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).

(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

**F. G. Bordwell,[1a] Robert R. Frame,[1a,2a] Richard G. Scamehorn,[1a,2b] Jerry G. Strong,[1a] and Seymour Meyerson[1b]**

*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

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

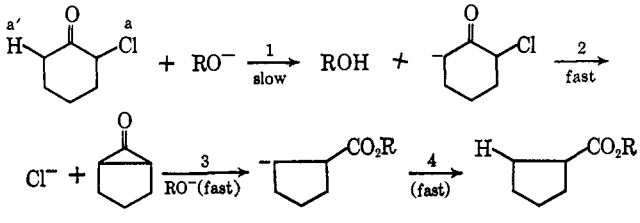
(2) (a) Texaco Company Fellow, 1964–1965. (b) National Institutes of Health Predoctoral Fellow, 1966 to present.

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

in α-chlorocyclohexyl phenyl ketone,[4] or α-bromo-α′,α′-dimethylcyclobutanone,[5] the reaction proceeds by attack at the carbonyl group by a mechanism similar to that of the benzilic acid rearrangement. This "semibenzilic rearrangement" mechanism is utilized when the α′-hydrogen atom is rendered relatively nonacidic by virtue of its attachment to a bridgehead carbon atom as in 1-bromobicyclo[3.3.1]nonan-9-one,[6] or cage-type α-halo ketones.[7] Most Favorskii reactions are initiated, however, by abstraction of the α′ proton by base.[3] It has been demonstrated for $PhCHClCOCH_3$ and $PhCH_2COCH_2Cl$ that loss of a proton and the chloride ion leads to a common intermediate.[8] For α-chlorocyclohexanone, the intermediate has been shown to be symmetrical.[9] The formation of the rearranged product(s) can be most readily rationalized in terms of a cyclopropanone intermediate,[9] and the stereochemistry (inversion) in heterogeneous media (solid alkoxides in ether) requires no other intermediate.[10] Theoretical arguments can be advanced, however, to support the formation of a dipolar ion intermediate[11] (first suggested by Aston[12]), and the change in stereochemistry to nonstereospecificity with sodium methoxide in methanol (homogeneous medium) can best be accommodated by this mechanism.[13]

The cyclopropanone and/or dipolar ion intermediate(s) can be visualized as being generated by a concerted 1,3 elimination,[14] or by way of expulsion of halide ion from a preformed carbanion.[9-13] The present paper is concerned with the choice between these two possibilities for α-halocyclohexanones, and with the question of whether or not the carbanion, if formed, is formed reversibly.

Loftfield formulated the detailed mechanism for the Favorskii reaction of α-chlorocyclohexanone in the following manner.[9]




The Aston–Dewar mechanism[11,12] differs from this by picturing step 2 as an ionization to give a dipolar ion, rather than as a displacement to give a cyclopropanone. The concerted 1,3 elimination differs from the Loftfield and Aston–Dewar mechanisms in that steps 1 and 2 are coupled to give the intermediate (cyclopropanone or dipolar ion).[14]

Loftfield's evidence for representing step 1 as rate determining was twofold. First, he pointed out that when chlorine is replaced by bromine in the α-halo ketone, side reactions, particularly epoxy ether formation, often became predominant. For example, α-bromocyclohexanone gives much lower yields of Favorskii rearrangement product than does α-chlorocyclohexanone.[3,9] Also, bromomethyl cyclohexyl ketone gives only by-products derived from the epoxy ether side reaction (attack of alkoxide ion at the carbonyl group), whereas chloromethyl cyclohexyl ketone, under comparable conditions, gives a 20% yield of ester.[15] (A large rate acceleration for epoxy ether formation is expected on replacement of Cl by Br, because the Br/Cl rate ratio for epoxide formation is known to be of the order of 100.[16]) The shift in products is understandable if the rate of the Favorskii reaction is not accelerated by the change from Cl to Br. This would be true if step 1 is rate determining; in fact, the rate of abstraction of the α′ proton by base might well be *less* for Br than for Cl, in view of the larger inductive effect of the latter. As a second piece of evidence for step 1 being rate determining, Loftfield observed that the rate of removal of a proton from acetone by hydroxide ion was of the same order of magnitude as that found for the rate of neutralization of α-chlorocyclohexanone by ethoxide ion in the Favorskii reaction.[9]

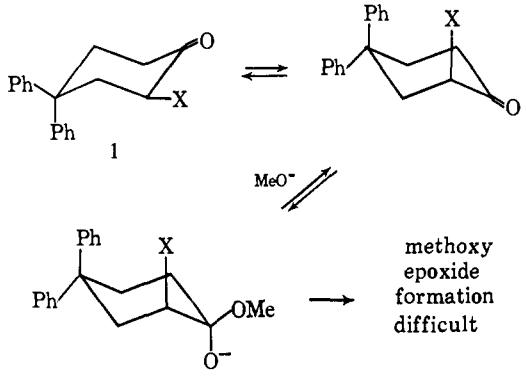
**Deuterium Exchange Studies.** Most subsequent results with α-halo ketones have supported Loftfield's postulate that proton removal is rate determining. No deuterium was incorporated into the recovered chloro ketone when the Favorskii reaction of 9-chloro-*trans*-1-decalone with sodium methoxide in methanol-*d* was run to partial completion.[17] Furthermore, Nace and Olsen[18] have shown in the reaction of 2,4,4-trideuterio-2α-halocholestan-3-ones with sodium ethoxide in ethanol that either all the deuterium is retained in the α′ positions of the halo ketone recovered after one half-life (bromide) or the loss of deuterium is small (chloride). The absence of an appreciable preequilibrium also appeared to be indicated in their work from the relatively small Br/Cl rate ratio (however, see Table III). A similar conclusion has been drawn from a study of the reaction of 17α-bromopregnenolone acetate with potassium carbonate in $CH_3OD$–$D_2O$. Deuterium, beyond that expected from cleavage of the cyclopropanone, was not present in the Favorskii product.[19] Here the α′ protons are contained in a methyl group.

On the other hand, under somewhat different experimental conditions, deuterium does appear in the chloro ketone recovered after one half-life from a reaction of 1-chloro-1-acetylcyclohexanone[20] or 2-chlorohexanone[21] with sodium phenoxide and O-deuteriophenol in anhydrous dioxane. No Favorskii rearrangement product is formed from α-chlorocyclo-

