Tetrahedron Letters No. 19, pp 1659 - 1662, 1978. 004 -4039/78/0501-1659. $02.00/0.

ON THE GENERALITY OF TWO MECHANISMS FOR THE ACID-CATALYZED α→α' MIGRATION OF HALOGEN IN α-HALO KETONES[1]

E. Warnhoff,* M. Rampersad, P. Sundara Raman, and F.W. Yerhoff
Department of Chemistry, University of Western Ontario, London, Canada N6A 5B7

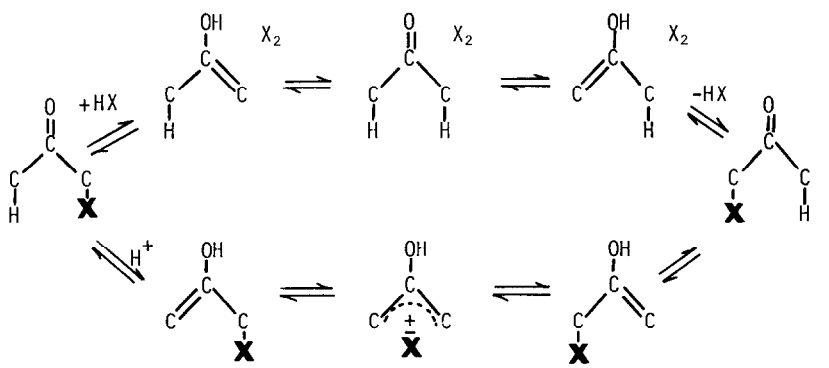
(Received in USA 23 November 1977; received in UK for publication 23 March 1978)

Numerous examples of α-bromo ketones rearranging to the α'-isomer in the presence of HBr are known.[2,3] It has been generally accepted that these rearrangements proceed through a reductive dehalogenation--rehalogenation sequence (loss of cationic halogen in the Scheme).[3,4] More recently, there have been reported a few examples of α-chloro ketones undergoing acid-catalyzed migration to the α'-isomer.[5] For these an α'-enol allylic rearrangement (loss of anionic halogen in the Scheme) has been suggested by ourselves[5d] and others.[5c,e] From the study of a series of 21 halogenated monoketones of varying structural type, we would now like to report the unexpected finding that both α-bromo and α-chloro ketones can rearrange by either of these two mechanisms or in some cases by both concurrently, and that contrary to general opinion,[3,4] the α'-enol allylic rearrangement is a common path for bromine migration.

Scheme:

cationic halogen path

anionic halogen path



The two mechanisms may be distinguished by different responses to several tests listed in the Table. An example for which reductive rearrangement is the only detectable pathway is 2,2-dibromo-3-cholestanone 1. In HOAc-anhydrous HCl[6] at room temperature the major products are 2α,4α-dibromo-3-cholestanone 2 and 2α-bromo-3-cholestanone 3 with no trace of 2-bromo-4α-chloro

Table. Differing Mechanistic Responses of α-Halo Ketones.

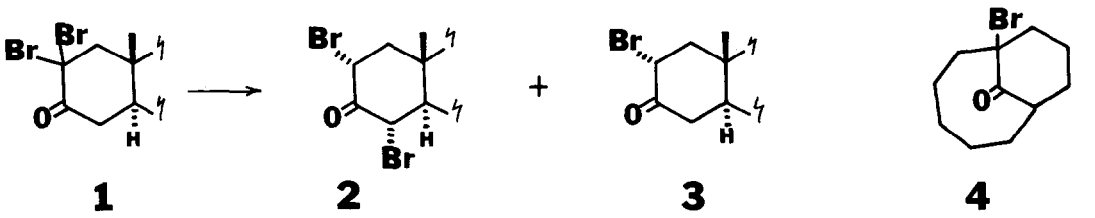
Test	Reductive dehalogenation mechanism (cationic halogen)	α'-Enol allylic rearrangement mechanism (anionic halogen)
Nature of acid	HBr or HCl required as specific catalyst	HBr or HCl or other strong acid, e.g. $HClO_4$, H_2SO_4, p-TsOH; rate with $HClO_4$>rate with HCl
HCl on Br ketone	No halogen exchange to form Cl ketone	Halogen exchange to form Cl ketone
HBr on Cl ketone	Formally halogen exchange can occur since BrCl is a brominating agent	Halogen exchange to form Br ketone
Trapping agent present	2-Naphthol → 1-Br-2-naphthol + reduced ketone or halo ketone	2-Naphthol → naphthofurans if ketone structure permits
Nature of products	Some reduced ketone formed	No reduced ketone formed

