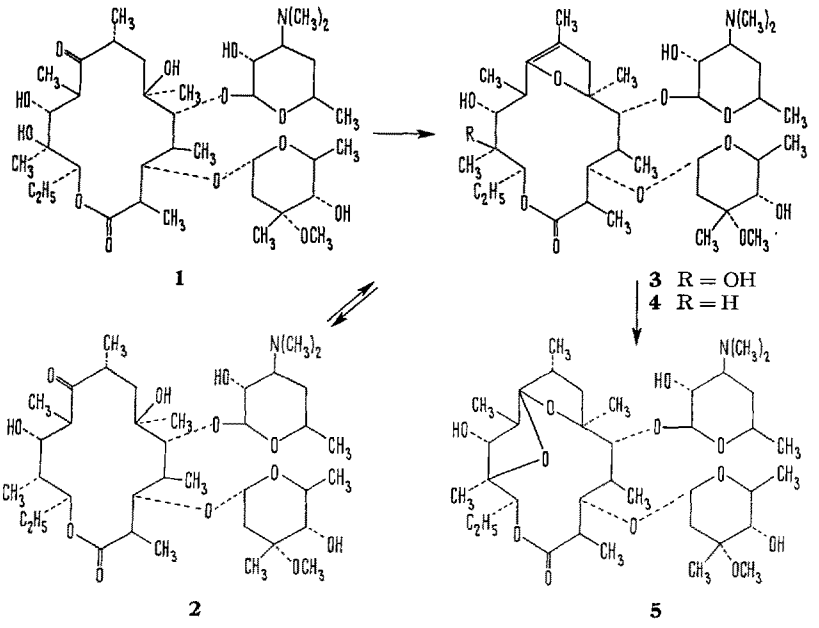
Acid Degradation of Erythromycin A and Erythromycin B

The recent isolation of 8,9-anhydroerythronolide B 6,9-hemiketal after treatment of erythronolide B under acidic conditions[1], 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 CONINE[2], 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° (c, 1.19 in MeOH); λ_{max}^{MeOH} 209 nm (ε 6640); $\tilde{\nu}_{max}^{CHCl_3}$ 3620, 3520–3550, 1718 cm^{-1}. Neither the analytical result nor the UV-absorption of this compound was compatible with the previously proposed 'hemiketal' structure[2]. 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° (c, 1.14 in MeOH); λ_{max}^{MeOH} 209 nm (ε 7120); $\tilde{\nu}_{max}^{CHCl_3}$ 3612, 3555, 3450, 1720 cm^{-1}.

The NMR-spectra of both, **3** and **4**, like that of 8,9-anhydroerythronolide B 6,9-hemiketal[1], 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 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 acid[1] 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 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 reagent[1]. 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.

P. KURATH, P. H. JONES,
R. S. EGAN and T. J. PERUN

Scientific Divisions, Abbott Laboratories,
North Chicago (Illinois 60064, USA), 5 October 1970.

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