Elimination Reactions. II. Hofmann Elimination in Bicyclic Compounds[1]

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Abstract: The Hofmann elimination of N,N,N-trimethyl-3-*exo*-d_1-bicyclo[2.2.1]heptyl-2-*exo*-ammonium hydroxide to bicyclo[2.2.1]hept-2-ene has been found to proceed by an exclusively *cis* elimination with not greater than 6% ylide mechanism. A primary isotope effect of $k_H/k_D = 1.86 \pm 0.10$ for the elimination was found. It was also found that the Hofmann elimination of N,N,N-trimethyl-3-*cis*-d_1-bicyclo[2.2.2]octyl-2-ammonium hydroxide to give bicyclo[2.2.2]oct-2-ene is an exclusively *cis* elimination with not greater than 13% ylide mechanism. It is concluded that these Hofmann eliminations proceed by a predominantly *cis* E2 mechanism and the reasons for the observed stereochemistry are discussed.

The Hofmann elimination of quaternary ammonium hydroxides has long been assumed to proceed by a *trans* elimination[3] and indeed there are many proven examples of this in acyclic compounds. Even in cyclic compounds in most cases investigated the general rule has been that a *trans* elimination is more favorable than a *cis* elimination. There have been many theories proposed[4] to explain this observed stereochemistry. It seemed to us that in order to formulate a sound theory to explain the stereochemistry of eliminations one should also have numerous examples of compounds in which *cis* elimination is the preferred mode of reaction. This would allow the examination of factors which are important in the *cis* process and any over-all theory would then have to take these factors into account.

In Hofmann eliminations of quaternary hydroxides one finds a great paucity of authentic cases of a *cis* elimination predominating when a *trans* elimination might be possible. One case involves a *cis* E2 elimination of N,N,N-trimethyl-*trans*-2-phenylcyclohexylammonium hydroxide to give 1-phenylcyclohexene.[5] This compound has a hydrogen *trans* to the trimethylammonium group but loss of the *cis*-benzylic hydrogen predominates. It is interesting to note, however, that the corresponding *cis*-2-phenyl isomer (*trans* elimination) also gives 1-phenylcyclohexene at a rate 133 times as fast as the *trans* isomer. Another rather unusual case involves a predominantly (approximately 75%) *cis* ylide elimination of N,N,N-trimethyl-2-*t*-butyl-3,3-dimethylbutylammonium-2-d_1 hydroxide to give trimethylamine-d_1.[6] The remainder of the reaction (25%) could have been either a *cis* or *trans* process. Mechanisms that involve an ylide formed by irreversible loss of a proton to such bases as phenyllithium[7] are not comparable to simple pyrolysis of quaternary hydroxides.

Very recently two examples have been reported which indicate that a *cis* mechanism may be fairly common in Hofmann eliminations. Sicher and co-workers[8] have found that the *trans*-olefin formed on elimination of an N,N,N-trimethylcyclodecylammonium methoxide is formed by a *cis*-elimination mechanism. The same group[9] also found that in an aliphatic case giving a mixture of *cis*- and *trans*-olefins the *cis*-olefin is formed by a *trans* mechanism and the *trans*-olefin is formed by a *cis* mechanism. This prompted these workers to suggest[9] that this may be a general condition for any Hofmann elimination which results in a mixture of *cis*- and *trans*-olefins.

DePuy and co-workers[10] have proposed that elimination reactions, whether *cis* or *trans*, should show a maximum rate when the two departing groups are coplanar. This idea can be used to find examples of *cis* Hofmann eliminations. There are two systems which form the basis of the present work and these are the 2-*exo*-bicyclo[2.2.1]heptyl and the 2-bicyclo[2.2.2]octyl derivatives. These structures are relatively rigid systems which allow coplanar *cis* eliminations but would require slightly noncoplanar *trans* eliminations. In addition to this the bond angles are fairly well known, at least in the starting materials.