ketone. If the same reaction is run with the addition of three equivalents of 2-naphthol, the only detectable product (≥ 95%) in addition to 1-bromo-2-naphthol is 2α-bromo-3-cholestanone. If any α'-enol allylic rearrangement had occurred under the latter conditions, the 2α,4α,-dihalo product would have survived (control experiments). The apparent contradiction that rearrangement of the 2,2-dibromo ketone 1 to 2 and 3 can also be catalyzed by both anhydrous $HClO_4$ and H_2SO_4 is removed when it is noted that the reaction is very slow with both of these acids, and for a matter of hours there is an induction period when no reaction occurs. Presumably some slow acid-catalyzed reaction liberates HBr which then causes reductive rearrangement. The induction period observed in the $HClO_4$ reaction also excludes the formal possibility of reduction occurring by attack of 2-naphthol on bromine atom of carbonyl protonated 2,2-dibromo ketone 1.

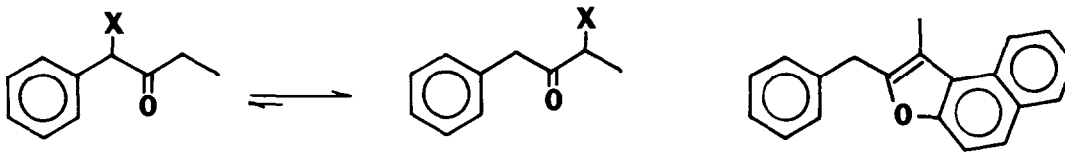
An example in which only enol allylic rearrangement occurs is 1-bromo-bicyclo[5.3.1]undecan-11-one 4. Optically active 4 undergoes racemization by ionization in the presence of HBr and

HCl in a variety of solvents. With HCl there is halogen exchange to yield chloro ketone. With added 2-naphthol, racemization and chloride exchange still occur, but no 1-bromo-2-naphthol or debrominated ketone is formed.

A more typical case is that of the 1-halo-1-phenyl-2-butanones 5. The 1-chloro ketone 5a rearranges to the 3-chloro isomer 6a (1:10 equilibrium ratio of 5a:6a in HOAc) only by the α'-enol allylic mechanism. The $HClO_4$-catalyzed reaction is faster than the HCl-catalyzed reaction; no reduced 1-phenyl-2-butanone is formed with or without 2-naphthol; if 2-naphthol is present 1-methyl-2-benzylnaphtho[2,1-b]furan 7 is formed, m.p. 70.5-71.5°C. In contrast, the bromo ketone 5b rearranges by both mechanisms. In HOAc with $HClO_4$ catalyst the equilibrium proportion (5b:6b ca. 1:10) is formed with at most a trace (≤ 2%) of debrominated ketone. With HBr-catalysis α→α' equilibration occurs but there is also considerable reduced phenylbutanone produced (10-15%). With 2-naphthol in $HClO_4$-HOAc medium, the initial reaction leads to α→α' migration and naphthofuran; in the later stages as HBr is released by naphthofuran formation, some reductive debromination to phenylbutanone (<10%) and 1-bromo-2-naphthol occurs. With 2-naphthol in the HBr-HOAc medium, phenylbutanone is apparent from the outset, and it is the major product after long reaction time although naphthofuran is also formed.



