constant. The plots remained linear until 2.5–3.0 of the four α protons were exchanged, after which the rate gradually dropped off, presumably due to isotope effects. The rate constants were reproducible within 5%.

Acknowledgment. This investigation was supported by Public Health Service Research Grant No. CA-07351 from the National Cancer Institute.

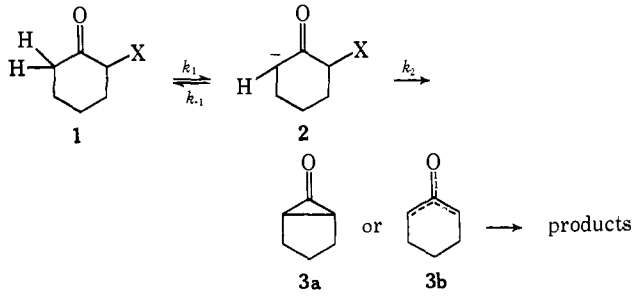
Favorskii Reactions. II. Evidence Concerning the Nature of Halide Release

F. G. Bordwell and Richard G. Scamehorn[1]

Contribution from the Chemistry Department, Northwestern University, Evanston, Illinois 60201. *Received May 4, 1968*

Abstract: The rates and products of the reaction of various *meta*- and *para*-substituted α-chlorobenzyl methyl ketones ($ArCHClCOCH_3$) with sodium methoxide in methanol have been studied. For the parent compound, $PhC^{\alpha}HClCOC^{\alpha'}H_3$, 79% of deuterium exchange at C-α' occurred prior to reaction. The yield of Favorskii ester increased from 9% at 0° with <0.05 *M* NaOMe to 61% at 65° with 2 *M* NaOMe. Evidence is presented to show that this increase is due to a higher activation energy and a greater acceleration in rate with increased ionic strength for the Favorskii reaction relative to a competing reaction to form hydroxy methyl ketal. The Hammett ρ for methoxyoxirane formation (leading to hydroxy methyl ketal) was found to be −0.9. The Hammett ρ for the Favorskii reaction was found to be −2.37. The yield of Favorskii ester was increased to 68% for Ar = *p*-MeOPh (0.05 *M* NaOMe) and was decreased to 0% for Ar = *p*-NO_2Ph. The relatively large negative value for ρ in the Favorskii reaction indicates a high degree of ionic character in the C–Cl bond at the transition state. A mechanism is suggested whereby the ionization of the halogen is aided by π-bond participation from the parallel p orbitals of the enolate ion. Evidence is presented to show that the $COCH_2^-$ grouping promotes bromide ion release from $PhCHBrCOCH_2^-$ *ca.* 10^5 more effectively than does the CO_2^- grouping from $PhCHBrCO_2^-$, but *ca.* 10^5 less effectively than does the $SO_2CH_2^-$ grouping from $PhCHBrSO_2CH_2^-$.

It has recently been shown that in several cyclohexanone systems the Favorskii reaction can be described as shown below, where reversible carbanion formation precedes the formation of a reactive intermediate **3**.[2] The formation and nature of **3** has been the subject of considerable discussion.[3–8] Direct displacement of halide ion by the α'-carbanion leading to a cyclopropanone (**3a**) was proposed by Loftfield[3] and supported by Stork and Borowitz.[4] Recent work has



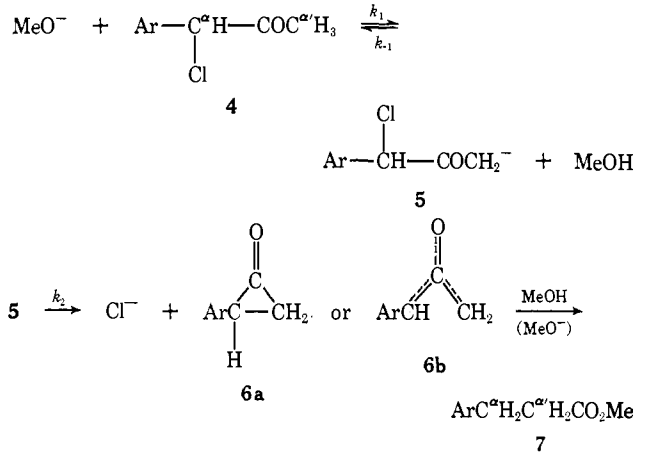
shown that cyclopropanones are indeed quantitatively converted to Favorskii products in the presence of base.[9] On the other hand, solvolysis of halide ion leading to a delocalized intermediate species (**3b**) has been suggested to account for stereochemical studies[7] and for methoxy ketone formation.[8] Theoretical arguments have also been advanced in support of the delocalized intermediate, and the difficulty of attaining the correct geometry for SN2 displacement in the cyclohexanone system has been pointed out.[6]

To date, however, no systematic study of the effect of electronic and structural variations on the rate and products of the Favorskii reaction has appeared. In order to learn more about the nature of the step in which the halide ion is lost, we have turned our attention to the acyclic system $ArCHClCOCH_3$. Here the electronic effect of *meta* and *para* substituents in the aromatic ring on the rate of loss of chloride ion would be expected to provide important information concerning the nature of the transition state.

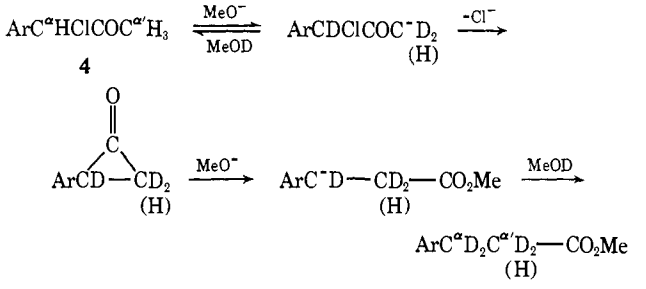
It was imperative to the success of this project that the halide ion be lost in the rate-controlling step of the reaction. In other words, it is necessary that at least partial equilibrium be established between the halo ketone **4** and the enolate ion **5**. This will be true if k_{-1} [MeOH] $\gg k_2$. If this condition does not hold, k_1 will be rate determining and changing the electronic nature of Ar will have but little effect on the rate of the Favorskii reaction.

Deuterium Exchange. Deuterium exchange studies similar to those used previously[2] showed that extensive deuterium exchange had occurred at the α' position of α-chlorobenzyl methyl ketone **4** (Ar = Ph). The Favorskii ester obtained from a reaction of **4** (Ar = Ph) with sodium methoxide in methanol-O-*d* was shown by

(1) National Institutes of Health Predoctoral Fellow, 1966–1968. This paper was presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, paper no. 119.
(2) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967).
(3) R. B. Loftfield, *ibid.*, 73, 4707 (1951).
(4) G. Stork and I. J. Borowitz, *ibid.*, 82, 4307 (1960).
(5) J. G. Aston and J. D. Newkirk, *ibid.*, 73, 2900 (1951); A. A. Sacks and J. G. Aston, *ibid.*, 73, 3902 (1951).
(6) J. G. Burr and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954).
(7) H. O. House and W. F. Gilmore, *J. Amer. Chem. Soc.*, **83**, 3980 (1961).
(8) A. W. Fort, *ibid.*, **84**, 2620 (1962).
(9) N. J. Turro and W. B. Hammond, *ibid.*, 87, 3258 (1965).



mass spectral analysis to contain 3.40 deuterons per molecule. Nmr analysis showed 3.32 deuterons per molecule, and 1.58 deuterons at C-2, or about 79% exchange at the α' position prior to rearrangement. When the reaction was quenched after one half-life no trace of the α'-methyl resonance could be detected in the nmr spectrum of the recovered halo ketone.