Since we wanted to study the parent compounds to avoid complications introduced by substituents deuterium was used to label the positions which were *cis* to the nitrogen function. Accordingly, bicyclo[2.2.1]hept-2-ene was converted to 3-*exo*-d_1-bicyclo[2.2.1]heptyl-2-*exo*-amine by treatment with diborane-d_6 followed by chloramine.[11] Brown and co-workers have already shown that the addition of diborane-d_6 is stereospecific, both bonds forming *exo* without rearrangement.[11] The fact that we find total loss of deuterium during the

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[1] (a) This investigation was supported in part by Public Health Service Research Grant HE 07050, from the National Heart Institute, U. S. Public Health Service. (b) A preliminary account of part of this work appeared as part I of this series: J. L. Coke and M. P. Cooke, Jr., *J. Am. Chem. Soc.*, **89**, 2779 (1967).

[2] Koppers Fellow 1966; Shell Fellow 1966–1967.

[3] A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1959); (b) W. H. Saunders, Jr., "The Chemistry of Alkenes," Interscience Publishers, Inc., New York, N.Y., 1964, p 149; (c) J. F. Bunnett, *Angew. Chem. Intern. Ed. Engl.*, **1**, 225 (1962); (d) D. J. Cram, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p 304.

[4] For a recent summary of these see ref 3b.

[5] (a) G. Ayrey, E. Buncel, and An. N. Bourns, *Proc. Chem. Soc.*, 458 (1961); (b) A. C. Cope, G. A. Berchtold, and D. L. Ross, *J. Am. Chem., Soc.*, **83**, 3859 (1961); (c) S. J. Cristol and F. R. Stermitz, *ibid.*, **82**, 4692 (1960); (d) J. Weinstock and F. G. Bordwell, *ibid.*, **77**, 6706 (1955); (e) R. T. Arnold and P. N. Richardson, *ibid.*, **76**, 3649 (1954).

[6] A. C. Cope and A. S. Mehta, *ibid.*, **85**, 1949 (1963).

[7] (a) G. Wittig and R. Polster, *Ann.*, **599**, 13 (1956); (b) G. Wittig and T. F. Burger, *ibid.*, **632**, 85 (1960); (c) A. C. Cope, N. A. LeBel, P. T. Moore, and W. R. Moore, *J. Am. Chem. Soc.*, **83**, 3861 (1961).

[8] J. Zavada, M. Svoboda, and J. Sicher, *Tetrahedron Letters*, 1627 (1966).

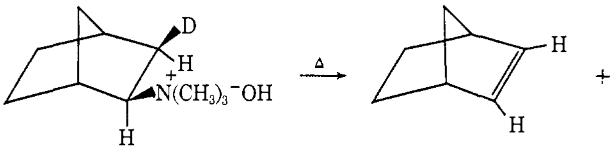
[9] M. Pankova, J. Sicher, and J. Zavada, *Chem. Commun.*, 394 (1967).

[10] C. H. DePuy, R. D. Thurn, and G. F. Morris, *J. Am. Chem. Soc.*, **84**, 1314 (1962).

[11] H. C. Brown, W. R. Heydkamp, E. Breuer, and W. S. Murphy, *ibid.*, **86**, 3565 (1964); H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, p 130.

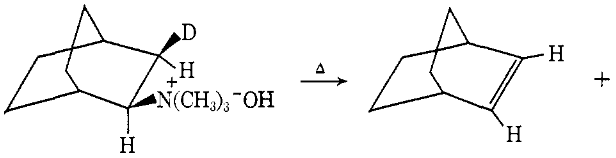
Hofmann elimination not only confirms this but also proves that no carbon skeletal rearrangement took place during the reaction with chloramine. The primary amine was converted to the N,N-dimethyl derivative with formaldehyde and formic acid and this was in turn quaternized with methyl iodide. Passage of the methiodide over Dowex 1-X8 resin and removal of the water under vacuum gave N,N,N-trimethyl-3-*exo*-d_1-bicyclo[2.2.1]heptyl-2-*exo*-ammonium hydroxide (I) which was used for Hofmann elimination. A similar series of reactions starting with bicyclo[2.2.2]oct-2-ene led to N,N,N-trimethyl-3-*cis*-d_1-bicyclo[2.2.2]octyl-2-ammonium hydroxide (III).

