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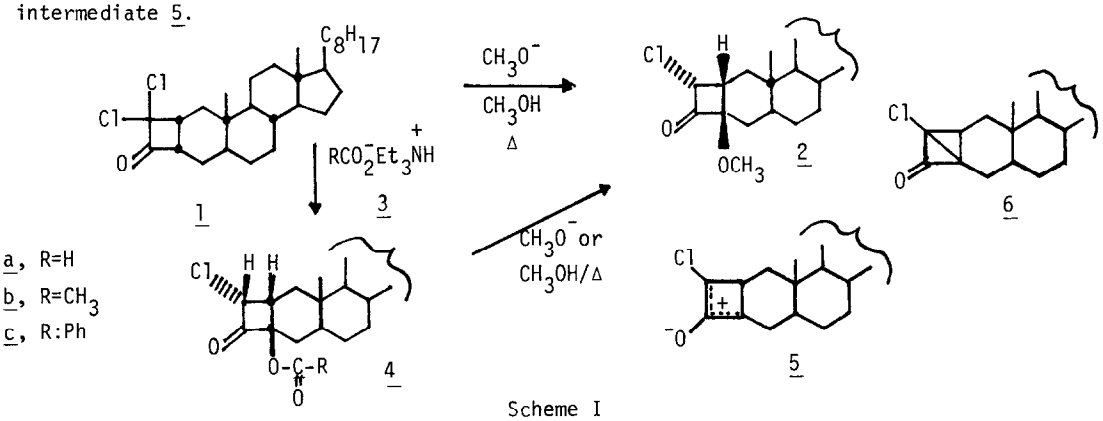
EFFECT OF CONFORMATION AND STEREOCHEMISTRY IN SUBSTITUTION REACTIONS OF FUSED CHLOROCYCLOBUTANONES: OXYALLYL CATION INTERMEDIATES[1]

Alfred Hassner,* John L. Dillon, Jr. and Larry R. Krepski
Department of Chemistry, State University of New York, Binghamton, New York 13901

Kay D. Onan*
Department of Chemistry, Northeastern University, Boston, Massachusetts 02115

Abstract: *Fused α-acyloxycyclobutanones, whose conformation and stereochemistry have been unambiguously established by X-ray analysis, undergo an unusual displacement with methoxide as nucleophile to produce α-methoxycyclobutanones. The success of this reaction, which suggests the intermediacy of an oxyallyl cation, is highly dependent on conformational and steric factors.*

Dichlorocyclobutanones, readily available by dichloroketene cycloadditions to olefins,[2] can undergo ring enlargements,[3] ring contractions[4] or ring opening[5] with nucleophiles. In some cases,[6] cine displacement, for instance 1→2,[2d] has been observed. One can visualize the latter reaction to involve an Sn2' process, a cyclopropanone (e.g., 6) or an oxyallyl cation intermediate 5.



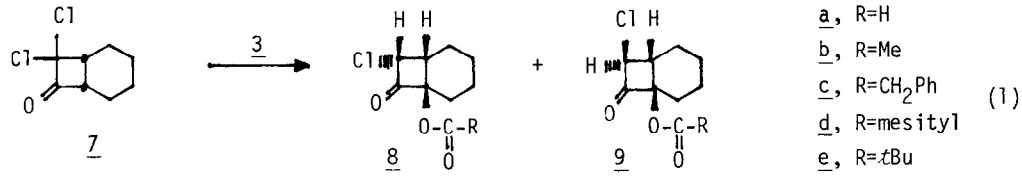
1 3 2 6 4 5

a, R=H
b, R=CH_3
c, R:Ph

Scheme I

We wish to report some interesting reactions of dichlorocyclobutanones and α-acyloxy-α'-chlorocyclobutanones with nucleophiles which proceed by an unusual substitution or by ring opening and which tend to point out the importance of structural features such as stereochemistry, ring flexibility and steric effects in the substrate.