In view of the extensive equilibration at the α' position in **4** (Ar = Ph), chloride ion loss must be involved in the rate-controlling step, and a study of the electronic effects of *meta* and *para* substituents on the rate of loss of chloride ion should provide significant information with regard to the step in which the intermediate (**6a** or **6b**) is formed.

Effect of Methoxide Ion Concentration and Substituents on the Nature and Yields of Products. The required substituted benzyl methyl ketones were synthesized from the corresponding arylacetic acids by established methods (see Experimental Section) and the corresponding chloro ketones, obtained by treatment of the ketones with sulfuryl chloride, were purified by chromatography and evaporative distillation.

Although it is possible to obtain the Favorskii ester in a yield as high as 69% from the reaction of α-chlorobenzyl methyl ketone with sodium methoxide under preparative conditions (concentrated base at 65°),[10] the yield was found to be only 13% at 0° using 0.05 *M* sodium methoxide (essentially kinetic conditions). Under these conditions the major product was the methyl ketal of 1-phenylpropan-2-on-1-ol.[11] Data showing the variation in yields of products with concentration and temperature are given in Table I.

The increase in yield of Favorskii ester from 13 to 37% by increasing the temperature from 0 to 65° using 0.05 *M* NaOMe is believed to be a consequence of a 2–3 kcal/mol higher activation energy for the Favorskii reaction as compared to hydroxy ketal formation.[12]

The increase in yield from 37 to 61% for an increase in [NaOMe] from 0.05 to 2 *M* is evidently due to a salt effect since essentially the same result was obtained by increasing the ionic strength of the medium with lithium perchlorate (Table I). Apparently the Favorskii reaction is accelerated to a greater extent by increasing the ionic strength than is hydroxy ketal formation.[13]

Increased yields also were obtained with increased methoxide ion concentration for most substituted α-chlorobenzyl methyl ketones (Table II).

Table I. The Effect of Methoxide Ion Concentration and Temperature on the Yield of Products Formed from α-Chlorobenzyl Methyl Ketone

[MeO⁻], *M*	*T*, °C	Yield of Favorskii ester (**7**), %	Yield of hydroxy ketal (**10**), %
Inverse addition[a]	0	9	68
0.05	0	13	81
1.0	0	17	77
2.0	0	21	70
0.05	65	37	51
2.0	65	61	35
0.05 (1 *M* $LiClO_4$)	65	57	17
0.05 (2 *M* $LiClO_4$)	65	63	19

[a] Slow addition of a 10% excess of 0.05 *M* sodium methoxide to a solution of halo ketone.

Table II. Yields of Products Obtained in the Favorskii Reaction of Some *meta*- and *para*-Substituted α-Chlorobenzyl Methyl Ketones (*m*- and *p*-$YC_6H_4CHClCOCH_3$)[a]

Y	Yield of ester, % [MeO⁻], 0.05 *M*	Yield of ester, % [MeO⁻], 1 *M*	Yield of hydroxy ketal, % [MeO⁻], 0.05 *M*
H	13	17	81
p-NO_2	0		62[b]
p-Cl	5	9	83
p-MeO	68	65[c]	
m-MeO	12	25	79
p-Me	25	36	56
m-Me	14	22	61
p-F	11	16	65

[a] Small amounts of other products were detected by glpc but were not isolated. Nmr and glpc analyses of the minor by-products from $PhCHClCOCH_3$ indicate that methoxy ketone is *not* formed. [b] *Ca.* 20% of products from *p*-nitrobenzyl chloride were obtained. [c] 0.2 *M*.

Variation of the methoxide ion concentration with **4** (Ar = Ph) showed the rate of chloride ion release to be first order in methoxide ion; **4** (Ar = Ph) was found to be stable in methanol in the absence of methoxide ion.

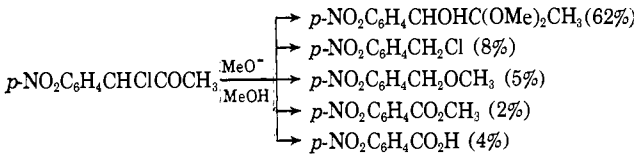
(10) W. D. McPhee and E. Klingsberg, *J. Amer. Chem. Soc.*, **66**, 1132 (1944).

(11) Hydroxy ketals are the most common by-products of the Favorskii reaction: see A. Kende, *Org. Reactions*, **11**, 261 (1960).

(12) This conclusion is derived from the observation that the activation energy for the reaction of $PhCHClCOCH_3$ with 0.05 *M* NaOMe (based on rates at 0 and 25°) is 17.2, as compared to 19.7 for the reaction of $PhCClMeCOCH_3$ with 0.05 *M* NaOMe (based on rates at 0 and 25°; unpublished results). For $PhCClMeCOCH_3$, the Favorskii ester is the major product, whereas for $PhCHClCOCH_3$ hydroxy ketal is the major product.

(13) A. Skrobek and B. Tchoubar [*C. R. Acad. Sci., Paris*, **263**, 80 (1966)] have observed a marked increase in yield of Favorskii ester from 1-chlorocyclohexyl methyl ketone on increasing the methoxide ion concentration or by adding salts. They found that with *trans*-1-chloro-2-methylcyclohexyl methyl ketone changing the methoxide ion or salt concentration affected the stereochemistry of the reaction.

The reaction of α-chloro-*p*-nitrobenzyl methyl ketone **4** (Ar = *p*-NO_2Ph) gave no detectable Favorskii ester. Aside from the hydroxy ketal, the products were those derived from *p*-nitrobenzyl chloride, which is no doubt formed in a reverse aldol reaction.[14]



Effect of Substituents on the Reaction Rates. The rates of chloride release from the *meta*- and *para*-substituted α-chlorobenzyl methyl ketones are summarized in Table III.

Table III. Rates of Chloride Ion Release in the Reaction of α-Chlorobenzyl Methyl Ketones (*m*- and *p*-$YC_6H_4CHClCOCH_3$) with Excess Sodium Methoxide in Methanol at 0°

Y	10^3k_{obsd}	$10^3k_{Favorskii}$[a]	10^3k_{cor}[b]	k_{rel}[a,b]
H	3.09	0.40	0.40	1.00
p-NO_2	5.09			
p-Cl	6.21	0.31	0.26	0.65
p-MeO	39.4[c]	26.8	36.3	91
m-MeO	2.72	0.33	0.29	0.73
p-Me	6.00	1.50	1.79	4.5
m-Me	3.23	0.45	0.49	1.2
p-F	7.5	0.83	0.77	1.9

[a] Corrected by multiplying k_{obsd} by the percentage yield of Favorskii ester. [b] Corrected for changes in K_{eq} (see discussion). [c] This is actually a minimal value because a deuterium exchange experiment revealed only 31% exchange at the α′ position prior to rearrangement. This means that k_{-1}[MeOH] = k_2, and that the measured rate increase (relative to Y = H) is a minimum value; the increase in k_2 is no doubt even larger than the increase in k_{obsd}.