(4) B. Tchoubar, *Compt. Rend.*, 228, 580 (1950); C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, 74, 5352 (1952).
(5) J. M. Conia and J. Salaun, *Bull. Soc. Chim. France*, 1957 (1964).
(6) A. C. Cope and E. S. Graham, *J. Am. Chem. Soc.*, 73, 4702 (1951); E. W. Warnhoff, C. M. Wong, and W. T. Tai, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. S120.
(7) P. E. Eaton and T. W. Cole, Jr., *J. Am. Chem. Soc.*, 86, 962, 3157 (1964).
(8) W. D. McPhee and E. Klingsberg, *ibid.*, 66, 1132 (1944).
(9) R. B. Loftfield, *ibid.*, 73, 4707 (1951).
(10) G. Stork and I. J. Borowitz, *ibid.*, 82, 4307 (1960).
(11) J. G. Burr and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954).
(12) J. G. Aston and J. D. Newkirk, *J. Am. Chem. Soc.*, 73, 2900 (1951); A. A. Sacks and J. G. Aston, *ibid.*, 73, 3902 (1951).
(13) H. O. House and W. F. Gilmore, *ibid.*, 83, 3980 (1961).
(14) A. W. Fort, *ibid.*, 84, 2620 (1962).
(15) R. B. Loftfield and L. Schaad, *ibid.*, 76, 35 (1954).
(16) C. L. McCabe and J. C. Warner, *ibid.*, 70, 4031 (1948).
(17) H. O. House and N. W. Thompson, *J. Org. Chem.*, 28, 164 (1963). The significance of this experiment is somewhat impaired by the fact that no Favorskii product is formed under these conditions, although good yields are obtained in heterogeneous medium.
(18) B. A. P. Olsen, *Dissertation Abstr.*, 25, 4413 (1965).
(19) R. Deghenghi, G. Schilling, and G. Papineau-Couture, *Can. J. Chem.*, 44, 789 (1966).
(20) M. Charpentier-Morize, M. Mayer, and B. Tchoubar, *Bull. Soc. Chim. France*, 529 (1965).

hexanone under these conditions, however.[20] The product isolated was 2-phenoxycyclohexanone; a "good yield" of Favorskii ester was isolated from chloromethyl cyclohexyl ketone.[21]

The present work had its inception in the preparative observation that 2-bromo-4,4-diphenylcyclohexanone (**1**, X = Br) reacted with sodium methoxide in methanol to give a good yield of Favorskii product (methyl 3,3-diphenylcyclopentane-1-carboxylate), and that the rate of this reaction was much greater than that for the corresponding chloro compound. The formation of a good yield of Favorskii product from an $\alpha$-bromo ketone is unusual, but not unique. The success of the reaction with an $\alpha$-bromo ketone appears to depend on the presence of some structural feature that will either inhibit the principal side reaction, namely, epoxy ether formation, or in some way make the Favorskii reaction competitive with it. In the 17-bromo 17-acetyl steroids the steric effect of the C-18 methyl group in shielding the C-20 carbonyl group to attack appears to provide an inhibitory factor. In 2-bromocholestan-3-one the C-19 methyl group makes it difficult for the bromine atom to assume the axial position preferred for epoxide formation.[22] Success of the Favorskii reaction with **1** (X = Br) presumably has its basis in the latter factor; the axial phenyl group in **1** should be even more effective than an axial methyl group in preventing the bromine atom from assuming the axial position most suitable for epoxy ether formation.




The results of rate measurements with 2-chlorocyclohexanone, **1** (X = Cl and Br), and deuterated samples of **1** (X = Cl and Br) are summarized in Table I.

Table I. Rates of Halide Ion Release from $\alpha$-Halocyclohexanones with Sodium Methoxide in Methanol at 0°

| $\alpha$-Halo ketone | $10^4k$, $M^{-1}$ sec$^{-1}$ | $k_H/k_D$ | $k_{Br}/k_{Cl}$ |
|---|---|---|---|
| $\alpha$-Chlorocyclohexanone | 40 | | |
| **1** (X = Cl) | 0.61 | | |
| **1** (X = Cl, 2,6,6-$d_3$) | 0.58 | 1.05 | |
| **1** (X = Br) | 71 | | 116 |
| **1** (X = Br, 2,6,6-$d_3$) | 17 | 4.1 | |

The relatively large $k_{Br}/k_{Cl}$ ratio strongly suggests that the carbanion from **1** (X = Cl) is being formed reversibly. The absence of a primary deuterium isotope effect for this compound confirms this conclusion. Since the $k_H/k_D$ rate ratio for **1** (X = Br) is relatively small,[23] it would appear that part of the deuterium is also lost here by exchange prior to halide release. This supposition was validated by a study of the extent of hydrogen exchange in deuterated **1** (X = Cl and Br). The results are summarized in Table II.

Table II. Hydrogen Exchange during the Reaction of Deuterated 2-Chloro- and 2-Bromo-4,4-diphenylcyclohexanones with Sodium Methoxide in Methanol at 0°

| Starting compd (**1**) | Material analyzed | Deuterons per molecule Nmr | Mass spectrum | |
|---|---|---|---|---|
| Chloride | Parent | ~2.0 | 1.80 | 3.2 $d_0$ |
| | | | | 24.7 $d_1$ |
| | | | | 60.5 $d_2$ |
| | | | | 11.6 $d_3$ |
| Chloride | Recovered chloride at $t_{1/2}$ | 0 | 0.03 | 96.7 $d_0$ |
| | | | | 3.3 $d_1$ |
| Chloride | Methyl 3,3-diphenylcyclopentanecarboxylate | 0 | 0.05 | 94.6 $d_0$ |
| | | | | 5.4 $d_1$ |
| Bromide | Parent | ~2.8 | 2.28 | 0.7 $d_0$ |
| | | | | 10.9 $d_1$ |
| | | | | 47.6 $d_2$ |
| | | | | 40.8 $d_3$ |
| Bromide | Recovered bromide at $t_{1/2}$ | 1.5 | 1.68 | 8.0 $d_0$ |
| | | | | 33.1 $d_1$ |
| | | | | 49.5 $d_2$ |
| | | | | 9.4 $d_3$ |
| Bromide | Methyl 3,3-diphenylcyclopentanecarboxylate | 0.7 | 0.78 | 22.2 $d_0$ |
| | | | | 77.1 $d_1$ |
| | | | | 0.7 $d_2$ |

The results in Table II show that essentially complete exchange has occurred at both the $\alpha$ and $\alpha'$ positions in the chloride (**1**, X = Cl); exchange with the bromide (**1**, X = Br) is appreciable, but not complete.

The parent halo compounds were prepared by halogenation of 4,4-diphenylcyclohexanone-2,2,6,6-$d_4$, which contained about 95% deuterium in the 2 ($\alpha$) and 6 ($\alpha'$) positions (nmr analysis). The mass spectral (and nmr) analysis of the chloride (Table II) revealed the loss of about two, rather than one, deuterium atoms in the preparation. The presence of only 11.6% $d_3$ in the parent suggests that loss of deuterium from the $\alpha$ position during processing has been particularly heavy. This is not unexpected, since the $\alpha$ protons in chloroacetone have been shown to exchange 37 times as rapidly as do those in acetone under hydroxide catalysis.[24]

The $\alpha$ protons adjacent to bromine are even more susceptible to exchange.[24] The larger amount of $d_3$ in the parent bromo compound than the parent chloro compound (Table II) is due to a shorter processing time. However, loss in processing accounts for some of the reduction in the quantity of $d_3$-labeled bromide recovered after one half-life, as compared to the parent.

The product ester loses little or no deuterium during processing, as shown by the retention of essentially all the deuterium by a partially deuterated ester during hydrolysis and reesterification. Therefore, the presence of only 0.05 deuterium atom per molecule in the

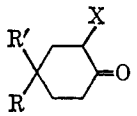
(21) H. Ginsburg, *Bull. Soc. Chim. France*, 3645 (1965).

(22) Preference for diaxial epoxide formation is expected since this is the microscopic reverse of epoxide opening wherein the diaxial stereochemistry is known to be favored (Fürst-Plattner rule); see R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 59, 737 (1959), for a discussion.

