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TORSIONAL EFFECTS IN THE BAEYER-VILLIGER OXIDATION[1]

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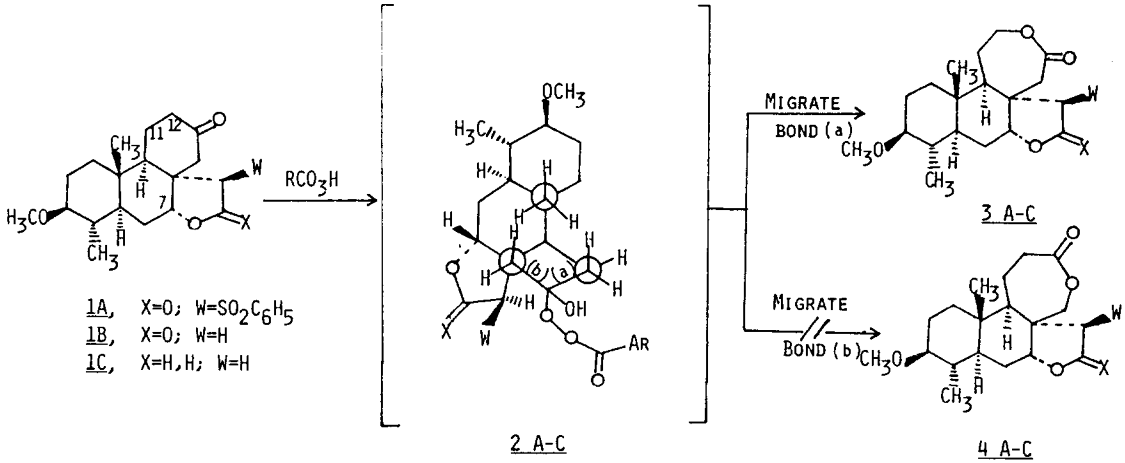
Abstract: The regioselectivity in the Baeyer-Villiger oxidation of tetracyclic ketones 1A-C have been interpreted in terms of torsional effects.

In connection with our program directed toward the total synthesis of the quassinoidal antileukemia agent bruceantin[1] we had occasion to examine the Baeyer-Villiger oxidation of alpha-sulfonyl lactone 1A.[2] The desired lactone 4A was expected to have been formed by selective migration of bond (b) since it can be readily seen from models that a substantial steric interaction is present between the "W" group and the acyl peroxy moiety in the transition state appropriate for migration of bond (a) leading to the undesired lactone 3A.[2,3] Implicit in this argument is the assumption that the peracid will reversibly attack from the axial direction because of the highly congested nature of the beta-face of 1A-C (the C-10 axial methyl group is, in effect, an axial C-4 t-butyl group in this cyclohexanone derivative). Evidence passively in support of this postulate is provided by the borohydride reduction of 1B to yield the corresponding equatorial alcohol in 80% purified yield. Furthermore, molecular mechanics calculations affirm the contention that 1C exists in an all chair conformation.[6]

In the event, treatment of 1A with meta-chloroperoxybenzoic acid in methylene chloride at 25°C for 18 hr in the presence of boron trifloride etherate (0.75 eq) affords 3A in 88% yield after recrystallization. Since Lewis acid catalysis was required for this reaction, we were concerned that the regiochemical outcome might have resulted from boron-mediated co-ordination between the sulfone and the acyl peroxide moiety thereby favoring alignment of bond (a) in a trans-antiparallel fashion with the peroxy group.

In order to more fully understand the factors controlling this reaction, the desulfonylated lactone 1B[2] was also subjected to Baeyer-Villiger oxidation (Lewis acid not required) with MCPBA in methylene chloride at 25°C for 18 hr to again generate the product of exclusive bond (a) migration, 3B (76%).[2,3] The absence of both the sulfone moiety and the Lewis acid catalyst seems to preclude the possibility of this rearrangement being favored by a specific acyl peroxy rotomer. The next possibility considered was an electronic effect based upon the gamma oxygen substituent at C-7.