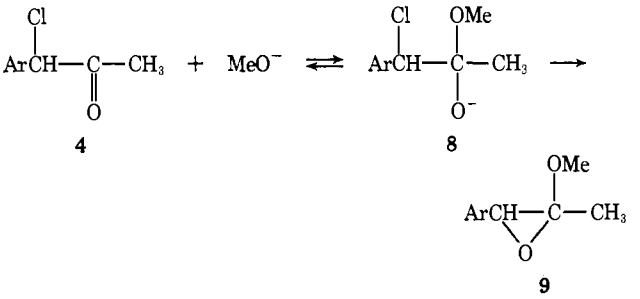
The differences in yields of Favorskii ester and hydroxy methyl ketal elicited by changes in temperature and in methoxide ion (or salt) concentration indicate that these products are formed in, competing reactions, each showing a first-order dependence on methoxide ion concentration. This view is supported by the effect of substituents in the benzene ring on the rates and on the product distribution. It is at once apparent from inspection of Table III that electron donation favors the Favorskii path while electron withdrawal hinders it. Note, for example, that the corrected rate for *p*-$MeOC_6H_4CHClCOCH_3$ is 91 times that for the parent, $C_6H_5CHClCOCH_3$, and that *p*-$NO_2C_6H_4CHClCOCH_3$ gives no Favorskii product whatsoever.

A plot of log *k* for the Favorskii reaction ($k_{Favorskii}$ from Table III) *vs.* Hammett σ values gave a poor correlation (ρ = −1.1; correlation coefficient = 0.875; standard deviation = 0.27). The plot was improved considerably by using σ^+ values,[15a] and, after correcting for the effect of the substituents on carbanion concentration (k_{cor} from Table III) an excellent plot was obtained (ρ = −2.37; correlation coefficient = 0.992; standard deviation = 0.13). The correction was made by means of the equation $\log k/k_0 = \sigma^+\rho + \sigma\rho'$, where ρ′ was taken as 0.5, which is the value for $ArCH_2CO_2H$ ionization constants.[15,16]

The observation of a negative ρ constant and a correlation with σ^+ constants is indicative of a transition state with carbonium ion character. The value found (ρ = −2.37) is comparable to the values of −1.43 to −2.18 observed in the hydrolysis of benzyl chlorides in aqueous acetone or ethanol,[15] or of benzyl tosylates in aqueous acetone (ρ = −2.2).[17] It is considerably smaller than the values recorded for the solvolysis of *t*-cumyl chlorides (−4.54)[15] or benzhydryl chlorides (−4 to −5),[15] and much smaller than the value of −7.31 obtained for the acetolysis of benzylmercuric perchlorates.[18]

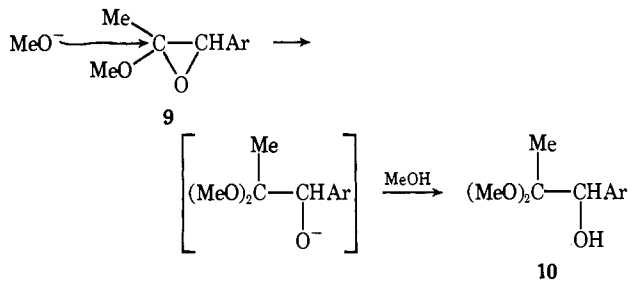
Substituents probably affect the two steps of the reaction to form the methoxyoxiranes (**9**, precursors of the hydroxy ketals) differently.

The first stage of the reaction, reversible addition of methoxide ion to the carbonyl group (**4** ⇄ **8**) should have a positive ρ value (ρ ≅ +0.8) judging from the



value of +0.824 found for the saponification of aryl acetates in aqueous ethanol.[15] Assuming this value for ρ′ and using the equation $\log k/k_0 = \sigma\rho' + \sigma^+\rho$, where *k* is k_{obsd} multiplied by the yield of hydroxy ketal, gave a fair Hammett correlation. The ρ value for halide release (**8** → **9**) is −0.9 (correlation coefficient = 0.95; standard deviation = 0.2).[19]

The methoxyoxiranes (**9**) appear to be opened by attack of methoxide ion to give the hydroxy ketals (**10**), since acid was not used in the work-up in preliminary runs.



(14) This result might have been expected since W. G. Dauben, C. F. Hiskey, and M. A. Muhs [*J. Amer. Chem. Soc.*, **74**, 2082 (1952)] found that 4,4′-dinitrobenzhydryl chloromethyl ketone with sodium methoxide in methanol gave 72% of 4,4′-dinitrodiphenylmethane.

(15) (a) H. C. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958); (b) see H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953), for a summary of Hammett ρ values.

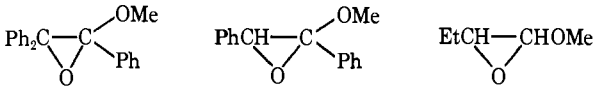
(16) The same number of carbon atoms intervene between the substituents and the acidic hydrogen atom in $ArCH_2CO_2H$ and in $ArCHClCOCH_3$.

(17) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3445 (1953).

(18) F. R. Jensen, G. Knutson, and D. Babbe, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963, p 29M.

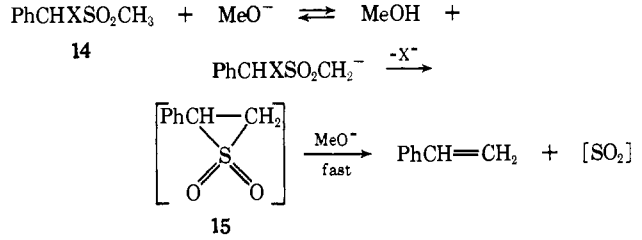
(19) The rate of the reaction of **4** ⇄ **8** → **9** is apparently not increased much by an increase in ionic strength since adding $LiClO_4$ causes a decrease in yield of hydroxy ketal relative to Favorskii ester (see above). It is of interest to note in this connection that L. O. Winstrom and J. C. Warner [*J. Amer. Chem. Soc.*, **61**, 1205 (1939)] found a zero salt effect in the reaction of ethylene chlorohydrin with base to give ethylene oxide.

This reaction is noteworthy both because of the unusual ease with which the epoxide ring is opened,[20,21] and because of attack by the nucleophile at the tertiary carbon atom in preference to the benzylic position. Both of these effects are attributable to activation toward SN2 attack by the methoxyl group.[22] Some α-methoxy epoxides are resistant to methoxide ion attack. Thus, 2,3,3-triphenyl-2-methoxyoxirane (**11**) is stable toward methoxide,[23] whereas 2,3-diphenyl-2-methoxyoxirane (**12**) and 3-ethyl-2-methoxyoxirane (**13**) are not.[24,25] The inertness of **11** is probably due to steric hindrance by the *gem*-diphenyl grouping to attack at the β position by methoxide ion;[26] the steric effect in **9**, **12**, and **13** is much less.