(23) The value for acetone at 0° with hydroxide ion is about 13 [see J. R. Jones, *Trans. Faraday Soc.*, 61, 95 (1965)].

(24) R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc.* (London), A176, 88 (1940).

Table III. Rates of Halide Release for 2-Halocyclohexanones with Sodium Alkoxides in Alcohols at 0°

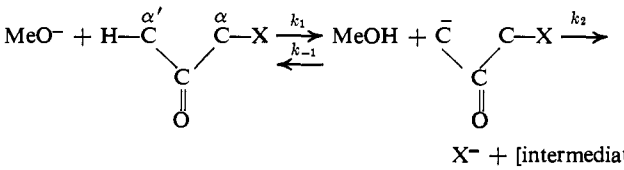


| No. | R | R′ | X | NaOMe $k$, $M^{-1}$ sec$^{-1}$ | Relative rate | $k_{Br}/k_{Cl}$ | NaOEt $k$, $M^{-1}$ sec$^{-1}$ | $k_{Br}/k_{Cl}$ |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | Ph | Cl | $6.1 \times 10^{-5}$ | 1.0 | | $1.9 \times 10^{-3}$ | |
| 1 | Ph | Ph | Br | $7.1 \times 10^{-3}$ | 116 | 116 | $1.5 \times 10^{-1}$ | 79 |
| 2 | $C_{20}H_{36}$ | Me[a] | Cl | $2.7 \times 10^{-4}$ | 4.4 | | $(7.56 \times 10^{-3})$[b] | |
| 2 | $C_{20}H_{36}$ | Me[a] | Br | $9.6 \times 10^{-3}$ | 160 | 36 | $(4.62 \times 10^{-2})$[b,c] | (6)[b,c] |
| 3 | Ph | Me | Cl | $2.1 \times 10^{-4}$ | 3.4 | | | |
| 3 | Ph | Me | Br | $1.1 \times 10^{-2}$ | 180 | 52 | | |
| | H | H | Cl | $4.0 \times 10^{-3}$ | 7.3[d] | | | |

[a] 2α-Halocholestan-3-one. [b] Data from ref 18. [c] This value is probably low since the half-life for bromide **2** under the experimental conditions used (0.2 $M$ base, 0.005 $M$ **2**) is only 74 sec. [d] Corrected on the basis of relative yield of Favorskii ester (see Experimental Section).

ester from the chloride demonstrates complete preequilibration at both the α and α′ positions. On the other hand, the presence of 0.78 deuterium atom per molecule in the ester from the bromide shows only partial deuterium exchange in a preequilibrium. The ester derived from a bromide containing 2.28 deuterium atoms per molecule should have at least 1.28 deuterium atoms per molecule, if no exchange had occurred. The observed loss of 1.5 deuterium atoms per molecule represents at least 40% exchange. Exchange at the α position will be faster, but there was no doubt less deuterium at this position to start with. Perhaps the best measure of the extent of exchange at the α′ position is given by the increase in the number of molecules containing $d_0$ from 0.7% in the parent bromide to 22.2% in the ester. At least 10.6% of these $d_0$ molecules must have arisen from exchange of $d_2$ or $d_3$ molecules, which indicates a minimum of 10.6% exchange at the α′ position. The presence of a partial preequilibrium involving the α′ position was further indicated by an experiment carried out with **1** (X = Br) in methanol-O-$d_1$. Analysis of the resulting ester showed 0.3% $d_0$, 2.4% $d_1$, 78.0% $d_2$, and 19.3% $d_3$, indicating at least 19.3% exchange at α′. This result differs from that with 17α-bromopregnenolone acetate where *no exchange* was observed at the α′ position. (Since the bromine in this molecule is tertiary, the possibility for exchange at the α position is excluded.)

**Kinetic Studies.** Using the steady-state approximations for steps 1 and 2 (carbanion formation and halide



$X^- + [\text{intermediate}]$

loss, respectively) allows the observed rate of halide ion release to be expressed as

$$k_{obsd} = k_1k_2/(k'_{-1} + k_2)$$

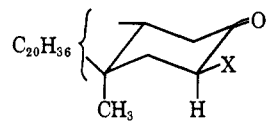
where $k'_{-1} = k_{-1}[\text{MeOH}]$. For chloride **1**, $k'_{-1} \gg k_2$ in order for preequilibration to be complete. This leads to

$$k_{obsd} = k_1k_2/k'_{-1} = Kk_2$$

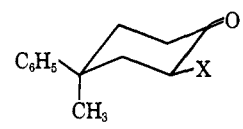
where $K$ is an equilibrium constant. For bromide **1**, the value of $k_2$ has increased to the point where it is somewhat *greater* than $k'_{-1}$. (Assuming 25% exchange at the α′ position, $k'_{-1} = 0.25k_2$.) As the value of $k_2$ increases, $k_{obsd}$ approaches $k_1$ as a limit.

Since $k_{obsd}$ for α-chlorocyclohexanone is appreciably less than that for bromide **1** (Table I), it would not be surprising to find that it too undergoes partial hydrogen exchange at the α′ position (C-6) prior to loss of chloride ion. This expectation was realized in a study carried out with sodium methoxide in methanol-O-$d_1$. The product ester contained 2.07 deuterium atoms per molecule (12% $d_1$, 69% $d_2$, and 19% $d_3$). This result show that a minimum of 19% of deuterium exchange occurred at the α′ position prior to loss of chloride ion.

These data are consistent with those obtained in the reaction of 1-chloro-1-acetylcyclohexanone and of 2-chlorocyclohexanone with $C_6H_5ONa$–$C_6H_5OD$ in anhydrous dioxane.[20,21] They differ to some extent, however, from the observations made for the reaction of 2α-halocholestan-3-ones (**2**, X = Br, Cl) with sodium ethoxide in ethanol.[18] In this system deuterated chloride **2** was observed to retain about 80% of its deuterium at the α′ position (C-4) at one half-life, and the Br/Cl rate ratio was reported as only 6:1.[18] In view of the presence of an axial methyl group in **2**, one might expect it to behave more like **1** (complete exchange at the α′ position; $k_{Br}/k_{Cl} = 116$ in methanol) than like α-chlorocyclohexanone. It seemed possible that the difference in base and solvent might account for the differences in behavior of **1** and that reported for **2**. If, for example, the change from methanol to ethanol resulted in a substantial decrease in $k'_{-1}$ for chloride **2**, or an increase in $k_2$, then $k_2$ might become larger than $k'_{-1}$, and $k_{obsd}$ for the chloride, as well as for the bromide, might approach $k_1$. Rate determinations were, therefore, carried out with sodium ethoxide in ethanol for **1** (X = Br and Cl). The Br/Cl rate ratio in this solvent was lowered somewhat ($k_{Br}/k_{Cl} = 79$ in ethanol). The rates in ethanol were 20–30 times faster than those in methanol, which indicated that accurate measurements would be difficult for bromide **2** in ethanol. The rates for **2** (X = Br and Cl) were, therefore, repeated in methanol solution. The rate data for **2** and the analogous system **3**, 2-halo-4-methyl-*cis*-4-phenylcyclohexanone, which has a similarly situated axial methyl group, are summarized in Table III.



