Acid Degradation of Erythromycin A and Erythromycin B

The recent isolation of 8,9-anhydroerythronolide B 6,9-hemiketal after treatment of erythronolide B under acidic conditions¹, led us to an investigation of the acid degradation products of erythromycin A (**1**) and erythromycin B (**2**). A solution of erythromycin A (**1**) in glacial acetic acid was allowed to stand at room temperature for 2 h and worked up in a manner similar to that of STEPHENS and CONINE², to give, after recrystallization from carbon tetrachloride, a 72% yield of a compound which gave an elemental analysis in agreement with the empirical formula $C_{37}H_{65}NO_{12}$. The compound had a melting point of 133–135°; $[\alpha]_D^{25} -43^\circ$ (c, 1.19 in MeOH);

of these couplings suggested that the allylic protons were geminal. This then established that the vinyl methyl groups were at C-8 and the allylic protons were at C-7. This confirmed that **3** and **4** were 8,9-anhydroerythromycin A and B 6,9-hemiketals, respectively.

The hydrolysis of **3** in dilute aqueous methanolic hydrochloric acid¹ for 45 min afforded, after work-up and recrystallization from methylene chloride-hexane, a 64% yield of 'anhydroerythromycin A' (**5**)⁴, mp 130–140°, identical with a reference sample of **5** prepared according to the procedure of WILEY et al.⁴ from **1** by criteria of thin layer chromatography, IR- and NMR-spectral

$\lambda_{\text{MeOH}}^{\text{max}}$ 209 nm (ϵ 6640); $\tilde{\nu}_{\text{CHCl}_3}^{\text{max}}$ 3620, 3520–3550, 1718 cm^{-1} . Neither the analytical result nor the UV-absorption of this compound was compatible with the previously proposed 'hemiketal' structure². The above physical constants strongly suggested that the product was an enol ether analogous to those obtained in the erythronolide B series^{1,3}. Consideration of the NMR spectral evidence presented below established the structure of this substance as 8,9-anhydroerythromycin A 6,9-hemiketal (**3**).

Treatment of erythromycin B (**2**) in acetic acid under the same conditions followed by recrystallization of the reaction product from acetone gave a 50% yield of 8,9-anhydroerythromycin B 6,9-hemiketal (**4**), $C_{37}H_{65}NO_{11}$, mp 80–82°; $[\alpha]_D^{25} -33^\circ$ (c, 1.14 in MeOH); $\lambda_{\text{MeOH}}^{\text{max}}$ 209 nm (ϵ 7120); $\tilde{\nu}_{\text{CHCl}_3}^{\text{max}}$ 3612, 3555, 3450, 1720 cm^{-1} .

The NMR-spectra of both, **3** and **4**, like that of 8,9-anhydroerythronolide B 6,9-hemiketal¹, revealed the presence of single vinyl methyl resonances (1.61 ppm in the pyridine- d_5 solution spectra of both compounds at 110°) and the absence of vinyl proton resonances. The vinyl methyl resonances were broadened by unresolved allylic couplings (ca. 1.0 Hz) with 2 ring protons, the chemical shifts of which (2.85 ppm and 2.07 ppm for **3**; 2.83 and 2.04 ppm for **4**) were determined by spin decoupling experiments. The resonances of the allylic protons of **3** and **4** appeared as AB quartets ($J_{AB} = 15$ Hz), the peaks of which were slightly broadened by allylic coupling to the vinyl methyl protons. The magnitudes

evidence. In contrast, acid hydrolysis of **4** under the same conditions furnished, after recrystallization from acetone, a 42% yield of erythromycin B (**2**), mp 200–203°. Examination of molecular models indicated that only one side of the double bonds of the enol ethers **3** and **4** were readily accessible to an attacking reagent¹. This observation was consistent with the formation of **5** and **2** (the crude reaction products were pure by thin layer chromatography) during the brief hydrolyses of **3** and **4**, respectively.

Zusammenfassung. Es wird die Bildung der 8,9-Anhydroerythromycin A und B 6,9-Hemiketale aus den entsprechenden Erythromycinen mit Essigsäure bewiesen.

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² V. C. STEPHENS and J. W. CONINE, *Antibiotics A. 1958–1959*, 346.

³ T. J. PERUN, *J. org. Chem.* **32**, 2324 (1967).

⁴ P. F. WILEY, K. GERZON, E. H. FLYNN, M. V. SIGAL JR., O. WEAVER, U. C. QUARCK, R. R. CHAUVETTE and R. MONAHAN, *J. Am. chem. Soc.* **79**, 6062 (1957).