11 **12** **13**

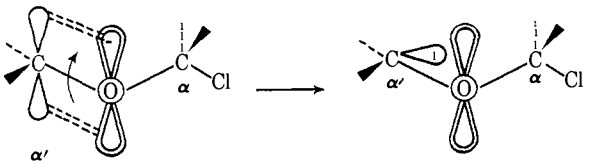
Mechanism for Halide Ion Loss in the Favorskii Reaction. In attempting to assess the manner of loss of chloride ion from the enolate carbanions $ArCHCl\text{-}COCH_2^-$, it will be helpful to examine two related systems. The best available model for determining substituent effects in a related intramolecular displacement of halide ion by a carbanion nucleophile appears to be the Ramberg–Bäcklund reaction of $ArCHXSO_2CH_3$. The reaction involves rapid, reversible carbanion formation followed by a rate-controlling intramolecular displacement of halide ion by the carbanion.[27] An intermediate episulfone (**15**) comparable in structure to cyclopropanone **6a** is formed thereby;[27] a delocalized intermediate comparable to **6b** has been ruled out.[28]



14 **15**

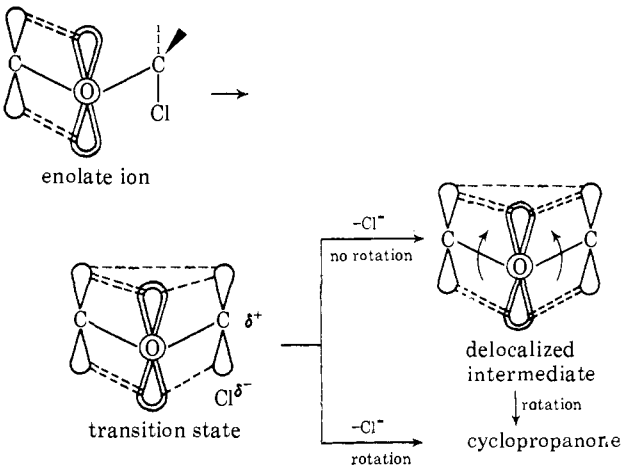
The ρ value for the Ramberg–Bäcklund reaction in the series $ArCHXSO_2CH_3$ is positive.[29] The large Br:Cl leaving group effects observed indicates that the C–X bond is extensively broken in the transition state.[27] The positive ρ value shows that, despite this relatively high degree of C–X bond breaking, *meta* and *para* substituents that increase the positive charge on the carbon atom of the C–X bond accelerate the rate of reaction. This requires that C–C bond formation in the transition state be nearly complete. In sharp contrast, in the Favorskii reaction *meta* and *para* substituents that increase the positive charge on the carbon atom of the C–X bond *retard* the rate of reaction, and substituents that can delocalize a developing positive charge on this carbon atom accelerate the rate. The relatively large Br:Cl leaving group effect observed[2] indicates that the C–X bond is extensively broken in the transition state, but formation of the C–C (or C–O) bond must be much less complete in the Favorskii reaction than in the Ramberg–Bäcklund reaction.

These results provide strong evidence against an internal SN2 type displacement of halide ion in the Favorskii reaction. Consideration of models shows that this is not unreasonable. The Favorskii carbanion is really an enolate ion in which the p orbital at C-α′ is held parallel to the p orbitals of carbon and oxygen of the carbonyl group. If it is to effect an SN2 displacement of halogen C-α′ must be rotated out of conjugation with the carbonyl group, and presumably rehybridized from sp^2 to sp^3. (This constitutes a fundamental difference between the carbanion in the Favorskii reaction and that in the Ramberg–Bäcklund reaction.) A schematic representation is given.



enolate ion unconjugated carbanion

As an alternative, dissociation could occur with the C–Cl bond parallel to the p orbital on the adjacent carbon atom. Dissociation is then aided by partial overlap of the orbital developing at C-α with that of the carbonyl carbon (and oxygen) atom, as well as possible π overlap between the p orbitals at C-α and C-α′.



enolate ion

transition state delocalized intermediate cyclopropanone

Dissociation of the chloride ion could be completed to form the delocalized (dipolar ion) intermediate without C–C bond rotation or could be accompanied by a disrotatory process to form a cyclopropanone[30] or al-

(20) Ordinary epoxides are completely inert to cold alkoxide or hydroxide ion. Reaction is slow with nucleophiles even at elevated temperatures. For example, opening of 1-phenylcyclohexene oxide by concentrated aqueous ammonia requires 21 hr at 150°.[21]

(21) D. Y. Curtin and S. Schmukler, *J. Amer. Chem. Soc.*, 77, 1105 (1955).

(22) The activating effect of an α-methoxyl group in SN2 reactions appears to be of the order of 10^3 to 10^5; see A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 26.

(23) C. L. Stevens and J. J. DeYoung, *J. Amer. Chem. Soc.*, 76, 718 (1954).

(24) C. L. Stevens, M. L. Weiner, and R. C. Freeman, *ibid.*, 75, 3977 (1953).

(25) C. L. Stevens, E. Farkas, and B. Gillis, *ibid.*, 76, 2695 (1954).

(26) V. S. Karavan and T. I. Temnikova, *Zh. Org. Khim.*, 2, 1417 (1966).

(27) See F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, 90, 435 (1968), and references cited therein.

(28) N. P. Neureiter, *ibid.*, 88, 558 (1966).

(29) M. D. Wolfinger [Ph.D. Dissertation, Northwestern University, June 1968] found ρ = +0.8 (corrected for changes in K_{eq}) for this reaction in 40% aqueous dioxane.

(30) The calculations of Burr and Dewar[6] indicate that stabilization of the σ bond in the cyclopropanone will more than compensate for the loss of conjugation in the delocalized intermediate caused by rotation.

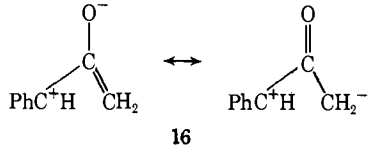
Table IV. Relative Effectiveness of Neighboring Group Participation by Carboxylate Ions, Enolate Ions, and α-Sulfonyl Carbanions in Methanol at 0°

Compound	k_{obsd}, M^{-1} sec^{-1}	k, sec^{-1}	k(rel)	Type of participation
$PhCHBrCO_2^-$		7×10^{-7} (estd[a])	1.0	Little or none
$PhCHBrCOCH_2^-$	3.2×10^{-2}	3.4×10^{-1} (calcd)	10^5	π participation
$PhCHBrSO_2CH_2^-$	2.5×10^{-5}	5×10^4 (calcd)	10^{10}	σ participation

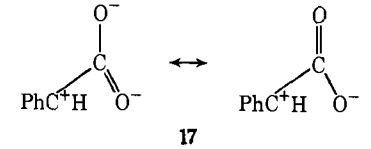
[a] See ref 32.

kylidene oxide.[31] If the delocalized intermediate is the primary intermediate, it could react with methanol or methoxide ion to give the Favorskii ester and other products, or could form a cyclopropanone or alkylidene oxide.[31]