**2** (X = Br or Cl)



**3** (X = Br or Cl)

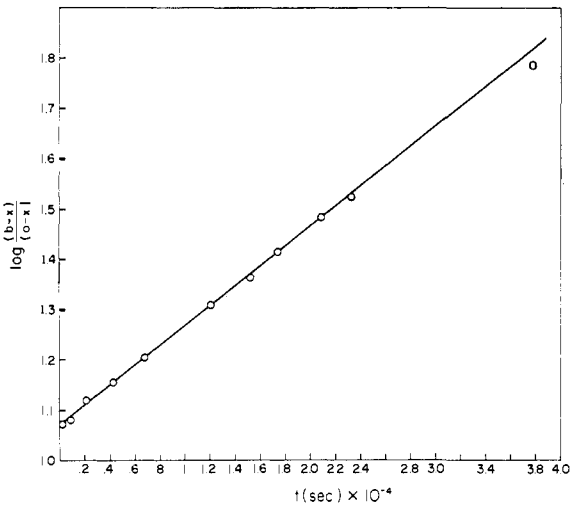



Figure 1. Plot of the data obtained in a typical kinetic reaction of 2-bromo-4,4-diphenylcyclohexanone (**1**, X = Br) with sodium methoxide in methanol at 0°.

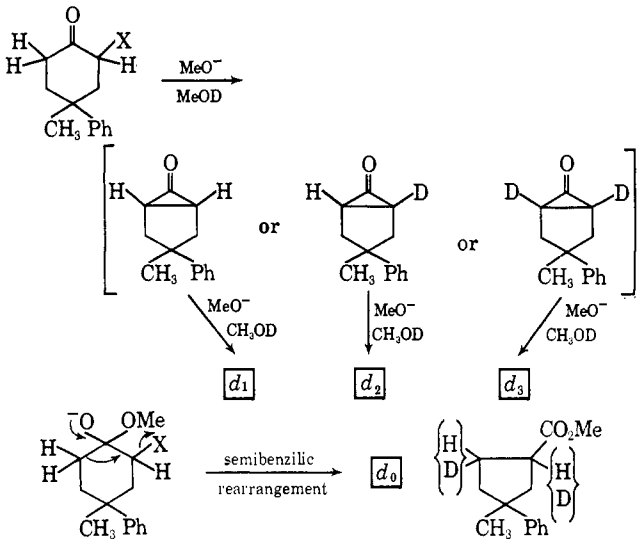
Examination of Table III reveals that the $k_{Br}/k_{Cl}$ ratios in methanol are appreciable for all three systems; compare, for example, the average value of 50 for $k_{Br}/k_{Cl}$ in SN2- and SN1-type displacements.[25] It should be noted, however, that leaving group effects in a 1,3-carbanion-type elimination in a somewhat analogous system, α-halo sulfones, are unusually large.[26] Also, it should be kept in mind that the $k_{Br}/k_{Cl}$ ratio of 116 for **1** is a *minimum* figure, since the rate for the bromide approaches that of $k_1$ and does not give a true picture of the size of $k_2$. It seemed likely, then, that the somewhat smaller $k_{Br}/k_{Cl}$ ratios for **2** and **3** were caused by less complete preequilibration of the chloride. This should be revealed by deuterium exchange experiments; the results for **3** are given in Table IV.

Table IV. Deuterium Exchange for 2-Halo-4-methyl-*cis*-4-phenylcyclohexanones (**3**, X = Br, Cl) with Sodium Methoxide in Methanol-O-$d_1$ at 0°

| Starting compd | Compd analyzed | Deuterons per molecule | Deuterium content, % | |
|---|---|---|---|---|
| **3**, X = Cl | Methyl 3-methyl-3-phenylcyclopentane-1-carboxylate[a] | 2.46 | $d_0$ | 0.0 |
| | | | $d_1$ | 4.4 |
| | | | $d_2$ | 45.3 |
| | | | $d_3$ | 50.3 |
| **3**, X = Br | Methyl 3-methyl-3-phenylcyclopentane-1-carboxylate[a] | 1.86 | $d_0$ | 0.3 |
| | | | $d_1$ | 14.4 |
| | | | $d_2$ | 84.2 |
| | | | $d_3$ | 1.1 |

[a] A mixture composed of about 75% of methyl 3-methyl-*trans*-3-phenylcyclopentane-1-carboxylate and 25% methyl 3-methyl-*cis*-3-phenylcyclopentane-1-carboxylate; J. G. Strong, unpublished results.

The carbanion mechanism requires that at least one deuterium atom be abstracted from the solvent in forming the ester. (Note that the semibenzilic acid rearrangement requires none.) Complete preequilibration requires three deuterons per molecule. The presence of 50% $d_3$ in the ester from chloride **3** indicates a minimum of 50% exchange at the α′ position prior




to loss of chloride ion. The presence of only about 1% $d_3$ in the ester from bromide **3** suggests that relatively little α′ exchange occurs prior to loss of bromide ion. Most of the 84% $d_2$ ester must arise from exchange at the α position, since the rate of abstraction of the α proton in α-bromoacetone by hydroxide ion is about 800 times faster than for acetone.[24] For bromide **3** $k_2$ must then be appreciably larger than $k'_{-1}$, and the observed rate (Table III) must be approaching the value for $k_1$. This probably holds also for bromide **2**; from the kinetic data in methanol it would appear that there is slightly less preequilibration for chloride **2**, as compared to chloride **3**.

## Discussion

The present results show that Loftfield was essentially correct in his conclusion that $k_1$ is rate limiting for α-bromocyclohexanones ($k_2 > k'_{-1}$). At least, our data indicate little or no deuterium exchange for 2-bromo-4-methyl-4-phenylcyclohexanone (**3**), and this will probably hold true for other α-bromocyclohexanones. On the other hand, this is not true for α-chlorocyclohexanones. With 4,4-disubstituted α-chlorocyclohexanones (**1**, **2**, and **3**, X = Cl) extensive or complete equilibrium with the α′ enolate ion is established prior to reaction ($k'_{-1} > k_2$). Even with α-chlorocyclohexanone itself at least partial equilibrium is established ($k'_{-1}$ and $k_2$ are of the same order of magnitude).

The large $k_{Br}/k_{Cl}$ ratio (116:1) for 2-halo-4,4-diphenylcyclohexanones (**1**) establishes a sizable leaving group effect for the Favorskii reaction of α-halocyclohexanones when the rate of halide ion loss enters into $k_{obsd}$ for both halides. Ordinarily, however, for bromides $k_2 > k'_{-1}$; $k_2$ does not then enter into the rate-controlling step and $k_1$ becomes the upper limit of $k_{obsd}$ for bromides. The $k_{Br}/k_{Cl}$ ratio then drops (Table III). For α-chlorocyclohexanone, assuming 20% exchange at the α′ position, $k_{obsd} \cong 0.8k_1$. Since the rate for α-bromocyclohexanone cannot exceed $k_1$, it is understandable that the Favorskii reaction with α-bromocyclohexanone should lose out to side reactions in which the Br/Cl ratio is large.[9,15]

(25) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956).

(26) For methoxide initiated elimination of H–X from $PhCHXSO_2CH_2Ph$ the $k_{Br}/k_{Cl}$ ratio is 620/1 at 0° in methanol: J. M. Williams, Jr., Ph.D. Dissertation, Northwestern University, Evanston, Ill., Aug. 1966.