Hofmann eliminations on compounds I[12] and III[13] were found to be surprisingly stereospecific. On pyrolysis compound I was found to give olefin II containing no deuterium.[14] The initial trimethylamine from I was found to contain 6% trimethylamine-d_1. When the pyrolysis was carried to completion the total trimethylamine was found to contain 17% trimethylamine-d_1[15] with the last traces of vapors containing 21%. This increase in incorporation of deuterium into the trimethylamine after the initial stages of the reaction has been studied by Cope and co-workers[7c] and is due to exchange between the methyl hydrogens of the quaternary hydroxide and the water (containing some deuterium) produced during the reaction. Compound III on pyrolysis was found to give olefin IV containing no deuterium. The initial trimethylamine from III was found to contain 13% trimethylamine-d_1 and when the reaction was carried to completion the total trimethylamine contained 19% trimethylamine-d_1.



I II

$(CH_3)_3N$ + $(CH_3)_2NCH_2D$
(94%) (6%)



III IV

$(CH_3)_3N$ + $(CH_3)_2NCH_2D$
(87%) (13%)

The mechanism of Hofmann elimination on I and III is required to be totally *cis* by the fact that neither olefin II nor IV contained any deuterium. Compound I could not have isomerized (through an ylide) to the *endo* isomer to give *trans* elimination because Cope and co-workers[12] have already shown that the *endo* isomer produces very little olefin. In any event, this kind of isomerization would have introduced some deuterium into the position bearing the nitrogen function and this would have given olefin containing deuterium. The initially produced trimethylamine indicates that I undergoes not greater than 6% *cis* ylide elimination and III undergoes not greater than 13% *cis* ylide elimination. At the present time it is not known if this ylide mechanism is an intra- or intermolecular process.

The possibility of a stereospecific E1cB elimination involving exchange or no exchange but rapid decomposition of the intermediate anion to product is unlikely on the following grounds. A test for exchange in compound I might be inconclusive because the hydrogen and deuterium are stereochemically nonequivalent in the sense of *exo* and *endo*. However in compound III due to the steric bulk of the trimethylammonium group and the stereochemical equivalence of the hydrogen and deuterium on the 3 position (except in relation to the trimethylammonium group) exchange should have resulted in introduction of deuterium in the 3-*trans* position of III and this deuterium would have been detected in olefin IV. One could propose a pure E1cB mechanism involving no protonation back to starting material and no actual breakage of the carbon–nitrogen bond in the transition state. If this were correct it is difficult to explain why proton removal would be completely stereospecific in compound III.

The most likely mechanism remaining for the Hofmann elimination of compounds I and III is a normal *cis* E2 elimination with concerted but not synchronous breakage of the deuterium and nitrogen bonds. This accounts for at least 94% of the product from I and 87% of the product from III. This mechanism demands a primary kinetic isotope effect and an actual $k_H/k_D = 1.86 \pm 0.10$ was observed for the bicyclo[2.2.1]heptyl case. This was determined as follows. An excess of bicyclo[2.2.1]hepta-2,5-diene (V) was treated with diborane followed by propionic acid-d_1 to give d_1-bicyclo[2.2.1]hept-2-ene (VI).[16] Compound VI was then converted to VII by the same reactions used to prepare I except that diborane was used instead of diborane-d_6. Compound VII gives olefin VI (one deuterium per molecule) on Hofmann elimination by loss of the 3-*exo* hydrogen whereas I gives olefin II (no deuterium) by loss of the 3-*exo* deuterium. A mixture of equimolar quantities of I and VII was prepared and subjected to partial pyrolysis at 50°. The initial olefin that formed was analyzed by mass spectrometry and the ratio of VI/II was then taken as k_H/k_D.

The isotope effect observed here is somewhat smaller than that found in other Hofmann eliminations.[17] It is

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(12) Hofmann elimination has been carried out on nondeuterated I: A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Am. Chem. Soc.*, **81**, 2799 (1959).

