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BASE HYDROLYSIS OF HALOLACTONES. THE MECHANISM OF KETONE FORMATION IN THE BICYCLO (2,2,1) HEPTYL SYSTEM

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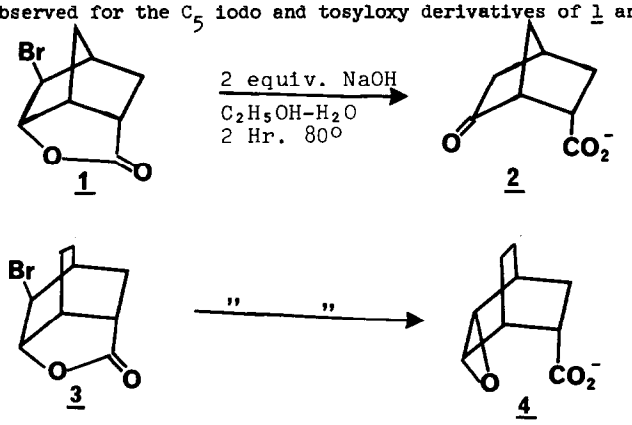
Earlier we reported upon the extremely large rate retardation effects observed in the solvolytic reactions of certain bridged bicyclic compounds possessing neighboring dipolar groups in the vicinity of the reaction center. For example, the rate of acetolysis of the p-toluenesulfonate esters related to 1 and 3 were 10^7 and 10^4 times slower than the parent norbornyl and bicyclo-(2,2,2) octyl systems compared at 25°.[2] The present communication describes the behavior of these compounds under hydrolytic conditions in which the rate retarding dipolar effect due to the neighboring lactone group is relieved.

Unexpected results were obtained in the reaction of 1 relative to 3 upon treatment with two equivalents of sodium hydroxide in aqueous ethanol at 80° for 2 hours. Bromolactone 3 yielded quantitatively epoxycarboxylate 4 while 1 yielded no oxide but 80% of ketocarboxylate 2.[3] The same behavior was observed for the C_5 iodo and tosyloxy derivatives of 1 and 3.



This difference in mode of reaction may be understood straightforwardly in terms of torsional strain interactions of the type applied by Schleyer in discussing the exo stereospecificity common to norbornane chemistry.[4] In the case at hand, endo epoxide formation in the treatment of 1 with base is precluded by the prohibitively large torsional strain inherent in the essentially eclipsed arrangement of the carbon-hydrogen bonds at C_1,C_6; C_5,C_6 and C_4,C_5 in transition state for intramolecular oxide ring closure.[5] However, favorable torsional angles for the relevant carbon-hydrogen bonds at C_1, C_6, C_5, and C_4 in endo epoxide 4 are possible and this reaction may be viewed as an intramolecular displacement by alkoxide ion of the halide anion.

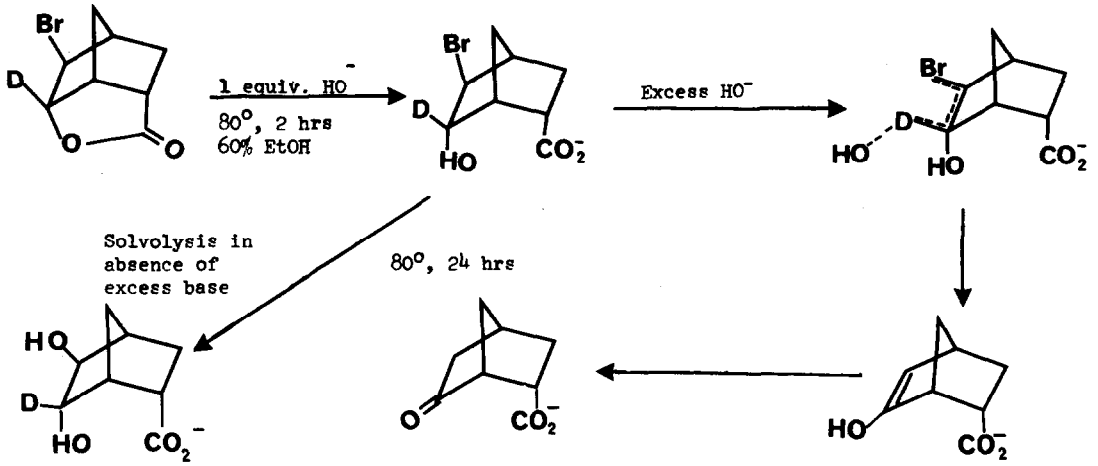
While arguments based on torsional strain sufficed to explain the non-formation of epoxide in the treatment of 1 with base, the question of the mechanism of formation of 2 remained open. A cursory view of this reaction might suggest as an initial step basic hydrolysis of the lactone ring, followed by solvolysis of the carbon-halogen bond to yield a carbonium ion. Hydride ion shift of the C_6 exo hydrogen could result in 2. This pathway is clearly reminiscent of the pinacolic type reactions investigated by Schleyer and Kleinfelter[6] and Collins.[7] An obvious confirmation of this mechanism would be demonstration of the transposition of deuteride from C_6 to the C_5 exo position in the process 1→2.