The reaction of α-halo ketones with alkoxides can lead to a variety of products.[3] With halides **1**, **2**, and **3** the Favorskii ester is the principal product, and the rate constants obtained by measuring the rates of halide ion release appear to truly represent the Favorskii reaction. With α-chlorocyclohexanone and a number of other α-halo ketones that we have studied the rate plots are equally as good as that in Figure 1, but the yields of Favorskii ester are very low under kinetic conditions. For this reason it is uncertain at this time whether the rate of the Favorskii reaction for α-chlorocyclohexanone should be represented by $k_{obsd}$ (Table I), by a value about one-tenth as large (Table III, based on the yield of Favorskii ester), or by some intermediary value. This point will be discussed in a later paper.

It is of interest to see whether these data can be accommodated by a concerted 1,3-elimination mechanism.[14] For chloride **1** the exchange data show that α′ carbanions (enolate ions) are being formed much more rapidly than chloride ions are being lost, but it can be rightly argued that the demonstration of the presence of α′ enolate ions does not necessarily mean that they are on the reaction pathway.[27] If one accepts a concerted mechanism for **1** (X = Br or Cl), a large leaving group effect for reactions of this mechanism is established thereby; one would expect this mechanism to be operative also for halides **2** and **3**, and for α-chloro- and α-bromocyclohexanones. But this mechanism predicts a relatively constant Br/Cl leaving group effect for **1**, **2**, and **3**, and this is clearly not the experimental observation (Table III); also it fails to explain why α-bromocyclohexanone gives a lower yield of Favorskii ester than does α-chlorocyclohexanone. The mechanism involving halide ion loss from an α′ enolate ion therefore provides a much better explanation of the Br/Cl leaving group effects.

## Experimental Section[28]

**2-Bromo-4,4-diphenylcyclohexanone (1, X = Br).** A solution of 12.05 g (74 mmoles) of bromine in 30 ml of chloroform was added dropwise during 35 min to a stirred solution of 18.91 g (75 mmoles) of 4,4-diphenylcyclohexanone[29] in 100 ml of chloroform at 0°. After 40 min the solution was poured into 300 ml of ether and washed with 200 ml of water. The aqueous phase was extracted with 100 ml of ether, and the combined organic fractions were dried and concentrated to give 19.16 g (58.2 mmoles, 77.1%) of solid **1**, X = Br. Crystallization from carbon tetrachloride afforded small prisms, mp 138.5–139.5°; $\lambda_{max}^{KBr}$ 5.78, 6.62, 6.84, 13.17, and 14.10 μ.

*Anal.* Calcd for $C_{18}H_{17}BrO$: C, 65.66; H, 5.21. Found: C, 65.80; H, 5.22.

**2-Chloro-4,4-diphenylcyclohexanone (1, X = Cl).** Sulfuryl chloride (10.2 g; 75.0 mmoles) was added in one portion to a solution of 19.0 g (75.9 mmoles) of 4,4-diphenylcyclohexanone in 300 ml of carbon tetrachloride. After refluxing for 5 hr the solution was concentrated to about 20 ml and the solid was collected on a filter (15.5 g, 54.4 mmoles, 72%). Further work with the mother liquors gave an additional 1.62 g; the total yield of **1** (X = Cl) was 79%. Crystallization from ether yielded an analytical sample, mp 142–143°; $\lambda_{max}^{KBr}$ 5.79, 6.62, 6.85, 12.38, 12.90, 13.30, and 14.15 μ.

*Anal.* Calcd for $C_{18}H_{17}ClO$: C, 75.91; H, 6.02. Found: C, 75.81; H, 6.08.

**Favorskii Reaction of 2-Bromo-4,4-diphenylcyclohexanone (1, X = Br).** 2-Bromo-4,4-diphenylcyclohexanone (1.0 g; 3.04 mmoles) was added to a solution of 0.25 g (4.64 mmoles) of sodium methoxide in 100 ml of absolute methanol at 0°. After stirring for 6 hr the solution was poured into 400 ml of water and 100 ml of ether. The aqueous layer was extracted with ether (three 100-ml portions), and the combined ethereal extracts were dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in a small amount of chloroform and adsorbed onto a silica gel column (2 × 25 cm). Elution with 3% ether in hexane yielded 703 mg (2.51 mmoles, 83%) of a colorless liquid, identified as methyl 3,3-diphenylcyclopentanecarboxylate by its infrared and nmr spectra. Evaporative distillation yielded an analytical sample (bp ~70° (0.15 mm)): $\lambda_{max}^{film}$ 5.77, 6.69, 6.90, 8.30, 8.52, 13.3, and 14.2 μ; $\delta_{TMS}^{CCl_4}$ 7.1 (phenyl), 3.50 (O–$CH_3$), and 3.0–1.8 (ring C–H).

*Anal.* Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.66; H, 7.19.

**Favorskii Reaction of 2-Chloro-4,4-diphenylcyclohexanone (1, X = Cl).** 2-Chloro-4,4-diphenylcyclohexanone (5.0 g; 17.5 mmoles) was added to a solution of 1.32 g (24.4 mmoles) of sodium methoxide in 50 ml of anhydrous methanol. After refluxing for 72 hr, the solution was poured into 100 ml of water and 200 ml of ether. The water layer was washed with an additional 100 ml of ether, and the combined ethereal phases were dried over anhydrous magnesium sulfate and concentrated. To the residue was added 5 ml of water, 10 ml of ethanol, and 0.7 g (18 mmoles) of sodium hydroxide. After refluxing for 2.5 hr, the mixture was diluted with 100 ml of water, washed with ether, acidified with phosphoric acid, and extracted with 100 ml of ether. The ethereal phase was dried over anhydrous magnesium sulfate and concentrated to give 2.29 g (9.5 mmoles, 56%) of 3,3-diphenylcyclopentanecarboxylic acid as a white solid. Crystallization from methanol–water yielded an analytical sample, mp 111–112°; $\lambda_{KBr}^{max}$ 5.86, 6.69, 6.91, 8.05, and 14.28 μ.

*Anal.* Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.82. Found: C, 81.36; H, 6.93.

**4,4-Diphenylcyclohexanone-2,2,6,6-$d_4$.** A mixture of 100 ml of dry benzene, 10.0 g (0.04 mole) of 4,4-diphenylcyclohexanone,[29] and 10 ml of deuterium oxide (>99% $D_2O$) was carefully treated with 0.30 g (0.006 mole) of a 51.6% oil dispersion of sodium hydride. After evolution of gas had ceased, the mixture was refluxed for 48 hr. The reflux condenser was replaced with a Dean–Stark water trap, and refluxing was continued until 9–10 ml of water had collected. The mixture was cooled, and 3 ml of deuterium oxide was added. The solution was again refluxed for 48 hr and the water removed as before. This procedure was repeated three more times. After the final equilibration the solution was dried and concentrated; a nearly quantitative yield of 4,4-diphenylcyclohexanone-2,2,6,6-$d_4$, mp 143–143.5°, was isolated. Nmr analysis showed 3.85 deuterons per molecule, or >96% exchange of the α hydrogen atoms.

