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SELECTIVE CHROMIC ACID OXIDATION OF ALCOHOLS IN THE ERYTHROMYCIN SERIES IN CONSEQUENCE OF CONFORMATIONAL IMMOBILITY

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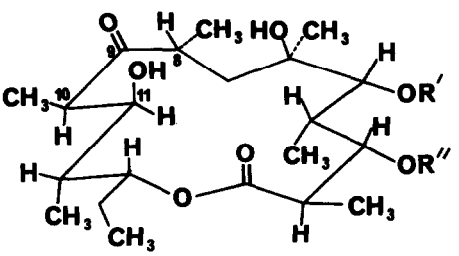
Strong evidence has accumulated in favor of a conformation for the erythronolide ring, the nucleus of the erythromycin antibiotics, which is approximated by the stereoformula 1.[1-3] This and



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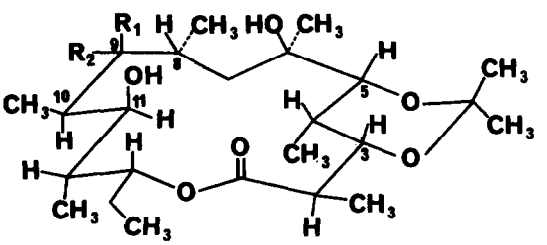

2, $R_1 + R_2 = O$

3, $R_1 = OH$, $R_2 = H$

4, $R_1 = H$, $R_2 = OH$

closely related[3] three-dimensional arrangements lie in a deep well in the conformational potential energy surface, since the pmr spectrum continues to exhibit sharp peaks and discrete fine structure due to spin-spin coupling even at 110° C.[2] The 3,5-isopropylidene derivative of erythronolide B (2)[4] also possesses this geometry for the macrolide ring as is clear from the correspondence of coupling constants observed for 2 and various derivatives[2] of 1. The conformational stability of the erythronolide macro ring and the occurrence at C-11 of an axial hydroxyl and a difficultly accessible equatorial-inside hydrogen suggested that the 11-hydroxyl function might be sufficiently resistant to chromic acid

oxidation to allow selective oxidation of other secondary hydroxyl groups (e.g., at C-9 or in the sugar units) of various erythromycin or oleandomycin derivatives. Such selectivity would be of considerable practical importance, since it would provide a way of circumventing the base instability of erythromycins and oleandomycins (due to the C-9, C-11 β-ketol unit) which markedly limits chemical modification of these antibiotics. It would also be of fundamental interest as a case in which the Curtin-Hammett principle[5] demonstrably does not apply either because of non-equilibrium between C-11 H-inside and C-11 H-outside conformations during reaction,[6] or because the large difference in energy of such ground state conformations is substantially preserved in the transition states accessed from these conformations. In addition, selectivity in oxidation at C-9 vs. C-11 would provide strong evidence for retardation of chromic acid oxidation due to inaccessibility of the carbinol proton.[7,8]

Reduction of 2 with sodium borohydride in methanol at -20° afforded a mixture of epimeric alcohols 3 and 4 in 81 and 16% yield, respectively, after chromatographic separation.[9] Oxidation of the 9,11-diol 3 with three equivalents of chromic acid in 95% acetone--5% water at 0° for 35 min resulted in complete consumption of starting material and, as anticipated, selective formation of 2 which was isolated in pure form in 76% (isolated) yield. Similarly, under these conditions diol 4 was oxidized to the β-ketol 2 in 86% (isolated) yield. The β-ketol 2 could be recovered largely unchanged when subjected to oxidation essentially under the same conditions.

Oxidation of the 9,11-diol 3 with 16 molar equivalents of Collins reagent[10] in methylene chloride at -6° for 2.3 hr produced a mixture of β-ketol 2 (81%) and starting diol 3 (19%).[11] Similar oxidation of the epimeric 9,11-diol 4 with Collins reagent resulted in the β-ketol 2 (79%) and unchanged diol 4 (18%).[11]

Parallel observations were made starting with the 3,5-benzylidene analogs of the 3,5-acetonides 3 and 4, i.e., in each case oxidation of the 9-hydroxyl group of the 9,11-diol system occurred selectively.

