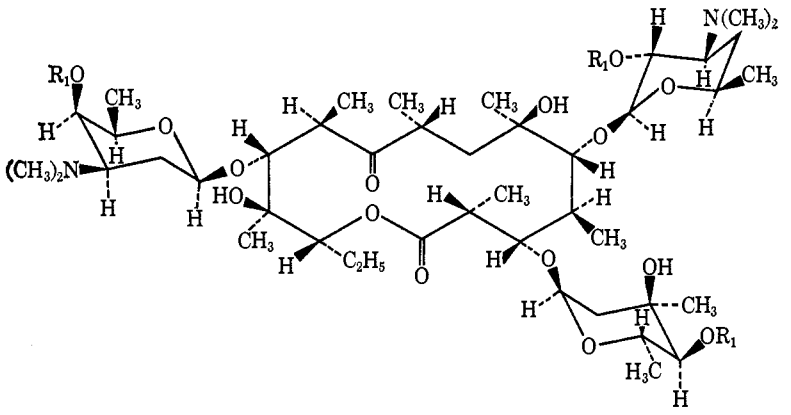
The Megalomicins. II.[1] The Structure of Megalomicin A

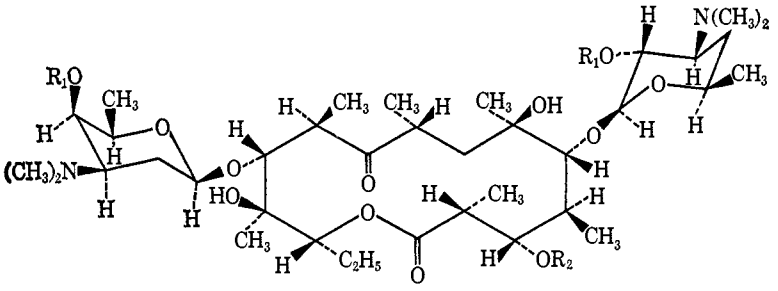
Sir:

Megalomicin A, which may be regarded as the parent antibiotic of a new family of macrolides elaborated by

(1) Part I: A. K. Mallams, *J. Amer. Chem, Soc.*, 91, 7505 (1969).



1, $R_1 = H$
2, $R_1 = CH_3CO$



3, $R_1 = R_2 = H$
4, $R_1 = CH_3CO$; $R_2 = H$
5, $R_1 = R_2 = CH_3CO$
6, $R_1 = CH_3CO$; $R_2 = CH_3SO_2$

Micromonospora megalomicea sp. n.,[2] has been shown by chemical degradation and spectroscopic studies to have structure **1**.

Megalomicin A (**1**, $C_{44}H_{80}N_2O_{15}$;[3] M^+ 876; mp 255–259° dec; $[\alpha]_D$ −90°; pK_a = 9.0; ν_{max} (Nujol) 3510, 2770, 1730, 1700, 1190 cm^{-1}) exhibited bands in the nmr due to an ethyl group (δ 0.8, t, J = 7 Hz), an envelope of methyl groups (δ 1.05–1.35), a deshielded tertiary methyl group (δ 1.60), and two dimethylamino groups (δ 2.27 and 2.33). The mass spectrum showed peaks at *m/e* 158 and 145 due to fragmentation at the glycosidic bonds of the sugar moieties.

Acetylation of megalomicin A gave a triacetate (**2**, $C_{50}H_{86}N_2O_{18}$; M^+ 1002; mp 199–202°; $[\alpha]_D$ −86°; pK_a = 7.5; ν_{max} (Nujol) 3520, 2780, 1736, 1692, 1242, 1163 cm^{-1}; δ 2.03, 2,08, and 2.14 (acetates)), and the decrease in the pK_a[4] of the triacetate relative to megalomicin A showed that an acetate was located in the vicinal position to each of the dimethyl amino groups. The mass spectrum showed a base peak at *m/e* 200, lending further support to the above conclusion, while a peak at *m/e* 187 suggested that the third acetyl group was located in the mycarose moiety.

Vigorous hydrolysis of megalomicin A with 6 *N* hydrochloric acid gave D-desosamine.[2d,4,5] Mild hydrolysis of megalomicin A with 0.75 *N* hydrochloric acid gave L-mycarose[6] and megalalosamine (**3**, $C_{37}H_{68}N_2O_{12}$; M^+ 732; mp 110–125°; $[\alpha]^{25}D$ −60.8°; pK_a = 8.8; ν_{max} 3450, 2740, 1730, 1685, 1170 cm^{-1}). The nmr indicated an ethyl group (δ 0.81, t, J = 7 Hz), an envelope of methyl groups (δ 1.08–1.32), a deshielded tertiary methyl group (δ 1.49), and two dimethylamino groups (δ 2.27 and 2.40). Acetylation of megalalosamine at 25° gave the diacetate **4** ($C_{41}H_{72}N_2O_{14}$; M^+ 816; mp 132–140°; $[\alpha]_D$ −62.7°; pK_a = 7.8; ν_{max} 3440, 2740, 1740, 1725, 1685, 1235, 1160 cm^{-1}; δ 2.08 and 2.20 (acetates), 2.28 and 2.33 (dimethylamino)), while acetylation at 90° gave a triacetate (**5**, $C_{43}H_{74}N_2O_{15}$; M^+ 858; mp 115–122°; $[\alpha]_D$ −48.8°; pK_a = 7.6; ν_{max} 3430, 2740, 1740, 1725, 1685, 1235, 1160 cm^{-1}; δ 2.09, 2.11, and 2.20 (acetates), 2.28 and 2.33 (dimethylamino)).