**2-Bromo-4,4-diphenylcyclohexanone-2,6,6-$d_3$ (1, X = Br, 2,6,6-$d_3$).** A solution of bromine (1.26 g; 7.9 mmoles) in 15 ml of carbon tetrachloride was added dropwise, as fast as the bromine was taken up, to a stirred solution of 4,4-diphenylcyclohexanone-2,2,6,6-$d_4$ (2.00 g; 7.9 mmoles) in 50 ml of carbon tetrachloride at 0°. The solution was concentrated, and the residue was dissolved in chloroform and adsorbed onto a silica gel column (2 × 35 cm). Elution with 2% ether in hexane yielded 2.18 g (6.6 mmoles, 83%) of **1** (X = Br, 2,6,6-$d_3$) as a white crystalline solid, mp 138–139.5°; $\lambda_{max}^{KBr}$ 5.81, 6.23, 6.68, 6.90, and 10.48 μ. Mass spectral analysis showed 2.28 deuterons per molecule. Nmr analysis showed 4.1 protons at positions C-3, C-5, and C-6 or 1.9 α′ deuterons.

**2-Chloro-4,4-diphenylcyclohexanone-2,6,6-$d_3$ (1, X = Cl, 2,6,6-$d_3$).** Sulfuryl chloride (1.10 g; 8.2 mmoles) in 10 ml of carbon tetrachloride was added to a solution of 2.0 g (7.9 mmoles) of 4,4-diphenylcyclohexanone-2,2,6,6-$d_4$ in 50 ml of dry carbon tetrachloride. After refluxing for 5 hr, the solution was concentrated to yield a white solid. Infrared analysis of the product revealed a mixture of chlorinated product and unreacted starting material. The mixture was dissolved in chloroform and adsorbed onto a silica gel column. Elution with 3% ether–hexane gave 0.62 g (2.4 mmoles) of unreacted starting material, and slightly impure **1** (X = Cl, 2,6,6-$d_3$). Further chromatography on a short silica gel column (2 × 25 cm) yielded 1.10 g (3.8 mmoles) of pure **1** (X = Cl, 2,6,6-$d_3$), mp 142–143°; $\lambda_{max}^{KBr}$ 5.78, 6.64, 6.90, 8.62, 12.49, 13.22, and 14.3 μ. Nmr analysis showed that there had been extensive

(27) R. Breslow, *Tetrahedron Letters*, 399 (1964).

(28) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analyses were performed by Miss Hilda Beck and by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were taken on a Beckman IR 5 or a Baird 4-55 spectrophotometer. Nmr spectra were measured on a Varian Associates A-60 instrument using tetramethylsilane as an internal reference.

(29) F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 2544 (1963).

loss of deuterium at C-2; mass spectral analysis showed 1.80 deuterons per molecule.

**Favorskii Reaction of 2-Bromo-4,4-diphenylcyclohexanone-2,6,6-$d_3$ (1, X = Br, 2,6,6-$d_3$).** A 1.0-g (3.0 mmoles) sample of **1** (X = Br, 2,6,6-$d_3$) was added to a solution of 0.22 g (4.0 mmoles) of sodium methoxide in 100 ml of absolute methanol at 0°. After stirring for 22 hr (about seven half-lives), the reaction solution was concentrated (without heat) to about 30 ml and poured into 100 ml of water and 75 ml of ether. The aqueous layer was washed with 500 ml of ether, and the combined ethereal fractions were dried over anhydrous magnesium sulfate. Concentration yielded a small amount of oil which was dissolved in chloroform and adsorbed onto a silica gel column (2 × 25 cm). Elution with 5% ether in hexane yielded 740 mg (87%) of methyl 3,3-diphenylcyclopentanecarboxylate as a colorless liquid; $\lambda_{max}^{KBr}$ 5.79, 6.26, 6.70, 6.91, 7.90, 8.19, 8.34, 12.9, 13.3, and 14.25 $\mu$. Nmr analysis showed 9.3 aliphatic protons or 0.7 deuteron per molecule.

**Favorskii Reaction of 2-Chloro-4,4-diphenycyclohexanone-2,6,6-$d_3$ (1, X = Cl, 2,6,6-$d_3$).** The same procedure as for the rearrangement of **1** (X = Br, 2,6,6-$d_3$) was employed for the reaction of 400 mg (1.39 mmoles) of **1** (X = Cl, 2,6,6-$d_3$) with 0.15 g (2.8 mmoles) of sodium methoxide in 75 ml of absolute methanol at 0°. The reaction was terminated after 13 days (about six half-lives), and chromatography on silica gel yielded 280 mg (1 mmole, 72%) of methyl 3,3-diphenylcyclopentanecarboxylate. Nmr analysis showed ten aliphatic protons per molecule.

**Reaction of 1 (X = Br, 2,6,6-$d_3$) with Sodium Methoxide in Methanol for One Half-Life.** A 500-mg (1.50 mmoles) sample of **1** (X = Br, 2,6,6-$d_3$) was added to a solution of 141 mg (2.61 mmoles) of sodium methoxide in 100 ml of methanol at 0°. After stirring for one half-live (4 hr 25 min), the reaction was stopped by addition of 5 ml of 0.5 *N* nitric acid. The solution was concentrated to about 50 ml and poured into 400 ml of water and 100 ml of ether. The water layer was washed with ether (three 50-ml portions), and the combined organic fractions were dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in a minimal amount of chloroform and adsorbed onto a silica gel column (2 × 25 cm). Elution with 3% ether in hexane yielded 205 mg of starting material **1** (X = Br): mp 136–138°; $\lambda_{max}^{KBr}$ 5.81 $\mu$ (C=O). Nmr analysis showed 5.5 aliphatic protons or 1.5 deuterons per molecule.

**Reaction of 1 (X = Cl, 2,6,6-$d_3$) with Sodium Methoxide in Methanol for One Half-Life.** In the same manner as for **1** (X = Br, 2,6,6-$d_3$) 400 mg (1.39 mmoles) of **1** (X = Cl, 2,6,6-$d_3$) was added in one portion to a stirred solution of 107 mg (4.67 mg-atoms) of sodium in 100 ml of anhydrous methanol at 0°. The reaction was terminated after one half-life (46 hr), and chromatography on silica gel afforded 169 mg of **1** (X = Cl), mp 141.5–142.5°. Nmr analysis showed seven aliphatic protons per molecule.

**Favorskii Reaction of 2-Chlorocyclohexanone in Methanol-O-$d_1$.** 2-Chlorocyclohexanone (4.1 g, 30.9 mmoles) was added quickly to a solution of 1.73 g (75.3 mg-atoms) of sodium in 30 ml of methanol-O-$d_1$ at 0°. After stirring for 30 min part of the methanol was removed under vacuum, and water (20 ml) was added. The resulting solution was refluxed for 15 min, extracted three times with ether, and acidified with hydrochloric acid. The aqueous solution was extracted three times with chloroform, and the combined organic fractions were dried over anhydrous magnesium sulfate. The chloroform was removed under vacuum, and the resulting acid was treated with an excess of diazomethane in ether. Excess diazomethane was destroyed by addition of acetic acid, and the resulting solution was washed with dilute sodium bicarbonate solution and with water, dried over sodium sulfate, and concentrated. The resulting crude ester when adsorbed onto a silica gel column (2 × 25 cm) and eluted with 2% ether in hexane yielded 1.44 g (11.25 mmoles, 36%) of deuterated methyl cyclopentanecarboxylate as a colorless liquid. Nmr analysis showed 7.0 ring protons or 2.0 deuterons per molecule. Mass spectral analysis showed 2.08 deuterons per molecule including 19% $d_3$.