The experimentally observed difference between the oxidation rates of the 9 and 11 hydroxyl groups in 3 and 4 indicates that the nmr-derived conformation of the erythronolide ring system has implications on the time scale of the oxidation reaction and provides the clearest demonstration so far that the rate of chromic acid oxidation of a secondary alcohol can be retarded by inaccessibility of the carbinol proton. Other instances of unusual functional group reactivity differences unique to macrocyclic structures can be anticipated. They will add a new and interesting dimension to conformational analysis as applied to such systems.[12]

References

1. X-ray crystallographic analysis of erythromycin A has revealed that the conformation of the aglycone ring in the crystal approximates 1. See D. R. Harris, S. G. McGeachin, and H. H. Mills, Tetrahedron Lett., 679 (1965).
2. For an excellent pmr study of the erythronolide conformation and summary of earlier work, see R. S. Egan, T. J. Perun, J. R. Martin, and L. A. Mitscher, Tetrahedron, 29, 2525 (1973). See

also T. J. Perun et al., Tetrahedron Lett., 4501 (1969).

3. The molecular geometry expressed by 1, termed the "Perun" conformation, represents a modification of a similar stereoformula ("Celmer" conformation) proposed earlier by W. D. Celmer, Antimicrob. Ag. Chemother., 144 (1966) and "Biogenesis of Antibiotic Substances" (edited by Z. Vanek and Z. Hostalek), Chap. 10, Academic Press, New York, N. Y., 1965. The essential arguments and conclusions of our study are compatible with either Perun or Celmer conformations or mixtures of the two in rapid equilibrium within the deep conformational energy well.
4. The acetonide 2 was prepared from erythronolide B by reaction with excess isopropenyl methyl ether in dichloromethane containing a catalytic amount of phosphorus oxychloride at 25° for 168 hr. Crystalline 2, m.p. 81.5°, $[\alpha]_D^{23}$ -84.4° (CH_3OH), molecular ion at m/e 442.2928, showed ν_{max} C=O at 1710 cm^{-1} (CCl_4), and pmr peaks (deuteropyridine, 25°, 100 MHz) at δ 0.79 (t, J = 7 Hz, CH_3-CH_2), 0.97 (d, J = 7 Hz, CH_3CH), 1.2-2.2 (m), 2.29 (q, J = 6 Hz, C-4 methine), 4.05 (d, J = 10 Hz, C-3 methine), 4.23 (s, C-5 methine), 4.36 (bd, J = 10 Hz, C-11 methine), 5.56 (bs, C-11 OH), and 5.96 (four peaks, C-13 methine). The structures of this and other new compounds reported here were confirmed by infrared, pmr, and high resolution mass spectral data on chromatographically homogeneous, crystalline samples.
5. (a) P. I. Pollak and D. Y. Curtin, J. Amer. Chem. Soc., 72, 961 (1950); (b) D. Y. Curtin, Record Chem. Progr. Kresge-Hooker Sci. Lib., 15, 111 (1954); (c) E. L. Eliel, "Stereochemistry of Carbon Compounds," Chap. 6, p. 149, McGraw-Hill, New York, N. Y., 1962.
6. See J. C. Martin and W. G. Bentrude, J. Org. Chem., 24, 1902 (1959).
7. To our knowledge such retardation has not previously been demonstrated. For reviews of the mechanism of chromic acid oxidation of alcohols, see (a) F. H. Westheimer, Chem. Rev., 45, 419 (1945), and (b) R. Stewart, "Oxidation Mechanisms," Chap. 4, W. A. Benjamin, Inc., New York, N. Y., 1964.
8. In most cases of alcohol oxidation by chromic acid, the rate-limiting step is decomposition of a chromate ester. However, one example has been reported of rate retardation due to steric encumbrance in the esterification step; see J. Rocek, F. H. Westheimer, A. Eschenmoser, L. Moldovanyi, and J. Schreiber, Helv. Chim. Acta, 45, 2554 (1962).
9. The stereochemistry of reduction of the 9-oxo group in 2 parallels that of erythronolide B (see ref. 2) as determined by pmr analysis. Thin layer chromatography was performed on silica gel plates using 6% methanol in dichloromethane for development. R_f values were as follows: 0.3 for 3, 0.15 for 4, and 0.4 for the starting material 2. Found for 3: m.p. 97°; $[\alpha]_D^{23}$ +10.4° (CH_3OH), and for 4: m.p. 68-70°; $[\alpha]_D^{23}$ +13.1° (CH_3OH).
10. J. C. Collins, W. W. Hess, and F. J. Frank, Tetrahedron Lett., 3363 (1968).
11. The diol persists in the reaction product even after extended times with excess reagent. It seems

likely that some fraction of starting diol becomes protected against oxidation in the reaction mixture in some way, perhaps as an unreactive chromium-containing complex [e.g., a chromium IV ester. Cf. G. Dyrkacz and J. Rocek, J. Amer. Chem. Soc., 95, 4756 (1973)].

12. This work was assisted financially by a grant from the National Institutes of Health.