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LEUCOMYCIN AGLYCONES. DEGLYCOSIDATION OF THE MACROLIDE ANTIBIOTIC LEUCOMYCIN A_3

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In view of a recent communication by Omura, Tishler et al.[1] pertaining to the title subject, we wish to report our findings at this time. These authors reported isolation of the aglycone 5 in ca 10% yield by submitting leucomycin A_3 N-oxide to Polonovski rearrangement conditions.[2] The nature and course of this transformation were not elucidated.

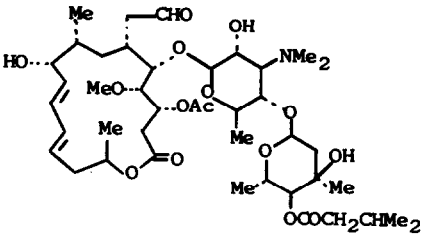
It has been our experience that the macrolide antibiotic 1[3] as its N-oxide on treatment with acetic anhydride in pyridine can be made to yield the ketolacetate 2 and the enamine 3 in a relative proportion dependent on the reaction conditions. Thus aqueous hydrolysis of the acetylation product (25°) yielded 2 almost exclusively. On the other hand, by heating the acylation mixture at 50° with simultaneous concentration in vacuo, 2 and 3 were obtained in essentially equal amounts.[4] Under the latter conditions incipient fragmentation 3 → 5a (18-acetate) was also observed.[1b] The two components 2 and 3 were separable by silica gel chromatography employing a chloroform-acetone (90:10) system.

The ketolacetate[5] 2 gave a positive blue tetrazolium reaction characteristic of ketols and their esters. Oxidation of 2 (CrO_3-Py/H_2O) in the form of its cyanohydrin derivative (mp 180-182°; Calcd for $C_{46}H_{68}O_{18}N_2$: N, 2.91; Found: N, 3.07) to the corresponding carboxylic acid followed by direct fragmentation of the latter in hot acetic anhydride-sodium acetate (140°/1 hr) yielded the aglycone lactone 4 (31%) mp ~110° $\lambda_{max}^{CH_3OH}$ 231nm (ε 25900): $[\alpha]_D$+27.9° (C=1, CH_3OH) Calcd for $C_{24}H_{34}O_9$: C, 61.79; H, 7.35. Found: C, 61.67; H, 7.40. λ_{max}^{chf}: 5.61, 5.74 (shoulder), 5.79 and 6.04μ. nmr ($CDCl_3$) δ1.02 (d, J=7Hz, C_8-CH_3), 1.28 (d, J=6Hz, C_{15}-CH_3), 2.02 (s, 3H, OAc), 2.15 (s, 3H, OAc),

3.60 (s, 3H, OCH_3), 4.33 (dd, 1H, C_5-H, J_1=4Hz, J_2=10Hz), mass spec 466m/e (MI), 406 (MI-CH_3CO_2H). To a less efficient extent ketolacetate 2 could be transformed directly under the same conditions to the corresponding aglycone 5a (18-acetate). Fragmentation is potentially assisted by the possibility of β-elimination of the modified mycaminose moiety. Hydrolysis of 5a (18-acetate) → 5a was readily effected at 25° with 0.3N aq. HCl in tetrahydrofuran.

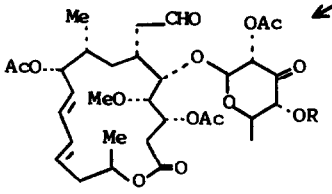
Hydrolytically it was only found possible to remove the mycarose entity without invoking deep-seated changes. Thus 0.2N HCl in aq. tetrahydrofuran at 60° followed by acetylation (Py-Ac_2O/25°) afforded 1-acetyl-4-isovaleroyl-β-mycarose (mp 87-88°; $[\alpha]_D$ -18.4° (C=1.03, $CHCl_3$) Calcd for $C_{14}H_{24}O_6$: C, 58.31; H, 8.39. Found: C, 58.27; H, 8.18; nmr ($CDCl_3$) δ6.12 (dd, C_1-H, J_1=3.5, J_2=8.5 Hz) and the α-isomer $[\alpha]_D$-124° (C=0.92, $CHCl_3$); (Found: C, 58.73; H, 8.23) together with the ketolacetate 2 (R=Ac) (Calcd for $C_{34}H_{48}O_{15}$: C, 58.61; H, 6.94. Found: C, 58.91; H, 7.15). Fragmentation of the latter in hot acetic anhydride-sodium acetate yielded aglycone 5a (18-acetate).