**Reaction of 2-Bromo-4,4-diphenylcyclohexanone with Sodium Methoxide in Methanol-O-$d_1$.** A 400-mg (1.22 mmoles) sample of **1** (X = Br) was added to a solution of 39 mg (2.1 mg-atoms) of sodium in 50 ml of methanol-O-$d_1$ at 0°. After stirring for 2.5 hr (3.2 half-lives) the reaction was stopped by addition of 0.5 *N* nitric acid, and the solution was poured into 200 ml of water and extracted three times with ether. The combined ethereal layers were washed with 5% sodium bicarbonate solution and with saturated brine, dried over sodium sulfate, and concentrated. The residue was adsorbed onto a silica gel column (2 × 25 cm); elution with 3% ether in hexane afforded 275 mg (0.99 mmole) of deuterated methyl 3,3-diphenylcyclopentanecarboxylate. Nmr analysis showed 2.6 deuterons per molecule, and mass spectral analysis showed 0.3% $d_0$, 2.4% $d_1$, 78.0% $d_2$, and 19.3% $d_3$.

**4-Methyl-4-phenylcyclohex-2-en-1-one.**[30] A solution of 44.2 g (0.34 mole) of 2-phenylpropionaldehyde, 27.4 g (0.39 mole) of methyl vinyl ketone, and 30 ml of *t*-butyl alcohol was added dropwise to a cold (8–12°), well-stirred solution of 8.6 ml of 40% methanolic trimethylbenzylammonium hydroxide in 55 ml of *t*-butyl alcohol over 27 min. *t*-Butyl alcohol (20 ml) was added, the cooling bath was removed, and the dark solution was stirred for 65 min longer. Concentrated hydrochloric acid (2 ml) was added, and the solution was concentrated. The oil was dissolved in ether (250 ml) and the ethereal solution was washed with water (250 ml) and with dilute sodium hydroxide (250 ml), dried, and concentrated. Vacuum distillation afforded 40.2 g (0.22 mole) of the cyclohexenone. An analytical sample was taken from the middle of the main fraction: bp 122° (2 mm); $n^{25}D$ 1.5613; $\lambda_{max}^{KBr}$ 5.95, 12.43, 12.73, and 13.1 $\mu$.

*Anal.* Calcd for $C_{13}H_{14}O$: C, 83.85; H, 7.58. Found: C, 83.54; H, 7.30.

**4-Methyl-4-phenylcyclohexanone.**[30] A mixture of 20.0 g (0.11 mole) of 4-methyl-4-phenylcyclohex-2-en-1-one, 50 ml of acetic acid, and 1.0 g of 10% palladium on carbon was shaken under 2–3 atm of hydrogen for 20 min. The mixture was filtered through diatomaceous earth, and the filtrate plus ether (three 50-ml portions) washings were poured into 400 ml of water and 150 ml of pentane. The aqueous layer was washed with 150 ml of 1:1 ether–pentane, and the combined organic fractions were washed with water and dilute bicarbonate. After drying and concentrating, the ether layer gave, after crystallization from pentane, 17.9 g (0.94 mole) of large prisms: mp 42–43°; $\lambda_{max}^{KBr}$ 5.86 and 13.07.

*Anal.* Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.90; H, 8.44.

**2-Bromo-4-methyl-*cis*-4-phenylcyclohexanone (3, X = Br).** A few drops of a solution of bromine in chloroform (4.2 g, 26.0 mmoles of bromine in 15 ml of chloroform) were added to a stirred solution of 5.0 g (26.6 mmoles) of 4-methyl-4-phenylcyclohexanone in 40 ml of chloroform. When the reaction was visibly initiated the reaction vessel was cooled to 0°, and the remainder of the bromine solution was added over 15 min. After an additional 5 min, the solution was poured into 100 ml of water, and the organic products were extracted with ether (three 10-ml portions). The ether layers were combined and washed with 5% sodium bicarbonate (two 100-ml portions) and with saturated brine (two 100-ml portions), dried over anhydrous magnesium sulfate, and concentrated. The remaining yellow oil was adsorbed onto a slurry-packed (2% ether in hexane) silica gel (300 g) column (97 × 2.5 cm) and eluted with ether in hexane mixtures as follows: 1000 ml each of 2%, 4%, 6% 8%, 10%, 15%. The 250-ml fractions no. 13, 14, 15, and 16 contained 3.45 g (12.9 mmoles) of **3** (X = Br), mp 70–71°. The structure of the compound was established by infrared analysis: $\lambda_{max}^{KBr}$ 5.80 (s) $\mu$, and by the 1 H, two doublet nmr peaks at 4.64 ppm ($J_{ae}$ = 5.5 Hz and $J_{aa}$ = 13.5 Hz).

*Anal.* Calcd for $C_{13}H_{15}OBr$: C, 58.44; H, 5.66. Found: C, 58.48; H, 5.70.

**2-Chloro-4-methyl-*cis*-4-phenylcyclohexanone (3, X = Cl).** A solution of 10.0 g (0.53 mole) 4-methyl-4-phenylcyclohexanone in 200 ml of carbon tetrachloride was refluxed for 5 hr with 7.2 g (0.53 mole) of sulfuryl chloride and a trace of benzoyl peroxide. The reaction mixture was poured into 100 ml of water, and the organic products were extracted into 200 ml of ether. The ethereal solution was washed with 5% bicarbonate (two 100-ml portions) and with saturated brine (two 100-ml portions), dried over magnesium sulfate, and concentrated to a light yellow oil. The oil was dissolved in a minimal volume of benzene and adsorbed onto a slurry-packed (7% ether in hexane) silica gel (500 g) column (96 × 3 cm) and eluted with ether in hexane mixtures as follows: 1000 ml each of 7%, 8%, 9%, 10%, 11%, and 12%. A trace of the dichloride came off with 9% ether in hexane and was followed by 5.43 g (24.3 mmoles) of 2-chloro-4-methyl-*cis*-4-phenylcyclohexanone, mp 63–65°. The structure was confirmed in the same manner as for **3** (X = Br); $\lambda_{max}^{KBr}$ 5.73 (s) $\mu$; $\delta_{TMS}^{CDCl_3}$ 4.50 ppm (1 H, a doublet of doublets, $J_{ae}$ = 5.5 Hz, $J_{aa}$ = 13.5 Hz).

*Anal.* Calcd for $C_{13}H_{15}OCl$: C, 70.10; H, 6.79. Found: C, 70.21; H, 6.82.

(30) This procedure was abstracted from the Ph.D. Dissertation of K. M. Wellman, Northwestern University, Evanston, Ill., 1963.