Evidence for participation of the enolate ion in the Favorskii reaction can be obtained by comparison of the first-order rate constant (k) for release of bromide ion from the enolate ion $PhCHBrCOCH_2^-$ with that from $PhCHBrCO_2^-$. The latter rate can be measured directly since the acid can be converted completely to the salt. The rate in methanol at 0° is *ca.* 7×10^{-7} sec^{-1}.[32] A comparable first-order constant for $PhCHBrCOCH_2^-$ can be estimated from k_{obsd} for the Favorskii reaction of $PhCHBrCOCH_3$, 3.4×10^{-2} M^{-1} sec^{-1},[33] by use of the equation $k = k_{obsd}K_{MeOH}/K_{HA}$.[27] A value of $10^{-16.7}$ was used for K_{MeOH}, the ion product constant for methanol,[34] and the pK_a for $PhCHBrCOCH_3$ was assumed to be 17.7 (pK_a = 20 for acetone corrected for the inductive effect of Ph and Br). The value of k thus obtained is 3.4×10^{-1} sec^{-1}. This shows that the α-enolate ion group, $COCH_2^-$, is *ca.* 5×10^5 more effective than the α-carboxylate group, CO_2^-, in promoting bromide ion release. Since this must be the result of some kind of neighboring group participation it supports the hypothesis of π participation presented above. If participation is not accepted for loss of halide ion in the Favorskii reaction, the 10^5 rate acceleration would have to be accounted for in terms of greater resonance stabilization of dipolar ion **16**, derived from the enolate ion, than of dipolar ion **17**, derived from the carboxylate ion. Actually, the reverse seems more likely to be true.



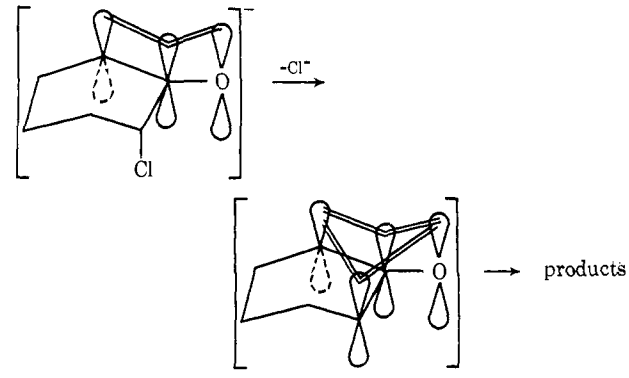
16



17

The calculation can be extended to allow an estimate of the relative effect of an α-sulfonyl carbanion, $SO_2CH_2^-$, in promoting the release of bromide ion from $PhCHBrSO_2CH_2^-$. Assuming pK_a for $PhCHBrSO_2CH_3$ equal to 26,[35,36] and k_{obsd}[37] = 2.5×10^{-5} M^{-1} sec^{-1} in methanol at 0° gives a value for k of *ca.* 5×10^4 sec^{-1}. It would thus appear that the anchimeric assistance rendered by the (more highly basic) α-sulfonyl carbanion is about 10^5 times that of the corresponding α-carbonyl carbanion (enolate ion). The results are summarized in Table IV.

This representation of π-bond participation can be extended to 2-chlorocyclohexanones. Here an axial (or pseudoaxial) position for the leaving halogen would be required.



Since a 4-axial substituent would inhibit attainment of the desired axial position by the halogen atom (because of a 1,3-diaxial interaction) this offers an explanation for the marked decrease in the rate of Favorskii reaction caused by its presence in 2-chloro-4,4-disubstituted cyclohexanones.[2] It is assumed that the halogen in these systems acquired a pseudoaxial position by epimerization or *via* a boat conformation, but that the concentration of the conformer with an axial halogen is severely decreased in the presence of an axial substituent at C-4. The result is a decrease in rate.

An essentially opposite conclusion has been derived from a study in another system.[38] The failure of 3-axbromo-*trans*-decalone to give Favorskii ester as contrasted to the 11–13% yield obtained from 3-eg-bromo-*trans*-2-decalone has been interpreted to mean that the halogen leaves preferentially from an equatorial position. It is true that these experiments rule out the possibility of epimerization of the equatorial halogen to an axial position as a route for the formation of Favorskii ester in this system. However, the equatorial isomer could react through a boat conformation and thereby provide a route by which the halogen can leave from an

(31) R. C. Cookson and M. J. Nye, *J. Chem. Soc.*, 2009 (1965).

(32) Estimated from unpublished kinetic data of A. C. Knipe for an aqueous ethanol solvent having a Grunwald–Winstein m value equal to that of methanol.

(33) This is probably the rate of proton abstraction. The calculated value for k is, therefore, probably a minimum value.

(34) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 37.

(35) The pK_a of $CH_3SO_2CH_3$ is *ca.* 28.5 in DMSO;[36] this value was reduced by 2.5 units to take into account the inductive effect of the bromine and phenyl groups.

(36) F. G. Bordwell, R. H. Imes, and E. C. Steiner, *J. Amer. Chem. Soc.*, **89**, 3905 (1967).

(37) Extrapolated from k_{obsd} = 1.83×10^{-4} M^{-1} sec^{-1} at 50° in methanol (ref 29) assuming an activation energy of 23 kcal/mol (the observed E_a in 40% aqueous dioxane).

(38) E. E. Smissman, T. L. Lemke, and O. Kristiansen, *J. Amer. Chem. Soc.*, **88**, 334 (1966).

Table V. Preparation and Properties of Some *meta*- and *para*-Substituted α-Chlorobenzyl Methyl Ketones (*m*- and *p*-$YC_6H_4CHClCOCH_3$)

Y	Reaction conditions	Bp (mm) or mp, °C	Yield, %	λ_{max}^{film} C=O (KBr)	Nmr, δ $^{CDCl_3}_{TMS}$ (CCl4) Ar	CH	α′-CH_3	Formula	Calcd, % C	H	Found, % C	H
p-NO_2[a]	Reflux 9.5 hr	29–30	75	(5.78)	7.98	5.53	2.32	$C_9H_8ClO_3N$	50.60	3.77	50.72	3.69
p-Cl	Reflux 3 hr	81–82 (0.4)	71	5.79	(7.32)	(5.20)	(2.17)	$C_9H_8Cl_2O$	53.29	3.98	53.08	3.96
p-MeO[b]	Stir 90 min, reflux 30 min	39.5–40.5	71	(5.79)	7.10	5.38	2.18	$C_{10}H_{11}ClO_2$	60.46	5.58	60.33	5.54
m-MeO[c]	Reflux 2 hr		78	5.78	6.7–7.4	5.22	2.14	$C_{10}H_{11}ClO_2$	60.46	5.58	60.72	5.60
p-Me[d]	Reflux 90 min	76–86 (1.0)	76	5.77	7.25	5.32	2.18	$C_{10}H_{11}ClO$	65.76	6.07	65.79	6.07
m-Me[e]	Reflux 45 min	65 (0.3)	67	5.79	7.18	5.19	2.13	$C_{10}H_{11}ClO$	65.76	6.07	66.01	5.93
p-F[f]	Reflux 3 hr		63	5.78	(6.8–7.5)	(5.20)	(2.10)	C_9H_8ClFO	57.93	4.32	57.94	4.21