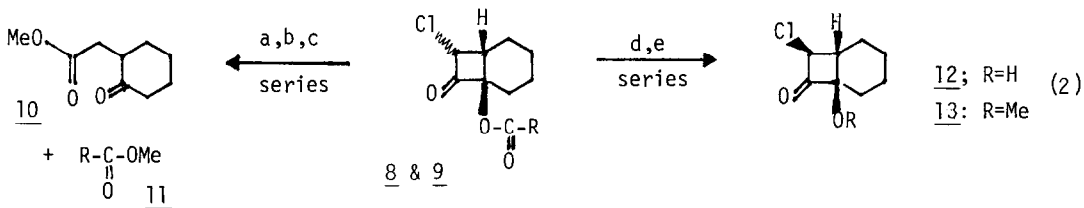
The steroidal dichlorocyclobutanone 1 reacts readily at room temperature with triethylammonium carboxylates 3 to produce regiochemically and stereochemically pure esters 4a-c (doublet for CHCl in the ^{1}H-nmr spectrum near δ5.5,J=9Hz) (Scheme I). Under the same conditions the cyclohexene cycloadduct 7 affords a mixture of isomers 8 (Cl and OCOR *trans*) and 9 (Cl and OCOR *cis*), exhibiting two doublets for CHCl (δ5.2,J=10Hz, δ4.5,J=9Hz) (Equation 1).



(1)

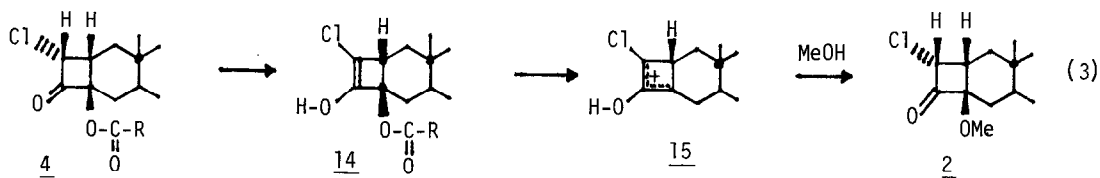
Treatment of keto esters 4 at 20° with NaOMe in MeOH-THF led neither to displacement of the α-chloroketone nor to attack at the ester carbonyl by methoxide but unexpectedly gave keto ether 2 in quantitative yield (Scheme I). This displacement of carboxylate by methoxide is unusual and becomes even more remarkable since it can be accomplished by simply refluxing 4b in MeOH for 3 days.

It is noteworthy that, unlike with 4, reaction of 8 and 9 (a-c) with NaOMe in MeOH produced ring-opened ketone 10 and the methyl ester of the appropriate acid 11. However, when the ester substituent R is more sterically encumbered (series d and e), only ether 13 is formed (Eq. 2).



(2)

The results obtained with 4 are not consistent with an Sn2' process or a cyclopropanone 6, but do suggest an enolization of 4 to 14 (or its anion when MeO^- is used) followed by ionization to an oxy stabilized allylic cation[7] intermediate which is trapped by the nucleophile (Eq. 3).



(3)

To understand the factors governing these reactions, a stereochemical assignment to 4, 8, and 9 becomes imperative. Since the close values of the *cis* and *trans* H-H coupling constants (J=9-10Hz) preclude a reliable stereochemical assignment and do not disclose any conformational features in these compounds, unambiguous assignment of stereochemistry and preferred conformation to esters 4b, 8d and 9d was achieved by X-ray analysis.[8]

Figure 1 indicates that ester 4b possesses the *trans* configuration (Cl and OCOR *trans*) and the preferred conformation 16. The bicyclic cyclobutanone chloro esters possess the *cis* (9d) and *trans* (8d) configurations shown in Figure 2. Based on the X-ray studies it is possible to generalize that the compounds possessing the *trans* configuration show CHCl as a doublet at δ5.2-5.5, while in the *cis* isomers the doublet is found at δ4.5.