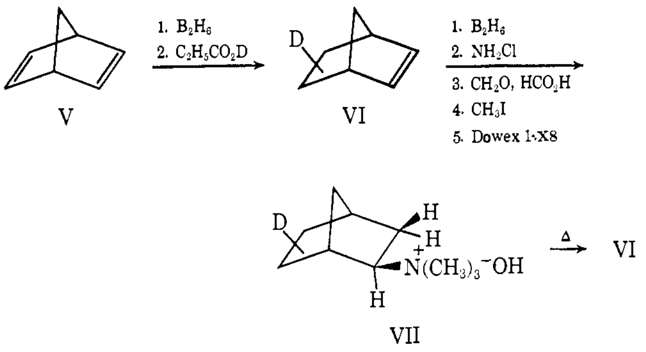
(13) Hofmann elimination has been carried out on nondeuterated III: R. Seka and O. Tramposch, *Ber.*, **75**, 1379 (1942).

(14) This reaction on I has been run previously by other workers and we wish to thank Professor R. C. Cookson for calling this to our attention. Credit should be given to C. W. Bird, R. C. Cookson, J. Hudec, and R. O. Williams, *J. Chem. Soc.*, 410 (1963). The reaction was used to test the stereochemistry of hydrocarboxylation of olefins but the fundamental conclusions that Hofmann elimination on compound I must be a *cis* elimination can be arrived at by the investigation of these earlier workers. Further details of the mechanism could not be deduced.

(15) For the method used for mass spectral analysis of trimethylamine see A. S. Mehta, Ph.D. Thesis, Massachusetts Institute of Technology, 1963.

(16) G. Zweifel, K. Nagase, and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 183 (1962); H. C. Brown and K. J. Murray, *J. Org. Chem.*, **26**, 631 (1961); H. C. Brown and K. Murray, *J. Am. Chem. Soc.*, **81**, 4108 (1959).

(17) W. H. Saunders, Jr., and D. H. Edison, *ibid.*, **82**, 138 (1960); V. J. Shiner, Jr., *ibid.*, **80**, 4095 (1958).



not known whether this difference is primarily due to different experimental conditions on different substrates or to the fact that the present case involves a *cis* mechanism while the systems studied by the earlier workers may have a *cis* or *trans* mechanism. We find that our isotope effect is also lower than that reported for two known *cis* Hofmann eliminations[8,9] run under a variety of conditions. In the one case run as a pyrolysis of the hydroxide[9] the temperature and reaction conditions were not given so our work cannot be compared directly. It is known that the conditions used for a Hofmann elimination have rather drastic effects on the course of the reaction and could alter the isope effect. We have found that when slightly wet samples of quaternary hydroxides are subjected to pyrolysis large amounts of N,N-dimethylalkylamines are formed along with the olefin. This results from displacement by hydroxide on one of the N-methyl groups. However, when the quaternary hydroxides are dried under very high vacuum (10^{-7} mm) prior to pyrolysis this side reaction disappears and the only reaction observed is elimination to give olefin.

It is interesting to note that while one might attribute the *cis* mechanism in compound I to some unusual difference in rate of proton removal from the *exo vs.* the *endo* position of the bicyclo[2.2.1]heptyl system as has been observed in corresponding ketones[18] or halides[19] the results from compound III indicate other factors are important. In compound III the two atoms on position 3 (deuterium and hydrogen) are stereochemically identical except in relation to the trimethylammonium group. If one examines models of compounds I and III it is apparent that a coplanar transition state can easily be achieved for *cis* elimination but that a coplanar transition state for *trans* elimination is forbidden without excessive torsional strain. The degree of departure from the ideal 180° *trans* coplanar orientation for *trans* elimination is difficult to determine but it could be in the order of 50–60°.

From the present work it appears that the large amount of *cis* ylide elimination (75%) observed by Cope and Mehta[6] does not occur simply because the proton to be eliminated is held rigidly *cis* to the nitrogen function. Examination of molecular models indicates that in the compound studied by Cope and Mehta the proton to be eliminated is so buried among two *t*-butyl groups and the trimethylammonium group that it is extremely sterically shielded from approach by an external base and the intramolecular attack by the anion formed on one of the N-methyls is the favored mode of elimination.