[a] Also isolated was 5% of 3-chloro-1-*p*-nitrophenyl-2-propanone, mp 90.5–91.5° (lit.[19] mp 91–92°). Separation was accomplished by chromatography on silica gel (eluted with 20% ether in hexane). [b] The sample turns brown soon after purification; the other chloro ketones are also unstable, but decompose more slowly. [c] Unstable on silica gel; purified by treatment with charcoal and evaporative distillation. [d] Some starting ketone (1.5 g) was recovered; purified by chromatography on silica gel with 3-cm band of alumina at bottom of column (to remove yellow color). Prepared previously by V. I. Veksler, *Zh. Obshch. Khim.*, **20**, 1285 (1950). [e] Color removed by treatment with charcoal followed by chromatography on silica gel. [f] Purified by chromatography on alumina which removed all color. Some loss of material on the alumina occurred, however.

axial position.[39] We prefer this interpretation since it can accommodate the retardation of rate observed on insertion of a 4-axial substituent.[40] If the halogen leaves preferentially from the equatorial position in the parent compound as was suggested,[38] there is no obvious reason why a 4-axial substituent should cause rate retardation. The failure of 3-ax-*trans*-2-decalone to give Favorskii ester tells us nothing about the relative rate of halide loss from this (axial) isomer as compared to the equatorial isomer; it merely shows that, when the bromine is axial, the side reactions are faster than the Favorskii reaction.[41]

Experimental Section[42]

Materials. The substituted phenylacetic acids were purchased from Aldrich Chemical Co. The required benzyl methyl ketones were prepared by methylation of the corresponding phenylacetyl chlorides. *p*-Nitrobenzyl methyl ketone[43] and *p*-chlorobenzyl methyl ketone[44] were prepared by treatment of the corresponding acid chloride with the methoxymagnesium salt of diethylmalonate. The intermediate acylmalonate was then decarboxylated to give the methyl ketone. The *p*-methoxy-, *m*-methoxy-, *p*-methyl-, *m*-methyl-, and *p*-fluorobenzyl methyl ketones were prepared by treatment of the acid chlorides with dimethylcadmium.[45]

1-Chloro-1-phenyl-2-propanone. Sulfuryl chloride (32.0 g, 0.24 mol) in 10 ml of carbon tetrachloride was added dropwise over a period of about 15 min to 30.0 g (0.023 mol) of phenylacetone in 30 ml of carbon tetrachloride. After warming for 15 min on a steam bath the solution was washed with sodium bicarbonate solution and with water, and the solvent was removed under reduced pressure. Distillation of the remaining yellow liquid gave a nearly colorless liquid: bp 91° (2.5 mm); $n^{28}D$ 1.5362 (lit.[10,46] $n^{20,26}D$ 1.5373, 1.5339). Further purification by chromatography on silica gel followed by distillation yielded a kinetic sample.

The other halo ketones were prepared in a similar fashion except on a smaller scale. In a typical experiment 4 g of ketone in 15 ml of carbon tetrachloride was used. The reaction conditions, yields, and the physical properties of the products are summarized in Table V. Purification was accomplished, except where noted otherwise, by chromatography on silica gel followed by evaporative distillation or crystallization.

Reaction of 4 (Ar = Ph) with Sodium Methoxide in Methanol-O-*d*. A solution of **4** (Ar = Ph, 4.0 g, 0.0237 mol) in 5 ml of methanol-O-*d* was added dropwise to a stirred solution of 1.5 g (0.065 mol) of sodium in 25 ml of methanol-O-*d* at 0°. After stirring for 3 hr, the mixture was poured into 100 ml of water and 200 ml of ether, and the aqueous layer was extracted with two more 50-ml portions of ether. The combined ether fractions were dried and concentrated, and the remaining oil was adsorbed onto a silica gel column (175 g, 3 × 55 cm) packed with 3% ether in hexane. Elution yielded a yellowish liquid which was identified by ir (λ_{max}(CO) 5.76 μ), nmr, and glpc retention time as methyl 3-phenyl propionate (92% pure). Nmr analysis showed 0.68 methylene protons per molecule.

Reaction of 4 (Ar = Ph) with Sodium Methoxide in Methanol-O-*d* for One Half-Life. 1-Chloro-1-phenyl-2-propanone (1.00 g, 0.0059 mol) was added to 50 ml of 0.25 *M* sodium methoxide in methanol-O-*d* solution at 0°. The reaction was stirred for 1040 sec (one half-life under these conditions), and then quenched by addition of 10 ml of 10% hydrochloric acid. The solution was poured into 150 ml of water and 75 ml of ether. The aqueous layer was extracted twice more with ether, and the combined organic fractions were washed with sodium bicarbonate solution and with sodium chloride solution, dried, and concentrated. The remaining oil was adsorbed onto a 2 × 25 cm silica gel column and eluted with 3% ether in hexane. The first material eluted was a lachramatory liquid (λ_{max} (CO), 5.80 μ) whose nmr spectrum showed no methyl resonance at 2.1 ppm, but was identical in all other respects with 1-chloro-1-phenyl-2-propanone, which was isolated from an identical experiment in methanol.

Standard Favorskii Reaction Procedure. The Reaction of 4 (Ar = Ph) with Sodium Methoxide in Methanol at 0°. A. With 0.05 *M* Sodium Methoxide. A 2.0-g (11.8 mmol) sample of **4** (Ar = Ph) was added rapidly to 400 ml of 0.05 *M* sodium methoxide in methanol at 0°. After stirring for 10 hr, the solution was neutralized with acetic acid and the bulk of the methanol was removed by distillation through a 15-cm Vigreux column. The residue was taken up in ether and water and the aqueous layer was extracted with two more portions of ether and one of hexane. The combined organic fractions were washed with sodium bicarbonate solution and with water and dried ($MgSO_4$). Concentration gave

(39) It is noteworthy in this connection that *cis*-4-*t*-butylcyclohexyl (axial) brosylate solvolyzes *via* a chair conformation at a rate only 4.5 times that of the *trans*- (pseudoaxial) brosylate, which solvolyzes *via* a boat conformation; see V. J. Shiner, Jr., and J. G. Jewett, *J. Amer. Chem. Soc.*, **87**, 1382, 1383 (1965).

(40) This retardation is *not* associated with hindrance to attack of the α′ proton by the base since deuterium exchange studies on the parent ketones failed to reveal any appreciable retarding effect: see F. G. Bordwell and R. G. Scamehorn, *ibid.*, **90**, 6749 (1968).

(41) 9-Chloro-*cis*- and 9-chloro-*trans*-2-decalones (tertiary chlorides) also fail to give Favorskii rearrangement products with sodium methoxide in methanol, but the reaction is successful in heterogeneous medium: see H. O. House and G. A. Frank, *J. Org. Chem.*, **30**, 2948 (1965).

(42) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were taken on a Beckman IR5 or a Baird 4-55 spectrophotometer. Nmr spectra were measured on a Varian Associates A-60 instrument using tetramethylsilane as an internal reference. The glpc analyses were performed on an F & M Model 5750 gas chromatograph equipped with a thermoconductivity cell and a Disc Chart integrator, Model 227. Either a 0.25 in. × 7 ft 8% Carbowax 20M on gas Chromosorb W, or a 0.125 in. × 6 ft 10% UC-W98 on Chromosorb W column was used for analytical determinations. A 0.50 in. × 10 ft 15% SE-30 on Chromosorb W column was used for preparative isolations.