Megalalosamine diacetate (**4**) on treatment with mesyl chloride gave a monomesylate (**6**, $C_{42}H_{74}N_2O_{16}S$; mp 140–145°; $[\alpha]_D$ −44.1°; pK_a = 7.5; ν_{max} 3430, 2740, 1740, 1725, 1685, 1335, 1235, 1170, 1160 cm^{-1}; δ 2.08

(2) Papers presented at the 8th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology, New York, N. Y., Oct 1968: (a) H. Reimann, R. S. Jaret, and A. K. Mallams, Abstracts, p 4; (b) M. J. Weinstein, G. H. Wagman, J. Marquez, G. Luedemann, E. Oden, and J. A. Waitz, Abstracts, p 4; (c) M. J. Weinstein, G. H. Wagman, J. A. Marquez, R. T. Testa, E. Oden, and J. A. Waitz, *J. Antibiot.*, **22**, 253 (1969); (d) J. A. Marquez, A. Murawski, G. H. Wagman, R. S. Jaret, and H. Reimann, *ibid.*, **22**, 259 (1969); (e) J. A. Waitz, E. L. Moss, Jr., E. Oden, and M. J. Weinstein, *ibid.*, **22**, 265 (1969).

(3) Elemental analyses were satisfactory for all new compounds. Unless otherwise stated optical rotations were recorded at 26° in ethanol; nmr spectra were run at 60 MHz in $CDCl_3$ with internal TMS standard; ir spectra were run in CCl_4; pK_a values were recorded coulometrically in 66% aqueous DMF; mass spectra were obtained on a Perkin-Elmer RMU-6D instrument.

(4) E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, and K. Gerzon, *J. Amer. Chem. Soc.*, **76**, 3121 (1954).

(5) (a) The identity was proved by direct comparison with an authentic sample obtained from erythromycin A; (b) all physical data agreed with published data; (c) P. W. K. Woo, H. W. Dion, L. Durham, and H. S. Mosher, *Tetrahedron Letters*, 735 (1962).

(6) D. M. Lemal, P. D. Pacht, and R. B. Woodward, *Tetrahedron*, **18**, 1275 (1962).

and 2.19 (acetates), 2.28 and 2.32 (dimethylamino), and 3.05 (methanesulfonate)).

When megalomicin A was treated with 0.6 *N* hydrogen chloride in methanol, erythralosamine,[4,5a,b,7] 1-*O*-methyl L-mycaroside,[8] and a new amino sugar, 1-*O*-methyl D-rhodosaminide,[1] were formed. The β-glycosidic attachment of the desosamine was evident from the nmr spectra of megalomicin A (**1**), megalalosamine (**3**), and erythralosamine, which showed doublets (J = 7 Hz) for the anomeric proton at δ 4.33, 4.42, and 4.26, respectively. Reduction of **1** with sodium borohydride followed by mild acid hydrolysis of the product gave 5-*O*-D-desosaminyl-9-dihydroerythronolide (**7**).[5a,b,9,10] The formation of erythralosamine and **7** from megalomicin A demonstrated the location of the desosamine moiety at C_5 and indicated that the aglycone of megalomicin A was identical with that of erythromycin A. When megalalosamine (**3**) was reduced with sodium borohydride, 5-*O*-D-desosaminyl-11-*O*-D-rhodosaminyl-9-dihydroerythronolide (**8**, $C_{37}H_{70}N_2O_{12}$; M^+ 734; mp 118–128°; $[\alpha]_D$ −31.5° (MeOH); pK_a = 8.9; ν_{max} ($CHCl_3$) 3440, 2790, 1725, 1170 cm^{-1}; δ 2.28 and 2.33 (dimethylamino) and 4.50 (d, J = 7 Hz, H_1 of desosamine)) was obtained. The application of Klyne's rule[11] to the molecular rotations[12] of **7**, **8**, and 9-dihydroerythronolide (**9**)[9] indicated that both the D-desosamine and the D-rhodosamine moieties were β-glycosidically attached to the aglycone in megalomicin A (**1**). The mass spectra of megalomicin A (**1**) and its derivatives indicated that the D-rhodosamine moiety was located in the C_9–C_{13} portion of the molecule,[14] while the formation of a triacetate from megalalosamine, under reaction conditions which would be expected to acetylate all of the secondary hydroxyl groups in the molecule, and not a tetraacetate, indicated that the D-rhodosamine was glycosidically attached to the secondary hydroxyl group at C_{11}.