Experimental Section[20]

Mass Spectral Analysis. Mass spectral analyses were performed on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Spectra were recorded at 75 ev and at approximately 10 ev when it was desired to remove M − 1 fragmentation that interfered with deuterium analysis. All deuterium analyses were corrected using standard nondeuterated samples run immediately after the analyses. Deuterium analyses on trimethylamine samples were carried out by the method of Mehta[15] because of the inability to reduce sufficiently the M − 1 fragmentation of this compound even at low voltage.

3-*exo*-d_1-Bicyclo[2.2.1]heptyl-2-*exo*-amine. Into a stirred solution of 18.8 g (0.200 mole) of bicyclo[2.2.1]hept-2-ene in 200 ml of dry tetrahydrofuran was passed a stream of diborane-d_6 prepared by the external generation method of Brown and Tierney[21] from slow addition of 2.20 g (0.0525 mole) of sodium borodeuteride in 45 ml of dry diglyme to 13.5 g (0.095 mole) of boron trifluoride etherate in 20 ml of dry diglyme. After the addition was complete the reaction was stirred for 0.5 hr and then 5 ml of water was slowly added to the alkylborane solution. The alkylborane solution was then treated under nitrogen according to the procedure of Brown and coworkers[11] by addition of 120 ml of 3 *N* sodium hydroxide followed by a solution of chloramine prepared at 0° from 210 ml of 5.25% sodium hypochlorite and 20 ml of 29% ammonium hydroxide diluted with 100 ml of water.[22] The resulting mixture was stirred for 1 hr, acidified with hydrochloric acid, and extracted repeatedly with ether. The aqueous layer was basified with sodium hydroxide, saturated with sodium chloride, and extracted repeatedly with ether. The latter ether solutions were combined, dried, and evaporated. The resulting residue was distilled to yield 10.1 g (45%) of 3-*exo*-d_1-bicyclo[2.2.1]heptyl-2-*exo*-amine, bp 159–163° (760 mm) (lit.[23] bp 78° (55 mm)).

An acetamide derivative, mp 141.5–142.5° (lit.[23] mp 140–141°), was prepared. Mass spectral analysis at low voltage showed no M − 1 peak and indicated 97% d_1 species.

N,N-Dimethyl-3-*exo*-d_1-bicyclo[2.2.1]heptyl-2-*exo*-amine. The general procedure of Icke, *et al.*,[24] was used to convert 8.3 g (0.074 mole) of the primary amine from the preceding experiment to 4.6 g (46%) of N,N-dimethyl derivative, bp 50–52° (6 mm); $n^{25}\text{D}$ 1.4690 (lit.[12] bp 71° (20 mm), $n^{25}\text{D}$ 1.4682).

N,N,N-Trimethyl-3-*exo*-d_1-bicyclo[2.2.1]heptyl-2-*exo*-ammonium Iodide. A solution of 4.1 g (0.029 mole) of the corresponding tertiary amine from the preceding experiment in 30 ml of dry ether and 17 g (0.120 mole) of methyl iodide was allowed to stand overnight. The solid was collected by filtration to yield 8.0 g (97%) of the methiodide, mp 297–299° dec (lit.[12] mp 295°).

3-*cis*-d_1-Bicyclo[2.2.2]octyl-2-amine. Using the same procedure that was followed for the bicyclo[2.2.1]heptyl system 9.2 g (0.085 mole) of bicyclo[2.2.2]octene was converted to 4.2 g (39%) of 3-*cis*-d_1-bicyclo[2.2.2]octyl-2-amine, mp 135–137° (lit.[25] mp 140–141.5°).