(43) C. G. Overberger and H. Beletch, *J. Amer. Chem. Soc.*, **73**, 4880 (1951).

(44) G. S. Hauser and C. R. Walker, *ibid.*, **68**, 1386 (1946).

(45) J. Cason, *ibid.*, **68**, 2078 (1946).

(46) G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935).

a yellow oil which was adsorbed onto a 70-g silica gel column packed with 4% ether in hexane. The first 1.5 l. of eluent was subjected to glpc and nmr analyses; it contained 252 mg (1.54 mmol, 13%) of methyl 3-phenylpropionate: λ_{max}^{film} 5.75 (C=O) and 8.6 μ; δ_{TMS}^{CCl} 7.18 (s, 5, Ph), 3.55 (s, 3, CH_3O–), and 2.4–3.0 (m, 4, CH_2). The ether content was increased gradually from 4 to 50% and the latter fractions gave 1.87 g (9.53 mmol, 81%) of 1-hydroxy-1-phenyl-2-propanone methyl ketal (with a small ketol impurity), a compound previously reported from this reaction:[10] λ_{max}^{film} only very weak 5.8 μ band; $\delta_{TMS}^{CCl_4}$ 7.30 (m, 5, Ph), 5.78 (s, 1, C–H), 3.31 and 3.23 (s, 6, CH_3O–), 2.77 (s, 1, OH), and 1.05 (s, 3, CH_3–). On brief treatment with 2% hydrochloric acid in methanol (or on standing) the hydroxy ketal was converted to the ketol: $\lambda_{TMS}^{CDCl_3}$ 7.32 (s, 5, Ph), 5.07 (partially resolved doublet, 1, C–H), 4.2 (partially resolved doublet, 1, OH), and 2.00 (s, 3, CH_3). Treatment with 2,4-dinitrophenylhydrazine reagent gave the 2,4-dinitrophenylosazone, mp 260–261° (lit.[10] mp 258°). Acidification of the bicarbonate extracts gave only a trace of acidic material.

In preliminary runs, the reaction was worked up without addition of acetic acid. In these cases, the solution was diluted with saturated brine and extracted with ether. The hydroxy ketal was also isolated under these conditions.

B. With 1 *M* Sodium Methoxide. The reaction of 1.00 g (5.92 mmol) of **4** (Ar = Ph) with 50 ml of 1 *M* sodium methoxide in methanol was carried out exactly as in part A, except that the reaction time was cut to 1 hr. Elution with 4% ether in hexane gave 165 mg (17%) of methyl 3-phenylpropionate, and elution with 50% ether in hexane gave 898 mg (4.58 mmol, 77%) of hydroxy ketal (with slight ketal impurity). There was no acidic product. With several of the substituted halo ketones, however, some of the corresponding hydrocinnamic acid was isolated under these conditions.

C. With 2 *M* Sodium Methoxide. A reaction as in B with 1.00 g (5.92 mmol) of **4** (Ar = Ph) gave 201 mg (1.23 mmol, 21%) of methyl 3-phenylpropionate and 816 mg (4.16 mmol, 70%) of hydroxy ketal. There was no acidic product.

D. With 2 *M* Sodium Methoxide, 65°. When carried out according to the procedure of McPhee and Klingsberg,[10] 2.5 g of **4** (Ar = Ph) gave 1.20 g (7.33 mmol, 50%) of methyl hydrocinnamate, and 235 mg (1.57 mmol, 10.6%) of hydrocinnamic acid. The yield of hydroxy ketone was 770 mg (5.13 mmol, 35%).

E. With 0.05 *M* Sodium Methoxide, 65°. A 1.016-g (6.00 mmol) sample of **4** (Ar = Ph) was added rapidly to 200 ml of 0.05 *M* sodium methoxide at reflux. After refluxing for 30 min, the solution was neutralized with acetic acid and worked up as before. Chromatography gave 366 mg (2.22 mmol, 37%) of methyl 3-phenylpropionate and 595 mg (3.04 mmol, 51%) of hydroxy ketal.

F. With 0.05 *M* Sodium Methoxide, 65°, 1 *M* Lithium Perchlorate. A reaction as in E was carried out with 1.010 g (5.97 mmol) of **4** (Ar = Ph) except that 21.3 g (0.2 mol) of lithium perchlorate was dissolved in the sodium methoxide solution. Chromatography gave 495 mg (3.02 mmol, 51%) of methyl 3-phenylpropionate, 52 mg (0.346 mmol, 6%) of hydrocinnamic acid (some of the methanol was distilled prior to acidification in this experiment), and 150 mg (1.00 mmol, 17%) of hydroxy ketone.

G. With 0.05 *M* Sodium Methoxide, 65°, 2 *M* Lithium Perchlorate. A 1.00-g (5.92 mmol) sample of **4** (Ar = Ph) gave 608 mg (3.72 mmol, 63%) of methyl 3-phenylpropionate and 170 mg (1.13 mmol, 19%) of hydroxy ketone. There was no acidic product.

H. With 0.05 *M* Sodium Methoxide, 0°, Inverse Addition Procedure. Sodium methoxide in methanol (120 ml, 0.05 *M*) was added dropwise over a period of 6 hr to a solution of 1.00 g (5.92 mmol) of **4** (Ar = Ph). The solution was allowed to warm to 25° and stirred for 4 hr. The work-up was as described in A. The yield of methyl 3-phenylpropionate was 85 mg (0.52 mmol, 9%), and the yield of hydroxy ketone was 608 mg (4.0 mmol, 68%). Small amounts of several other products were also formed but not identified. There was *no* methoxy ketone detected in the glpc analysis (no peak with a retention time the same as that of an authentic sample was detected), and no product with peaks at 2.06 (α'-CH_3), 3.33 (CH_3O), and 4.62 ppm could be detected by nmr.

I. Product Stability and Recovery. A 204-mg sample of methyl 3-phenylpropionate was dissolved in 150 ml of 0.05 *M* sodium methoxide and allowed to stand for 12 hr at 0°. The solution was neutralized and worked up as described above (no chromatography). Concentration gave 199 mg of recovered ester. Analysis of the recovered ester by glpc and nmr showed almost no change in purity; no hydroxy ketal or ketone was detected. A similar experiment with the hydroxy ketal showed no conversion to Favorskii ester.

Favorskii Reaction of 1-Chloro-1-*p*-chlorophenyl-2-propanone. The reaction of 1.00 g (0.00494 mol) of **4** (Ar = *p*-ClPh) with 150 ml of 0.05 *M* sodium methoxide was carried out exactly as described above and yielded 52 mg (0.000262 mol, 5.3%) of methyl 3-*p*-chlorophenylpropionate:[47] λ_{max}^{film} 5.75 μ (CO); $\delta_{TMS}^{CDCl_3}$ 7.28 (phenyl), 3.68 (s, 3, CH_3–O), and 2.4–3.1 (m, 4, CH_2).

