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SCH 23831, A NOVEL MACROLIDE FROM MICROMONOSPORA ROSARIA

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A novel macrolide elaborated by Micromonospora rosaria, SCH 23831, was assigned structure 2 on the basis of spectroscopic data. Several derivatives are also discussed.

Rosaramicin [‡], 1, whose structure and biosynthesis have been the subject of previous investigations,[1,2] is a 16-membered macrolide antibiotic elaborated by Micromonospora rosaria[3]. From its earlier production batches, a new related component of the fermentation was isolated. We report here the structure of this unique macrolide by-product, Sch 23831, compound 2.

Compound 2 ($C_{31}H_{48}N_2O_7$, m/e = 560.3454)[4] is basic in nature (pKa=8.6); λ max 229 nm (ε =8800); ν max ($CHCl_3$)(cm^{-1}) 3480(m,OH), 2980(s,CH_2), 1699(s,-OC=O), 1598 and 1552(w,-C=C-,-C=N), 1452(s,CH_2bend), 1175(s,-C-O-C=O); 1100(s,C-O-C); PMR $\boxed{(CD_3)_2CO}$ δ 0.85(t,7.0,CH_3), 0.98 (d,6.5,CH_3), 1.11 (d,6.5,CH_3), 1.28(d,6.5,2CH_3 groups), 1.79 (s,CH_3), 2.32 (s,$N(CH_3)_2$), 4.30 (d,7.5.CH(O)O), 4.80 (m,8.0,7.5,3.0,CHOCO), 7.02 (s,$W_{1/2}$=3.0 Hz,=CH) and 8.45 (s,$W_{1/2}$ =2.5 Hz,=CH) The CMR spectrum in $CDCl_3$ showed the presence of eight methyl carbons at δ 8.5, 9.4, 14.8, 16.1, 18.3, 21.3 and 40.3 ($N(CH_3)_2$), four methylene carbons at δ 25.9, 28.9, 38.1 and 41.1, twelve methine carbons at δ 35.4, 36.8, 42.1, 49.6, 65.6, 67.4, 69.3, 70.7, 72.1, 80.3 and 104.1, two olefinic (=CH) carbons at δ 111.8 and 144.6 and five quarternary carbons at δ 62.5, 138.4, 160.0, 161.9 and 175.5 (OC=O). In the mass spectrum the major fragment ions were 560(M^+), 432 $(C_{23}H_{32}NO_4\text{-OCHOH})^+$, 403 $(C_{23}H_{32}NO_4\text{-OH})^+$, 386 $(C_{23}H_{32}NO_4)^+$ with additional fragments at 316, 300 and 298. The definition of the composition of the sugar, desosamine ($C_8H_{16}NO_3$, m/e

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[‡] It is also known as Sch 14947, 67-694 and Rosamicin.

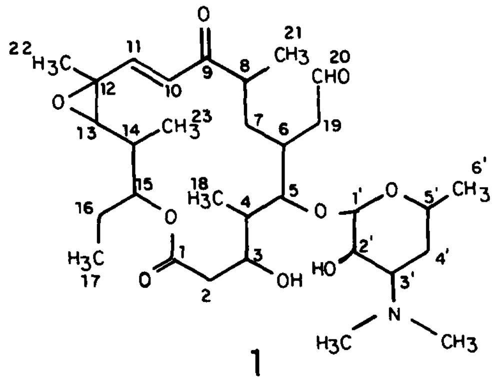
174.1144), ($C_8H_{16}NO_2$, m/e 158.1183, base peak), 116 $(C_5H_{10}NO_2)^+$ and 98 $(C_6H_{12}N)^+$ defined the aglycone moiety as having one nitrogen. The comparison of the PMR data of 2 with that of 1 indicated the absence of the aldehydic group and the olefinic protons of the enone system. In addition the CH_3 singlet attributed to C_{22} in 1 was shifted downfield by 0.3 ppm.

Similar comparison of the CMR data indicated that the carbons of rosaramicin at δ 200.3 (C_9), 202.9 (C_{20}), 122.8 (C_{10}), 150.9 (C_{11}) and 43.9 (C_{19}) were missing and were recognized as new peaks at δ 111.8 (=CH), 144.6 (=CH), 138.4 (C*), 160.0 (C*) in the new compound. The chemical shifts of the carbon atoms due to the desosamine sugar were identical in both compounds.[5] Non-aqueous titration indicated two curves in agreement with two types of basic nitrogen atoms. The pKa and the UV data suggested a pyridine type moiety. On the basis of the above data[6], structure 2 is proposed for the new compound.

In the PMR, the decoupling at δ 8.45 (H_{20}) transformed the δ 7.02 (H_{10}) resonance to a doublet (J=1.0 Hz), whereas, the same experiment at δ 7.02 sharpened the δ 8.45 resonance. Irradiation at δ 3.22 (C-5'H and the CH region) collapsed the methyl doublet ($2CH_3$ groups, $21CH_3$ and $6'CH_3$) at δ 1.28 into a singlet, eliminated the long-range coupling to δ 8.41 (N=CH) and 7.02 (=CH) resonances, and made possible the interpretation of residual coupling (J=1.0 Hz) between H_{10} and H_{20}, consistent with the presence of para interactions observed in substituted pyridines. Irradiation at δ 1.28 in a degassed sample resulted in approximately 15% N.O.E. between the secondary methyl and the δ 7.02 resonance.