The data are consistent with the operation of Scheme II.[11] The *trans* isomer 8 enolizes readily to an enol or enolate corresponding to 14 which can reprotonate either to 8 or to its *cis* isomer 9. Enol 14 is capable of ionization to an oxyallyl cation or to a dipolar oxyallyl

Figure 1: Computer-generated perspective drawing of 4b based on X-ray data; hydrogen atoms and the mesityl group have been omitted for clarity.[9]

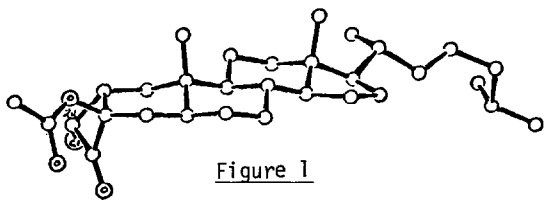


Figure 1

Figure 2: Computer-generated perpsective drawings of (a) 9d and (b) 8d; hydrogen atoms and the mesityl group have been omitted for clarity.[9]

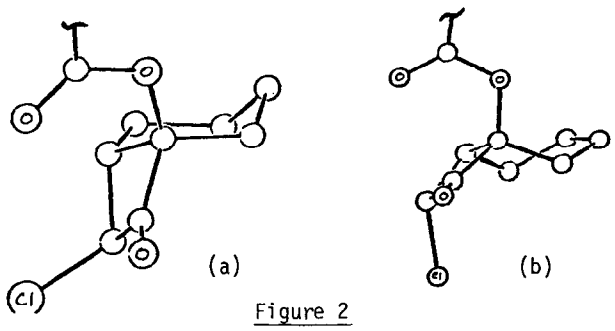
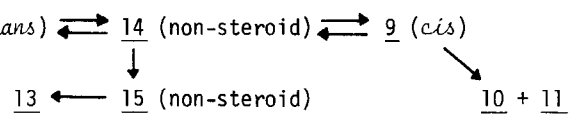


Figure 2

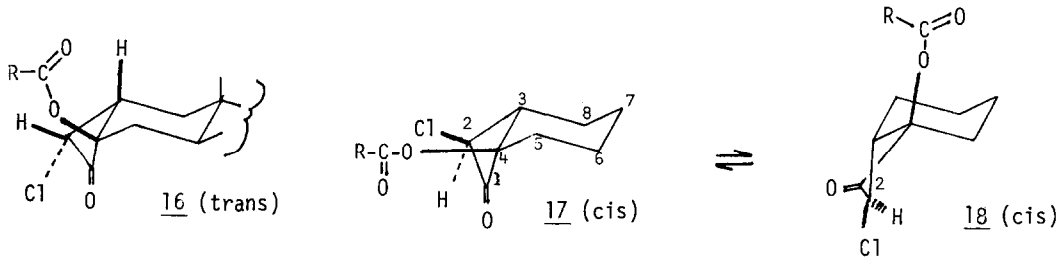
species[10] which can be trapped by methanol to produce 13. In competition with this process is attack of methoxide at the ester carbonyl of 9 to produce the cleavage products 10 (presumably via 12) and 11.

Scheme II:



In support of this scheme are equilibration studies which indicate that the *cis* isomer 9 is more stable than the *trans* isomer 8 (e.g., 8c:9c at equilibrium is 3:14). In order to establish the identity of the kinetic isomer, 7 was reacted with formic acid and triethylamine at -78°C. NMR spectroscopy initially showed a doublet at δ5.2 (8a) which, upon warming the sample to room temperature, converted primarily to a doublet at δ4.5 (9a). Apparently, *trans-cis* equilibration 8 ⇄ 9 is favored over attack at the ester carbonyl, because when 8c was reacted with 0.5 equiv. of methoxide, the products were the *cis* isomer 9c and cleavage products 10, 11. *Trans-cis* isomerization is unfavorable in the rigid steroid system (4) because of non-bonded Cl:acyloxy interactions in 17, but does take place in the flexible cyclohexane system (8 ⇄ 9), where conformation 18 for the *cis* isomer can be established (Cl and acyloxy equatorial to the 4-membered ring). Indeed, X-ray analysis indicate 18 to be the conformation for 9d (see Fig. 2a).

When R is bulky (d and e series), attack at the ester function is effectively absent and the equilibrating esters react via the enol 14 and the oxyallyl species 15.[11] As in the steroidal case, this produces the methyl ether 13 (this time as the more stable *cis* isomer).



16 (trans) 17 (cis) 18 (cis)

Further work to elucidate the scope and mechanism of this reaction is in progress.