1 2 3 4



5 6 7

a) X = Cl b) X = Br

Although rare, reductive dechlorination has been observed with 1-chloro-1,1-diphenylacetone and HCl in CF_3COOH from which reaction chlorine was detected and dechlorinated ketone obtained. Also the reaction of 1,1-dichlorobutanone with HBr-HOAc probably proceeds by dechlorination-rebromination because 1,1-dichloro-3-bromobutanone and 1-chlorobutanone are formed.

These α→α' rearrangements are quite general if the acid is not bound by too strong a base, e.g., H_2O. Recently reported failures[7] of HBr to cause equilibration between the 2-bromo- and 4-bromo-isomers of 3-oxo-5β-steroids were apparently due to the use of aqueous HBr. When anhydrous HBr in HOAc is used, we find that pure 4β-bromo ketone is transformed into a mixture of 2β-bromo, 4β-bromo, and 2β,4β-dibromo ketones plus 5β-3-cholestanone.

Acknowledgment. We are grateful to the National Research Council of Canada for financial support.

REFERENCES and NOTES

1. α-Halo Ketones VIII. For part VII see K.E. Teo and E.W. Warnhoff, *J. Am. Chem. Soc.*, 95, 2728 (1973).

2. We are not concerned here with α-bromo β-dicarbonyl compounds such as ethyl α-bromoacetoacetate which apparently rearranges mainly by a radical pathway; M.S. Kharasch, E. Sternfeld, and F.R. Mayo, *J. Am. Chem. Soc.*, 59, 1655 (1937).

3. Inter alia: T. Barr, I.M. Heilbron, E.R.H. Jones, and F.S. Spring, *J. Chem. Soc.*, 334 (1938); H.H. Inhoffen and G. Zuhlsdorff, *Chem. Ber.*, 76, 233 (1943); E.J. Corey, *J. Am. Chem. Soc.*, 76, 175 (1954); C.W.P. Crowne, R.M. Evans, G.F.H. Green, and A.G. Long, *J. Chem. Soc.*, 4351 (1956); C. Djerassi, N. Finch, R.C. Cookson, and C.W. Bird, *J. Am. Chem. Soc.*, 82, 5488 (1960); M.D. Mehta, D. Miller, and D.J.D. Tidy, *J. Chem. Soc.*, 4614 (1963); C. Rappe, *Ark. Kemi*, 23, 81 (1965); 24, 73 (1965); H. Durr, G. Ourisson, and B. Waegell, *Chem. Ber.*, 98, 1858 (1965).

4. (a) F. Kröhnke and H. Timmler, *Chem. Ber.*, 69, 614 (1936); (b) R. Altschul and P.D. Bartlett, *J. Org. Chem.*, 5, 623 (1940); (c) M.S. Newman, *J. Am. Chem. Soc.*, 73, 4993 (1951)

5. (a) F. Caujolle and D.C. Quan, C.R. Acad. Sci., Paris, Ser. C, 264, 269, 320 (1967); (b) F.G. Bordwell and M.W. Carlson, *J. Am. Chem. Soc.*, 92, 3377 (1970); (c) A.M. Bianchi, V. Rosnati, A. Saba, F. Soccolini, and G. Zecchi, *Gazz. Chim. Ital.*, 103, 79 (1973); (d) E.W. Warnhoff and M. Rampersad, Abstr. 57th Can. Chem. Conf., Regina, Sask., June 1974, paper 203; (e) P. Metzger, A. Casadevall, and E. Casadevall, *Tetrahedron*, 31, 469 (1975).

6. It has been shown previously that HCl can act as a reducing agent toward α-bromo ketones; E.W. Warnhoff, *J. Org. Chem.*, 28, 887 (1963). If HBr is used, some reduction of the 2α,-4α-dibromo ketone to 4α-bromo-3-cholestanone occurs.

7. A.J. Liston, *J. Org. Chem.*, 31, 2105 (1966); Y. Yanuka and G. Halperin, *J. Org. Chem.*, 39, 3047 (1974).