The protonation of pyridine nitrogen induces chemical shift changes of -7.8, +5.1 and +12.4 ppm at the α-, β- and γ- positions, respectively[7]. CMR data on protonation of 2 in $CDCl_3$-TFA resulted in chemical shift changes of -7.6 and -3.5 for the α-carbons 20 and 11, +4.9 for the β-carbons 10 and 19 and +11.8 for the γ carbon 9. These chemical shift changes are in complete agreement with the presence of pyridine ring in 2.

Acetylation of 2 gave a diacetate, 4, which, after selective hydrolysis, resulted in a monoacetate, 3. NMR (^1H and ^{13}C) and mass spectral data were consistent with the assigned structures. The acetylation of 2 caused a downfield shift of H_3 under the methine protons envelope. The chemical shift of H_3 is upfield because of the strong shielding influence of the aromaticity of the pyridine ring. However, the elimination of the intramolecular hydro-



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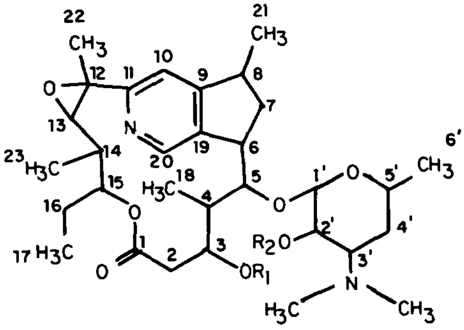

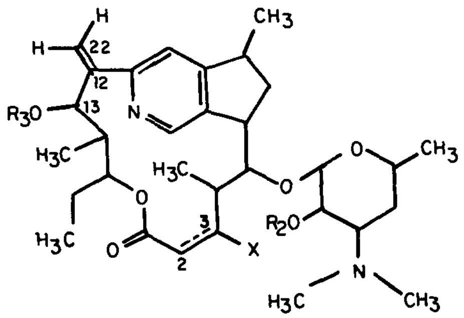

2 R_1 = H, R_2 = H

3 R_1 = $COCH_3$, R_2 = H

4 R_1 = $COCH_3$, R_2 = $COCH_3$

5 R_2 = H, R_3 = H, $^2\Delta$

6 R_2 = $COCH_3$, R_3 = $COCH_3$, $^2\Delta$

7 R_2 = H, R_3 = H, X = OH

gen-bond between 3-OH and 1-CO groups resulted in an upfield shift (~5 ppm) of the lactone C=O (δ 170.6) in 3 and 4[8].

Attempted dehydration of 2 via mesylate, 4a (R_1 = SO_2CH_3, R_2 = $COCH_3$), resulted not only in the creation of a double bond at C-2,3 but also generation of an exocyclic double bond. PMR suggested the presence of protons at δ 5.33 and 5.70 (2H,$=CH_2$) with concurrent loss of the δ 1.80 methyl group (22-CH_3) and additional vinylic protons at δ 5.04 (dd,16.0,2.0) and 6.25 (dd, 16.0,4.5) assigned to $-CH=CH-CH(CH_3)$ moiety. CMR confirmed the presence of additional carbons; δ 165.3 (OCO, now shifted upfield), 117.8 (2,=CH), 146.1 (3,=CH), 145.5 (12,C) and 116.7 (22,$=CH_2$). These results are consistent with structure 5 ($C_{31}H_{46}N_2O_6$, m/e = 542.3351) for the dehydration product. The presence of two OH groups at positions 13 (δ 75.9) and $2'$ was confirmed by the formation of diacetate, 6 (m/e 626) and supported by PMR decoupling experiments. Another attempt[9] to dehydrate 2 in refluxing pyridine resulted in a compound with the same molecular ion ($C_{31}H_{48}N_2O_7$, m/e 560.3508). However, the PMR spectrum indicated the loss of $22CH_3$ group at δ 1.80 and the presence of an exocyclic methylene group at δ 5.40 and 5.85 ($=CH_2$). The spectrum also lacked the presence of another double bond. Structure 7 was assigned to this product.

In Vitro MICs indicate that SCH 23831 has weak gram positive activity.[10]

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4. Other physical data: chemical analysis:found (%) C=65.67, H=8.95, N=4.64; calcd. (%) C=66.40, H=8.63, N=5.00; UV (λ_{max} CH_3OH)=229 (ε =8800), 269 (ε=2350), 278 (ε=2100); Rot $[\alpha]^{25} = -60.2^{o}$ in C_2H_5OH.
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6. Proton and C-13 NMR data were obtained by utilizing a Varian XL-100-15 Spectrometer. Proton NMR were obtained in $(CD_3)_2CO$ and $CDCl_3$, whereas, C-13 data (both fully decoupled and off-resonance) were obtained in $CDCl_3$. The present data, along with the structures of other minor macrolides from rosaramicin fermentations, will be reported at a later date.
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9. Under these conditions, 1 was quantitatively transformed to des-epoxy derivative (unpublished results).
10. Since no nitrogen source was used during the isolation and purification of this compound the possibility that it is an artifact is very remote.

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