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References and Notes

1. Stereochemistry 73. For paper 72 see A. Hassner, D. Middlemiss, J. Murray-Rust and P. Murray-Rust, Tetrahedron, 38, 2539 (1982).
2. For earlier leading references see (a) J.C. Stevens, D.A. Reich, D.R. Brandt, K.R. Fountain and E.J. Gaughan, J. Am. Chem. Soc., 87, 5257 (1965); (b) R. Montaigue and L. Ghosez, Angew. Chem. Int. Ed., Engl., 7, 221 (1968); (c) W.T. Brady and O.H. Waters. J. Org. Chem., 32, 3703 (1967); (d) A. Hassner, V.R. Fletcher and D.E.O. Harmon, J. Am. Chem. Soc., 93, 264 (1971).
3. P.D. Bartlett and T. Ando, J. Am. Chem. Soc., 92, 7518 (1970).
4. (a) V.R. Fletcher and A. Hassner, Tet. Letts., 1071 (1970); (b) D.L. Garin and K.L. Cammack, Chem. Commun., 333 (1972).
5. For instance see J.M. Conia and J.L. Ripol, Bull Soc. Chim.France, 763 (1963).
6. For instance (a) J.B. Conia and M.J. Robson, Angew. Chem. Int. Ed., 14, 473 (1975); (b) K.E. Harding, J.W. Trotter and L.M. May, J. Org. Chem., 42, 2715 (1977); (c) P. Martin, H. Greuter, G. Rihs, T. Winkler and D. Bellus, Helv. Chim. Acta, 64, 2571 (1981).
7. (a) A.W. Fort, J. Am. Chem. Soc., 84, 2620 (1962); (b) F.G. Bordwell and M.W. Carlson, J. Am. Chem. Soc., 92, 3377 (1970); (c) H.M.R. Hoffmann, Angew. Chem. Int. Ed., Engl., 12, 819 (1973); (d) S.S. Edelson and N.J. Turro, J. Am. Chem. Soc., 92, 2770 (1970).
8. Molecules of 4b crystallize in the monoclinic space group $P2_1$, a=11.140(1), b=6.518(1), c=23.342(4) Å, β=117.7(1), ° Z=2; molecules of 8d crystallize in the orthorhombic space group Pbca, a=16.062(2), b=25.989(4), c=8.215(1) Å, Z=8. Two crystalline forms of 9d were studied; one crystallizes in the monoclinic space group $P2_1/c$, a=11.280(1), b=8.613(1) Å, β=102.6(1), ° Z=4; the other, in the triclinic system, a=11.280(1), b=10.112(13), c=11.704 (17) Å, α=113,5(9), β=89.1(1), γ=111.4(1), ° Z=2. The structure of molecule 4b was elucidated by direct phasing methods using MULTAN 77 (S. Germain, P. Main and M.W. Woofson, Acta Cryst., A27, 368 (1971), while the others were solved by the heavy atom method. Refinement in each case was by full-matrix least squares. Molecule 4b, which suffered disorder in the C(17) side chain, was refined to an R of 0.102 over 1500 observed reflections and molecule 8d was refined to an R of 0.066 over 1553 observed data. The gross structure of 9d was determined from each of the sets of data, however, each was affected by disorder at C(16) and C(8). At present the monoclinic data have been refined to R 0.141. Atomic coordinates for this work has been deposited with the Director of the Cambridge Crystallographic Data Centre, University Chemical Lab., Lensfield Road, Cambridge CB2 1EW.
9. C.K. Johnson, ORTEP Oak Ridge National Laboratory Report ORNL-3794 (1965).
10. At this point it is difficult to differentiate between a dipolar oxyallyl species which will presumably be formed in basic medium and an oxyallyl cation which may form in the absence of base.
11. It is equally possible to account for the resulting products by assuming that the *trans* isomer 8 forms an enol or enolate slightly puckered and different in conformation from the enol obtained from the *cis* isomer 9. In this case stereoelectronic factors would favor ionization of the former possessing a pseudoaxial acyloxy group, while 9 or its enol would be attacked at the acyloxy carbonyl. This intriguing possibility must await further support

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