Noyori has recently very convincingly demonstrated in a series of closely related gamma-oxygenated ketones 5A-D that increasing the electron-withdrawing ability of the substituent at the gamma position led to a decrease in the migratory aptitude of the alpha-methylene group.[4] While the Noyori experiments (5A-D to 6A-D/7A-D)[4] suggest that this effect is only worth ca. 1 kcal/mole for systems where the oxygen substituent is able to freely rotate, it seemed possible that in the present instance (where a fixed stereoelectronic oxygen relationship exists (1A-C)) that this effect might be enhanced to a sufficient extent such as to completely preclude the migration of bond (b). Since the Noyori data demonstrate that a simple ether (5B) is not sufficient to elicit this effect, we next examined the Baeyer-Villiger oxidation of tetrahydrofuran 1C.[2] Once again, a single bis lactone 3C[2,3] was isolated (65%).

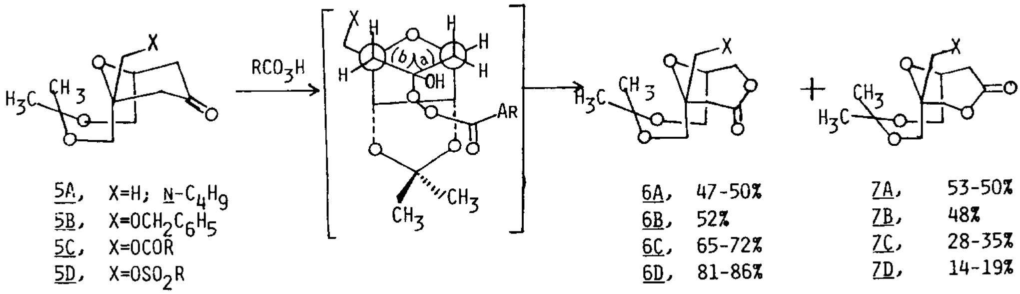


1A, X=O; W=$SO_2C_6H_5$
1B, X=O; W=H
1C, X=H,H; W=H

2 A-C

3 A-C

4 A-C

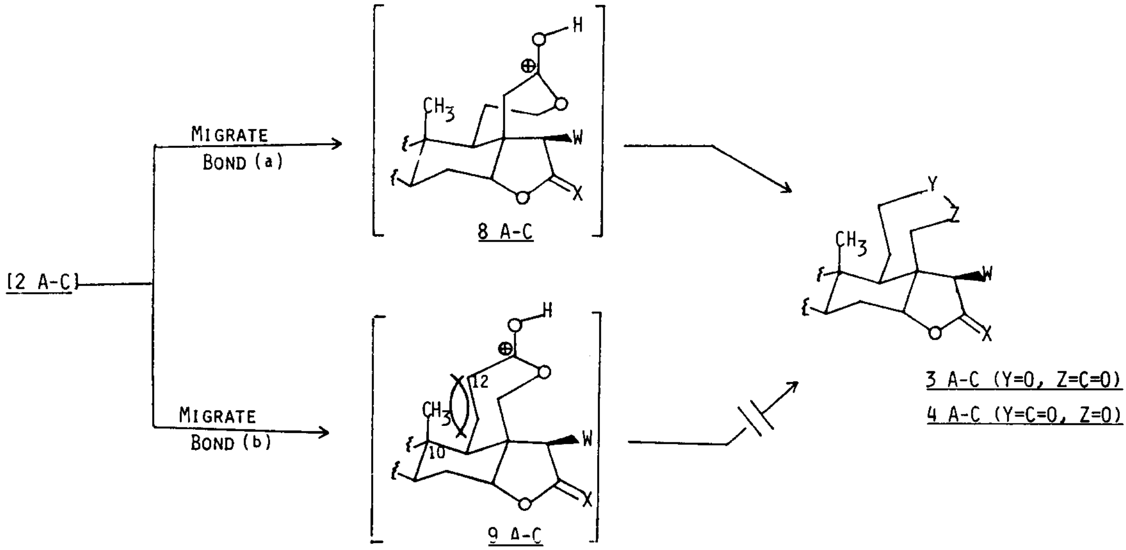


5A, X=H; N-C_4H_9
5B, X=$OCH_2C_6H_5$
5C, X=OCOR
5D, X=OSO_2R

6A, 47-50%
6B, 52%
6C, 65-72%
6D, 81-86%

7A, 53-50%
7B, 48%
7C, 28-35%
7D, 14-19%

A satisfactory explanation for the specificity of these reactions would seem to lie in the area of torsional effects. As the reaction proceeds from intermediate [2] it seems clear that migration of bond (a) (to intermediate [8]) serves to remove an unfavorable 1,3 diaxial interaction between the C-12 methylene and the axial C-10 methyl group which is maintained by migration of bond (b) (to intermediate [9]). Besides accomodating the data, this proposal is further supported by two additional points concerning the reaction profiles. (1) Concern could be expressed that the resonance energy of the protonated lactone carbonyls might differ significantly in the transition states leading to 3 and 4; however, inspection of models reveals that for both intermediates [8] and [9] the incipient lactone carbonyl is substantially twisted out of conjugation with the electron lone pairs of the ether oxygen. (2) An additional concern is for the overall thermodynamics of the reactions; however, molecular mechanics calculations reveal that lactones 3 and 4 are essentially isoenergentic in the lowest energy extended conformation where the lactone C=O moiety enjoys full resonance delocalization.^{5,6} Thus, it seems quite likely that the preference for migration of bond (a) is determined early in the transition state where the selection between dioxolenium ions 8A-C and 9A-C strongly favors intermediates 8A-C. Rehybridization^{7} and conformational isomerization^{5} of 8A-C to 3A-C occur subsequently but do not affect the initial locus of migration.