The mycarose moiety was shown to be located at C_3 by the following series of reactions. Methanolysis of the mesylate **6** derived from megalomicin A gave 2′-acetyl-3-mesylerythralosamine ($C_{32}H_{53}NO_{11}S$; M^+ − CH_3SO_3H 563; mp 100–104°; $[\alpha]_D$ +33.5°; pK_a = 7.1; ν_{max} 2780, 1740, 1235, 1175 cm^{-1}; δ 1.78 (J = 1.5 Hz) (-(CH_3)C=CH-), 2.07 (acetate), 2.30 (dimethylamino), 3.20 (methanesulfonate), 5.48 (J = 1.5 Hz) (vinylic proton)). Methanolysis of 4′,2″-diacetylerythromycin A[4] gave 2′-acetylerythralosamine ($C_{31}H_{51}NO_9$; mp 140–150° (dec); $[\alpha]_D$ +30.8°; ν_{max} 3430, 2780, 1740, 1235 cm^{-1}; δ 1.81 (J = 1.5 Hz) (-(CH_3)C=CH-), 2.07 (acetate), 2.29 (dimethylamino), 5.51 (J = 1.5 Hz) (vinylic proton)), which on treatment with mesyl chloride gave 2′-acetyl-3-mesylerythralosamine, which was identical with that prepared from megalomicin A above.

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Participation by Neighboring Aryl Groups. V. Determination of Assisted and Nonassisted Rates in Primary Systems. Rate–Product Correlations

Sir:

Recently we applied three purely kinetic analytical methods[1] to the dissection of the titrimetric solvolysis rates (k_t) for a series of secondary β-arylalkyl substrates

Table I. Titrimetric Acetolysis Rate Constants (k_t) for a Series of β-Arylethyl Tosylates, $XC_6H_4CH_2CH_2OTs$ (I)

X	Temp, °C	k_t, sec^{-1}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
p-CH_3O	75.1	$(8.66 \pm 0.05) \times 10^{-6}$	25.1	−10
	100.5	$(1.09 \pm 0.01) \times 10^{-4}$		
	90[a]	3.98×10^{-5}		
	115[a]	4.00×10^{-4}		
p-CH_3	90[b]	4.08×10^{-6}	25.6	−13
	115[b]	4.30×10^{-5}		
H	90[b]	1.31×10^{-6}	24.8	−18
	115[b]	1.27×10^{-5}		
p-Cl	100.7	$(2.38 \pm 0.01) \times 10^{-6}$	24.6	−19
	124.8	$(1.90 \pm 0.01) \times 10^{-5}$		
	90[a]	8.80×10^{-7}		
	115[a]	8.45×10^{-6}		
m-F	100.2	$(2.10 \pm 0.01) \times 10^{-6}$	24.2	−20
	124.5	$(1.64 \pm 0.01) \times 10^{-5}$		
	90[a]	8.24×10^{-7}		
	115[a]	7.61×10^{-6}		
m-Cl	100.2	$(2.03 \pm 0.01) \times 10^{-6}$	23.9	−21
	124.5	$(1.59 \pm 0.01) \times 10^{-5}$		
	150.0	$(9.89 \pm 0.05) \times 10^{-5}$		
	90[a]	8.07×10^{-7}		
	115[a]	7.28×10^{-6}		
m-CF_3	100.3	$(2.01 \pm 0.01) \times 10^{-6}$	23.4	−22
	124.8	$(1.49 \pm 0.01) \times 10^{-5}$		
	90[a]	8.00×10^{-7}		
	115[a]	6.89×10^{-6}		
p-CF_3	100.3	$(1.92 \pm 0.02) \times 10^{-6}$	24.6	−19
	124.8	$(1.57 \pm 0.01) \times 10^{-5}$		
	90[a]	7.30×10^{-7}		
	115[a]	6.99×10^{-6}		
p-NO_2	100.6	$(1.87 \pm 0.01) \times 10^{-6}$	23.7	−22
	124.9	$(1.40 \pm 0.03) \times 10^{-5}$		
	90[a]	7.15×10^{-7}		
	115[a]	6.35×10^{-6}		
3,5-$(CF_3)_2$	100.3	$(1.67 \pm 0.01) \times 10^{-6}$	23.8	−22
	124.8	$(1.28 \pm 0.01) \times 10^{-5}$		
	90[a]	6.54×10^{-7}		
	115[a]	5.84×10^{-6}		

[a] Calculated from data at other temperatures. [b] Calculated from a combination of literature data at other temperatures: S. Winstein, C. R. Lindegren, H. Marshall, and L. L. Ingraham, *J. Am. Chem. Soc.*, 75, 147 (1953), and ref 5.

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