The appropriate C_6 exo deuterio analog of 1 yielded 2 containing no deuterium under the conditions of two equivalents of sodium hydroxide in aqueous ethanol at 80° for 2 hrs. Furthermore, treatment of 1 with 2 equivalents of NaOEt-D_2O at 80° for 2 hrs. yielded purely the C_5-exo deuterio derivative of 2.[8]

These results indicate the intermediacy of an enol form as the primary reaction product in the process 1⟶2, and by implication a base induced dehydrohalogenation reaction. The overall reaction is formally related to the so-called "vinyl dehydration" mechanism[9] suggested for the pinacol rearrangement, but never before authenticated in any cases studied.[10]

In order to learn whether there was a solvolytic component in the transformation 1⟶2, the behavior of 1 was examined when subjected to one equivalent of base in aqueous ethanol under the same conditions, namely, 80° for 2 hrs. After acidification, only unchanged 1 was obtained. Under more severe conditions, 80° for 2 hrs., the major product formed was 5-exo 6-endo dihydroxybicyclo (2,2,1) hept - 2 endo carboxylic acid γ-lactone (23%). Only a trace of 2 was formed under these conditions and 40% unchanged 1 was also recovered. The dependence upon the presence of a second equivalent of base points to either an E2 or ElcB mechanism.

The following scheme may be written:



The lactone reacts instantly with the first equivalent of sodium hydroxide to yield the hydroxycarboxylate; the second equivalent of base is required for the dehydrohalogenation. The heightened acidity of C_6 exo proton and cis coplanar relationship of the relevant atoms provide the driving force for elimination.[11]

It is of further interest to note that the elimination reaction 1→2 occurs at a rate three times faster than the reaction 3→4 at 50°.

Future work will be aimed at investigating the generality of the E2 elimination as the pathway for ketone formation from 1,2 halohydrins upon treatment with strong base.

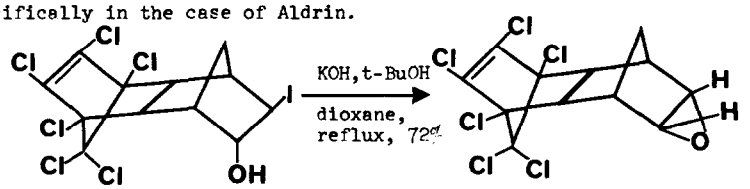
1) Present address: The University of Illinois, Chicago Circle Campus, Chicago, Illinois.

2) R. M. Moriarty, C. R. Romain and T. O. Lovett, J. Am. Chem. Soc., 89, 3927 (1967).

3) The reaction 1→2 has been reported previously by S. Beckmann and H. Geiger, Chem. Ber., 94, 48 (1961). These authors obtained a 61% yield of 2 but reported that this compound existed in an intramolecular 2,6-lactol form. No evidence was found for this structure in the present investigation. The infrared spectrum of 2 is in complete agreement with expectation.

4) P. von R. Schleyer, J. Am. Chem. Soc., 89, 699 (1967).

5) The endo-epoxide has been observed in the norbornane series from base treatment of halohydrins, specifically in the case of Aldrin.



Ph.D. Thesis S. B. Soloway, University of Colorado (1955), private communication, S. J. Cristol.

6) D. C. Kleinfelter and P. von R. Schleyer, J. Am. Chem. Soc., 83, 2329 (1961).

7) C. J. Collins, Z. K. Cheema, R. G. Werth, B. M. Benjamin, J. Am. Chem. Soc., 86, 4913 (1964).

8) Obviously no decision about possible intramolecular deuteride shift can be made if exchange occurs after ketocarboxylate 2 is formed. The following experiments indicate that this does not occur.

Two equivalents of base are consumed in the reaction 1→2. The product of this reaction is actually the sodium salt of the ketocarboxylate 2 in neutral solution. Therefore, treatment of 2 with one equivalent of base simulates the final reaction milieu for its formation. Under these conditions the C_5 exo proton of 2 does not undergo exchange. Treatment of 2 with one equivalent of NaOEt in D_2O under the conditions of the reaction 1→2 caused no introduction of deuterium; nor did the C_5 exo deuterio derivative of 2 undergo exchange in the presence of one equivalent of base under comparable protic conditions.

These experiments above do not rule out the possibility of a hydride shift mechanism followed by rapid base catalysed exchange via the enol form of 2. This possibility is excluded by the observed necessity of a second equivalent of base for the formation of 2. The hydride shift mechanism is a solvolytic one, and the same products should be observed regardless of the concentration of base. Treatment of 1 with one equivalent of base yields essentially no ketocarboxylate under conditions aqueous ethanol for 24 hrs. at 80°.

9) M. Tiffeneau, Bull. Soc. Chim. 33, 759 (1923).

10) C. J. Collins, Quart. Rev. (London), 14, 363 (1960). This of course is not strictly a valid comparison because the reaction in question is not a pinacolic reaction. The comparison is not based upon mechanistic grounds but rather upon the similarity of the reaction with respect to change from reactant to product. In this sense the overall transformation is a case contrary to the more familiar hydride shift mechanism.

11) H. Kwart, T. Takeshita and J. L. Nyce, J. Am. Chem. Soc., 86, 2607 (1964) and references therein.