N,N-Dimethyl-3-*cis*-d_1-bicyclo[2.2.2]octyl-2-amine. The general procedure of Icke, *et al.*,[24] was used to convert 4.2 g (0.033 mole) of primary amine from the preceding experiment to 1.6 g (31%) of the corresponding N,N-dimethyl derivative, bp 94–98° (28 mm); $n^{20}\text{D}$ 1.4810 (lit.[12] bp 82° (14 mm), $n^{20}\text{D}$ 1.4833).

N,N,N-Trimethyl-3-*cis*-d_1-bicyclo[2.2.2]octyl-2-ammonium Iodide. A solution of 1.6 g (0.0104 mole) of tertiary amine from the preceding experiment and 7.4 g (excess) of methyl iodide in 50 ml of dry ether was allowed to stand overnight. The solid was collected by filtration to give 2.4 g (78%) of product, mp 303–305° dec (lit.[12] mp 296°).

Hofmann Pyrolysis. A. Preparation of Quaternary Hydroxides I and III. An aqueous solution of the corresponding iodide was

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[18] A. F. Thomas, R. A. Schneider, and J. Meinwald, *ibid.*, 89, 68 (1967); A. F. Thomas and B. Willhalm, *Tetrahedron Letters*, 1309 (1965).

[19] J. K. Stille and F. M. Sonnenberg, *ibid.*, 4587 (1966); J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *J. Am. Chem. Soc.*, 88, 4922 (1966).

[20] No distinction will be made in physical constants for deuterated and nondeuterated compounds.

[21] H. C. Brown and P. A. Tierney, *J. Am. Chem. Soc.*, 80, 1552 (1958).

[22] F. Raschig, *Ber.*, 40, 4586 (1907).

[23] J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, 76, 4501 (1954).

[24] R. N. Icke, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 723.

[25] W. C. Wildman and D. R. Saunders, *J. Am. Chem. Soc.*, 76, 946 (1954).

placed on a column of Dowex 1-X8 ion-exchange resin in the basic form and eluted with water. The water was removed from the eluent under vacuum, keeping the temperature below 40°. The resulting hydroxides I and III were used directly.

B. Pyrolysis of Quaternary Hydroxides I and III. The hydroxides were decomposed at 100–130° (40–60 mm) and the olefins were collected, washed with dilute acid, and then either sublimed (IV, mp 114–117°; lit.[26] mp 116.4–117.5°) or distilled (II, retention time on vpc shown to be identical with authentic sample). Mass spectral analysis of olefins II and IV at 75 ev and approximately 10 ev indicated no deuterium.

To test for a *cis* ylide mechanism operating on compounds I and III the trimethylamine was analyzed as early in the reaction as it could be detected by direct introduction of the vapors into the mass spectrometer or the trimethylamine was trapped as a hydrochloride and then the liberated vapors of trimethylamine were introduced into the mass spectrometer. The mass spectra at 75 ev were analyzed by the procedure of Mehta[15] and the results are shown in Table I.

Table I

Compd	Stage of reaction	$(CH_3)_3N$, %	$(CH_3)_2NCH_2D$, %
I	Initial	94	6
	Total	83	17
	Final	79	21
III	Initial	87	13
	Total	81	19

d_1-Bicyclo[2.2.1]hept-2-ene (VI). The procedure of Brown and co-workers[16] was used. A solution of 36.8 g (0.40 mole) of freshly distilled bicyclo[2.2.1]hepta-2,5-diene in 200 ml of dry ether was prepared and 72 ml of diborane in tetrahydrofuran[27] (1 *M* in BH_3) was added slowly with cooling. The resulting solution was allowed to stir at room temperature for 2 hr, and all volatile materials were removed at reduced pressure. The foamy residue was maintained at 50° (0.05 mm) overnight to remove all traces of excess diene. A total of 40 ml of propionic acid-d_1[28] was added to the dry trialkylborane, and the resulting mixture was heated on a steam bath for 4 hr and then at 150° for 2 hr taking care to exclude moisture. The reaction mixture was then distilled until the temperature reached 145°, and the distillate was collected, washed with sodium carbonate solution, and redistilled to yield 9.7 g (51%) of d_1-bicyclo[2.2.1]hept-2-ene (VI), bp 98–99° (lit.[29] bp 94–97°).

d_1-N,N,N-Trimethylbicyclo[2.2.1]heptyl-2-*exo*-ammonium Iodide. In a manner exactly analogous to the preparation of the methiodide corresponding to compound I except that diborane was used instead of diborane-d_6 a sample of 9.5 g (0.10 mole) of VI was converted to d_1-N,N,N-trimethylbicyclo[2.2.1]heptyl-2-*exo*-ammonium iodide in 12% over-all yield, mp 297–299° dec (lit.[12] mp 295°).