**Reaction of 2-Bromo-4-methyl-*cis*-4-phenylcyclohexanone (3, X = Br) with Sodium Methoxide in Methanol-O-$d_1$ at 0°.** To a solution of 6.0 mmoles of sodium methoxide in 50 ml of methanol-O-$d_1$, freshly prepared by addition of 0.15 g (6.0 mg-atoms) of sodium to 50 ml of anhydrous methanol-O-$d_1$, was added at 0° 1.0 g (3.74 mmoles) of solid **3** (X = Br). The flask was briefly shaken and then thermostated at 0° for 82 min (seven half-lives). The excess base was quenched with 0.5 *M* nitric acid, and the total contents were poured into 100 ml of water The organic products were extracted into ether (two 150-ml portions), and the ether layer was washed with 5% bicarbonate (two 100-ml portions) and with saturated brine (two 100-ml portions), dried over magnesium sulfate, and concentrated. Separation of the products by column chromatography (45 × 2 cm) over silica gel (60 g) with 3% ether in hexane yielded 0.5 g (2.28 mmoles) of a mixture of the deuterated *cis* and *trans* isomers of methyl 3-methyl-3-phenylcyclopentane-1-carboxylate.[31] A mass spectral analysis determined the quantities of deuterium incorporation (Table IV).

**Reaction of 2-Chloro-4-methyl-*cis*-4-phenylcyclohexanone (3, X = Cl) with Sodium Methoxide in Methanol-O-$d_1$ at 0°.** The same procedure as for the rearrangement of **3** (X = Br) was employed for the reaction of 0.70 g (3.14 mmoles) of **3** (X = Cl) with 6.28 mmoles of sodium methoxide in 50 ml of methanol-O-$d_1$. The reaction was terminated after 59 hr (seven half-lives), and chromatography over silica gel yielded 0.47 g (2.13 mmoles) of a mixture of the isomeric deuterated esters.

**Exchange of the Deuterated Esters with Sodium Methoxide and in Processing, A. Methyl 3,3-diphenylcyclopentanecarboxylate.** A 250-mg (0.89 mmole) sample of deuterated methyl 3,3-diphenylcyclopentanecarboxylate (0.78 deuteron per molecule) was dissolved in 20 ml of $2.1 \times 10^{-2}$ *M* sodium methoxide solution at 25°. After stirring for 6 hr the solution was poured into 100 ml of water and extracted with ether. The ethereal portion was dried and concentrated, and the slightly colored ester was adsorbed onto a silica gel column and eluted with 3% ether in hexane. The recovered ester contained 0.8 deuteron per molecule as determined by nmr.

B. **Methyl Cyclopentanecarboxylate.** A 60-mg sample of deuterated methyl cyclopentanecarboxylate (12% $d_1$, 69% $d_2$, 19% $d_3$) was dissolved in 4 ml of methanol and to it was added 1.6 g (40 mmoles) of sodium hydroxide in 16 ml of water. After refluxing for 15 min, the solution was acidified with 10% hydrochloric acid and extracted with chloroform (three 20-ml portions). The combined organic fractions were washed with water, dried, and concentrated. The resulting acid was taken up in ether and treated with excess diazomethane in the usual manner. The resulting solution was concentrated and adsorbed onto a silica gel column (2 × 17 cm). Elution with 2% ether in hexane yielded 30 mg of methyl cyclopentanecarboxylate (13% $d_1$, 71% $d_2$, and 16% $d_3$ isomers).

**Kinetic Materials.** 2-Chlorocyclohexanone was purchased from Aldrich Chemical Co. and was purified by washing with sodium bicarbonate solution and with water, drying, and distilling. 2α-Bromocholestan-3-one (**2**, X = Br) was prepared by the method of Butenandt and Wolff,[32] and 2α-chlorocholestan-3-one (**2**, X = Cl) was prepared according to Berreboom, Djerassi, Ginsburg, and Fieser.[33] The methanol-O-$d_1$ was prepared by the method of Streitwieser, Verbit, and Stang[34] and was >98.5% $d_1$. Baker Analyzed solute methanol was used without further purification. Sodium ethoxide solutions were made by distilling commercial absolute ethanol from sodium into the desired amount of sodium.

**Kinetic Procedure.** The rate of halide release was determined by withdrawal of aliquots at timed intervals from a solution of the halo ketone and base, quenching with nitric acid, and titrating with silver nitrate solution.

The titration of halide ion was carried out potentiometrically, using a glass and a silver electrode, a Sargent Model C constant rate buret, a Leeds and Northrup pH meter (No. 7664) with the internal resistance replaced by a decade box, and a Varian G-11 strip chart recorder connected to the output of the pH meter.

In a typical run, 90 ml of a $10^{-3}$ *M* halo ketone solution and 50 ml of a $2 \times 10^{-2}$ *M* sodium methoxide in methanol solution (both equilibrated at 0° for 30–45 min) were rapidly combined (base was delivered into halo ketone using a rapid delivery pipet), and the flask was swirled to mix the reactants. The temperature was maintained to 0 ± 0.03° by use of an Aminco Model 4-8600 constant temperature bath. Aliquots (5.36 ml) were withdrawn at various intervals with an automatic pipet and delivered into a quenching solution of 2 ml of acetone and 4 ml of 0.25 *N* nitric acid, and then titrated. The value for the halide ion concentration was, in each case, corrected for recorder lag and initial halide ion concentration by subtraction of a "blank." The initial concentration of the halo ketone was determined from titrated infinity aliquots taken after ten half-lives, and the initial base concentration was calculated from its known concentration prior to dilution and was corrected for changes resulting from cubic contraction upon cooling to 0°. The second-order rate constants were determined from the slope of a plot of $\log (b - x)/(a - x)$ *vs. t*. The reactions were followed for two to four half-lives (except for **1**, X = Cl) and the experimental values presented are averages of at least two runs. The rate constants were reproducible to within 5%. Figure 1 shows a plot of the data obtained in a typical run.

The rate constant for **1** (X = Br, 2,6,6-$d_3$) and the corresponding $k_H/k_D$ value is corrected for isotopic impurity by use of the equation $k_{obsd} = k_H(\%\ H) + k_D(\%\ D)$. Nmr analysis showed 1.9 α′ deuterons per molecule in **1** (X = Br, 2,6,6-$d_3$); $k_H/k_D$ (observed) was 3.6.

The yields of Favorskii product from **1** and **3** (X = Cl or Br) ranged from 45 to 85%, and did not change appreciably over the concentration range of 0.05–1 *M* sodium methoxide. In contrast, the yield of methyl cyclopentanecarboxylate dropped from 40% in 1 *M* sodium methoxide to 8% in 0.05 *M* sodium methoxide. The relative rate for 2-chlorocyclohexanone (to **1**, X = Cl) in Table III was corrected by multiplying by the ratio of yields of Favorskii products (8:72).

**Isotopic Analysis.** Isotopic distributions were estimated from parent peaks in mass spectra measured on a modified[35] Consolidated Model 21-103 instrument with the inlet system at 250°. For each compound, instrumental conditions were chosen on the basis of behavior of the unlabeled species. The spectra of 2-bromo- and 2-chloro-4,4-diphenylcyclohexanones and methyl 3,3-diphenylcyclopentanecarboxylate contain no fragment-ion peaks in the immediate vicinity of the parent peaks, so their isotopic compositions were derived from spectra obtained with 70-v electrons. The 70-v spectra of methyl cyclopentanecarboxylate and methyl 3-methyl-3-phenylcyclopentanecarboxylate contain parentless H peaks, which would interfere with isotopic analysis; the interferences were removed by appropriately reducing the ionizing voltage.[36] For the low-voltage measurements, the repellers were maintained at an average potential of 3 v, the exact values being selected to give maximum sensitivity.

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(31) The composition of this mixture and the structures of the isomeric esters will be discussed in a later paper.

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