Enamine 3 exhibited $\lambda_{max}^{CH_3OH}$ 231nm (ε 31400), $[\alpha]_D$-41.0° (C=0.91, CH_3OH); Calcd for $C_{46}H_{71}O_{17}N$: C, 60.77; H, 7.86; N, 1.54. Found: C, 60.61; H, 7.75; N, 1.56. nmr ($CDCl_3$) δ2.02 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.27 (s, 3H, OAc), 2.53 (s, 6H, $-N(CH_3)_2$), 3.57 (s, 3H, OCH_3) and 9.75 (s, 1H, CHO). The presence of an additional double bond in 3 was deduced from its chemistry and corroborated by C_{13}-nmr. Thus, in addition to the macrolide double-bonded carbons C_{10},C_{11},C_{12} and C_{13} each bearing one proton with resonances at δ137.9, 133.8, 131.3 and 121.9 ($CDCl_3$), two additional double-bonded carbons bearing no protons with resonances at δ144.2 and 127.3 were observed. These results further establish that the enamine double bond is positionally homogeneous. The enamine double bond is assigned to the indicated allylic position in structure 3 which is thereby formulated as 2',3'-dehydroleucomycin A_3 diacetate for reasons contingent on its behavior to acid catalyzed fragmentation. Thus treatment of 3 at 25° with 0.3N HCl in aq. tetrahydrofuran afforded the aglycone 5a in 70-75% yield,[6] mp 167-171°; Calcd for $C_{24}H_{36}O_9$: C, 61.52; H, 7.75. Found: C, 61.34; H, 7.51. $\lambda_{max}^{CH_3OH}$ 231nm (ε 29500); $\lambda_{max}^{CHCl_3}$ 2.80 (sharp), 2.95 (broad), 5.75 (shoulder), 5.78, 6.0μ. nmr ($CDCl_3$) δ0.98 (d, J=7Hz, C_8-CH_3), 1.27 (d, J=6Hz, C_{15}-CH_3), 2.02 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.52, 3.58 (OCH_3, each singlet indicative of the isomeric nature at C_{18}) and 4.05 (dd, 1H,

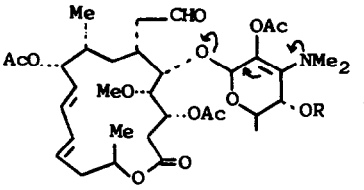


1

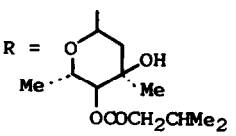
1. OH^+
2. Ac_2O/py



2 Ketolacetate

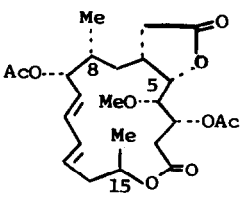


3 Enamine



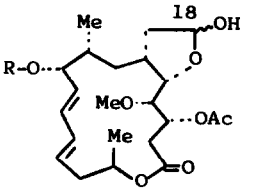
1. ox.
2. Ac_2O/NaOAc

H_3O^+



4

red. ⇌ ox.



5 R = H

5a R = Ac

C_5-H, J_1=4Hz, J_2=10Hz), mass spec 468m/e (MI), 450 (MI-H_2O) and 408 (MI-CH_3CO_2H) on trimethylsilylation it exhibited a peak at 540m/e corresponding to its mono-trimethylsilyl derivative. This sequence, namely, formation of the enamine 3 followed by acid catalyzed fragmentation provides a relatively good procedure for preparing the aglycone 5a.

Interconversion of the cyclic hemiacetal 5a, and the lactone 4 could be effected essentially quantitatively by oxidation (CrO_3-pyridine/25°) of the former and reduction ($LiAlH(OBu^t)_3$-THF/25°) of the latter respectively.

Acknowledgment

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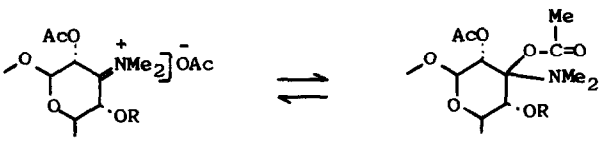
References

1. S. Omura, A. Nakagawa, K. Suzuki, T. Hata, A. Jakubowski and M. Tishler, The Journal of Antibiotics 27, 147 (1974); (b) First prepared by these authors by acetylation of 5.

2. M. Polonovski and M. Polonovski, Bull. Soc. Chim. France 39, 1147 (1926); 41, 1190 (1927).

3. Revision of the orientation of the 9-OH in the leucomycins has been reported recently: L. A. Freiberg, R. S. Egan and W. H. Washburn, J. Org. Chem. 39, 2474 (1974).

4. The formation of 2 and 3 is presumed to be mediated by an immonium salt i in equilibrium with its carbinolamine counterpart ii. The latter can independently



i ii

yield 2 and dimethyl acetamide by a thermocyclic process; cf., e.g., R. Huisgen, F. Bayerlein and W. Heydkamp, Ber. 92, 3223 (1959).

5. A. Nakagawa, K. Suzuki, K. Iwasaki, T. Hata and S. Omura, Chem. & Pharm. Bull. 22, 1426 (1974).

6. Ketolacetate 2 might normally have been anticipated as the product of acid hydrolysis of 3. There was no evidence of formation of 2, however, even from attempts to reconstitute the immonium species i (Ref. 4) with anhydrous HOAc followed by aqueous hydrolysis.