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1. Bruceantin Support Studies 7. For Paper 6 See S. N. Suryawanshi, P. L. Fuchs, Tet. Lett., 24, 0000 (1983).
2. All new compounds have satisfactory 470 MHz ^{1}H NMR, ^{13}C NMR, exact mass and/or combustion analysis. Experimental details for this transformation will be published in a full paper in due course.
3. Yields refer to purified material, but 470 MHz evaluation of the crude reaction mixture fails to reveal evidence for the presence of any of the alternative Baeyer-Villiger products 4A-C.
4. (a) R. Noyori, T. Sato, H. Kobayashi, Tet. Lett., 2569 (1980); (b) ibid., 2573 (1980).
5. An often cited method[5a,5b] for the identification of the low energy conformation of a complex molecule is geometry optimization from models whose components imitate the geometry of known low energy conformations of similar but simpler systems. In this case, the model chosen to represent both lactones in question consisted of a dimethyl-cyclohexane (i.e. ring B with enforced axial methyl group at C-10) to which a five-membered cyclic ether and seven-membered lactone had been fused. Investigation of the low energy forms of the tricyclic model proceeded with MM2 geometry optimization of the combined chair form of the six-membered ring, the near planar conformation of the five-membered ring and several low energy conformations of the lactone described below. Allinger reports three equilibrium conformations for the seven-membered lactone with the chair form 2.72 kcal/mol lower in energy than the boat form which, in turn, is 2.59 kcal/mol lower in energy than the trans form.[5c] He contends that the equilibrium concentrations of the boat and trans conformations are negligible. After reproducing Allinger's results for the chair and boat geometries of the seven-membered lactone three forms along with a modification of the chair were used to find the minima for the tricyclic model. In each case the energy of the optimized structure was equal to or greater than that previously obtained from MM2 optimization using a program featuring direct graphic input.[6] The calculated steric energy of the lowest energy forms of the models for 3C and 4C are within 0.06 kcal/mole. (5a) Corey, E. J., Feiner, N.F., J. Org. Chem. 45, 757 (1980); (5b) DeClerq, P. J., J. Org. Chem., 46, 667 (1981); (5c) Allinger, N. L., Burkert, U., "Molecular Mechanics"; American Chemical Society: Washington, D. C., 1982, p 226.
6. D. C. Spellmeyer, C. J. Swenson, W. L. Jorgensen, Unpublished Work.
7. Ab Initio calculations suggest that for cis esters it requires ca. 6 kcal/mole to attain fully orthogonal relationship between the oxygen and carbonyl moiety (i.e. no resonance delocalization): (a) L. Radom, W. A. Lathan, W. J. Hehre, J. A. Pople, Aust. J. Chem., 25, 1601 (1972); (b) M. Perricaudet, A. Pullman, J. Peptide Protein Res., 5, 99 (1973).

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