The acetamide derivative of the corresponding primary amine was analyzed by mass spectrometry at 10 ev and was found to be 92% d_1 and 8% d_0. A correction for this was made in the isotope effect experiment.

Kinetic Isotope Effect for Hofmann Elimination on Bicyclo[2.2.1]-heptyl System. A typical experimental run is described. Equimolar quantities of the two compounds, N,N,N-trimethyl-3-*exo*-d_1-bicyclo[2.2.1]heptyl-2-*exo*-ammonium iodide and d_1-N,N,N-trimethylbicyclo[2.2.1]heptyl-2-*exo*-ammonium iodide, were mixed and passed through a column of Dowex 1-X8 resin in the basic form. Evaporation of the water under vacuum below 40° gave an equimolar mixture of the two hydroxides I and VII. This mixture was placed in a flask attached directly to the mass spectrometer and dried at 10^{-7} mm. The dried mixture of I and VII was then heated at 50°, taking care not to let the reaction proceed to more than approximately 5–10% completion, and the resulting olefin mixture was analyzed directly in the mass spectrometer at approximately 10 ev. After correction for isotopic purity the kinetic isotope effect was calculated from the ratio of per cent olefin-d_1/per cent olefin-d_0 and was found to be *cis* $k_H/k_D = 1.86 \pm 0.10$ (average of four determinations).

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(26) H. L. Goering and M. F. Sloan, *J. Am. Chem. Soc.*, **83**, 1397 (1961).

(27) Solution of diborane purchased from Ventron Corporation, Beverly, Mass.

(28) Prepared from freshly distilled propionic anhydride and deuterium oxide.

(29) J. Meinwald and N. S. Hudak, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 738.

Favorskii Reactions. I. The Nature of the Rate-Determining Step

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Contribution from the Chemistry Department of Northwestern University, Evanston, Illinois 60201, and the Research and Development Department, American Oil Company, Whiting, Indiana. *Received May 20, 1967*

Abstract: Kinetic studies of the reaction of three α-halo 4,4-disubstituted cyclohexanones (**1**, **2**, and **3**) with sodium methoxide in methanol have revealed Br/Cl rate ratios of 36, 52, and 116. The chloro compounds react at rates 15- to 66-fold slower than that of α-chlorocyclohexanone. Deuterium exchange at the α' position occurs to the extent of at least 19% for α-chlorocyclohexanone prior to chloride loss, and is much more extensive (50 to 100%) in the 4,4-disubstituted α-chlorocyclohexanones. The data indicate that in the Favorskii rearrangement of α-chlorocyclohexanones reversible carbanion formation at the α' position occurs prior to chloride loss ($k_{obsd} \cong K_{eq}k_2$). For α-bromocyclohexanones there is little deuterium exchange at the α' position prior to bromide loss, although extensive exchange occurs at the α position. Here, proton abstraction at the α' position is essentially rate determining, and k_{obsd} approaches k_1 in magnitude. A concerted 1,3-elimination mechanism is unlikely for these reactions.

The formation of acids (or esters) from α-halo ketones on treatment with hydroxide (or alkoxide) ion (the Favorskii rearrangement) can occur by at least two mechanisms.[3] If no α' hydrogen atom is present, as

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(1) (a) Northwestern University. (b) American Oil Company.

(2) (a) Texaco Company Fellow, 1964–1965. (b) National Institutes of Health Predoctoral Fellow, 1966 to present.

(3) See A. S. Kende, *Org. Reactions*, **11** (1960), for an excellent review.