The yield of 1-hydroxy-1-*p*-chlorophenyl-2-propanone methyl ketal was 733 mg (0.00312 mol, 63%): $\delta_{TMS}^{CDCl_3}$ 7.38 (m, 4, Ar), 4.80 (s, 1, CH), 3.32 and 3.26 (s, 6, CH_3O), 2.75 (s, 1, OH), and 1.02 (s, 3, CH_3). On treatment with methanolic 2% HCl acid for 2 min, the ketal gave the corresponding ketol:[48] λ_{max} 2.92 (OH), 5.83 (CO), and 9.14 μ; $\delta_{TMS}^{CDCl_3}$ 7.34 (s, 4, Ar), 5.01 (s, 1, CH), 4.30 (s, 1, OH), and 2.05 (s, 3, CH_3). The 2,4-dinitrophenylosazone derivative melted at 275–276°.

Anal. Calcd for $C_{21}H_{15}ClN_8O_8$: C, 46.46; H, 2.79. Found: C, 46.45; H, 3.05.

Favorskii Reaction of 1-Chloro-1-*m*-tolyl-2-propanone. **4** (1 g, 5.48 mmol; Ar = *m*-CH_3Ph) yielded 136 mg (14%) of methyl 3-*m*-tolylpropionate: λ_{max}^{film} 5.75 (CO) and 8.5 μ; $\delta_{TMS}^{CDCl_3}$ 7.0–7.4 (m, 4, Ar), 3.67 (s, 3, CH_3O), 2.4–3.1 (m, 4, CH_2), and 2.33 (s, 3, CH_3). Treatment of the ester with sodium hydroxide solution gave *m*-methylhydrocinnamic acid: mp 44° (lit.[49] mp 43°); $\delta_{TMS}^{CDCl_3}$ 11.7 (s, 1, COOH), 6.9–7.4 (m, 4, Ph), 2.4–3.1 (m, 4, CH_2), and 2.30 (s, 3, CH_3).

The yield of 1-hydroxy-1-*m*-tolyl-2-propanone methyl ketal was 709 mg (3.38 mmol, 61%) (isolated with small amount of ketol impurity): λ_{max}^{film} 2.90 (OH), 8.80, and 9.50 μ; $\delta_{TMS}^{CDCl_3}$ 7.0–7.4 (m, 4, Ar), 4.81 (CH), 3.34, 3.27 (s, 6, CH_3O), 2.67 (OH), 2.35 (s, 3, $ArCH_3$), and 1.07 (s, 3, CH_3). Treatment of the ketal with 2% hydrochloric acid in methanol for 2 min gave the corresponding hydroxy ketone: λ_{max}^{film} 2.92 (OH), 5.84 (CO), and 9.3 μ; $\delta_{TMS}^{CDCl_3}$ 7.16 (s, 4, Ar), 5.03 (s, 1, CH), 4.46 (s, 1, OH), 2.35 (s, 3, $ArCH_3$), and 2.00 (s, 3, CH_3). Treatment with semicarbazide hydrochloride gave the disemicarbazone derivative, mp 218–220°.

Anal. Calcd for $C_{12}H_{16}O_2N_6$: C, 52.17; H, 5.84. Found: C, 51.92; H, 6.00.

Favorskii Reaction of 1-Chloro-1-*m*-methoxyphenyl-2-propanone. In the same manner described above 1.00 g (5.04 mmol) of **4** (Ar = *m*-CH_3OPh) yielded 116 mg (0.598 mmol, 12%) of methyl 3-*m*-methoxyphenylpropionate: mp 28° (lit.[50] mp 29–30°); λ_{max}^{film} 5.78 (CO), 8.0, and 8.6 μ; $\delta_{TMS}^{CDCl_3}$ 6.7–7.4 (m, 4, Ph), 3.80, 3.70 (s, 6, CH_3O), and 2.4–3.1 (m, 3, CH_3). Several milligrams of a dark yellow acidic oil were isolated but could not be identified. The yield of 1-hydroxy-1-*m*-methoxyphenyl-2-propanone methyl ketal was 901 mg (3.99 mmol, 79%): $\delta_{TMS}^{CDCl_3}$ 6.7–7.4 (m, 4, Ar), 4.81 (s, 1, CH), 3.78 (s, 3, $ArCH_3$), 3.32 and 3.24 (s, 6, CH_3O), and 1.05 (s, 3, CH_3). Upon brief treatment of a methanol solution of the ketal with 2% hydrochloric acid, the hydroxy ketone was obtained: $\delta_{TMS}^{CCl_4}$ 6.7–7.5 (m, 4, Ar), 4.98 (s, 1, CH), 4.30 (s, 1, OH), 3.78 (s, 3, CH_3O), and 2.00 (s, 3, CH_3). Treatment with 2,4-dinitrophenylhydrazine reagent in the cold gave an orange 2,4-dinitrophenylosazone derivative, mp 238–239°.

Anal. Calcd for $C_{22}H_{18}N_8O_9$: C, 49.08; H, 3.37. Found: C, 48.79; H, 3.41.

Favorskii Reaction of 1-Chloro-1-*p*-methoxyphenyl-2-propanone.

A. With 0.05 *M* Sodium Methoxide. In one portion 800 mg (4.03 mmol) of **4** (Ar = *p*-CH_3OPh) was added to a solution of 115 mg of sodium in 100 ml of methanol-O-*d* (0.05 *M*) at 0°. After stirring for 25 min, the reaction was worked up as previously described. The yield of methyl 3-*p*-methoxyphenylpropionate, mp 36–37°, was 532 mg (2.74 mmol, 68%). Nmr analysis showed 1.39 α protons, indicating 31% exchange prior to rearrangement.

B. With 0.2 *M* Sodium Methoxide. **4** (1 g, 5.04 mmol; Ar = *p*-CH_3OPh) was added in several portions to 50 ml of 0.193 *M* sodium methoxide in methanol solution at 0°. After stirring for 10 min, the reaction was worked up as previously described. Chromatography gave 640 mg (3.3 mmol, 65%) of methyl 3-*p*-methoxyphenylpropionate: mp 37.5° (lit.[51] mp 38°); $\lambda_{max}^{CCl_4}$ 5.74 (CO), 8.01, and 8.48 μ; $\delta_{TMS}^{CCl_4}$ 6.94 (m, 4, Ar), 3.75 (s, 3, $ArOCH_3$), 3.62 (s, 3, CH_3O), and 2.4–3.1 (m, 4, CH_2). Later fractions yielded 350 mg of

(47) D. Y. Curtin and S. Dayagi, *Can. J. Chem.*, **42**, 867 (1964).
(48) T. I. Temnikova and E. I. Kulachkova, *Zh. Obshch. Khim.*, **22**, 1380 (1952).
(49) J. Frederick, J. Dippy, and J. E. Paye, *J. Chem. Soc.*, 357 (1938).
(50) R. S. Livshits, G. I. Bazelevskaya, M. S. Bainova, O. E. Dobrovinskaya, and N. A. Probrazhenski, *J. Gen. Chem. USSR*, **17**, 1671 (1947).
(51) N. R. Campbell and E. P. Taylor, *J. Pharm. Pharmacol.*, **2**, 229 (1950).

1-*p*-methoxyphenyl-1-hydroxy-2-propanone methyl ketal, together with some ketol.

Favorskii Reaction of 1-Chloro-1-*p*-fluorophenyl-2-propanone. **4** (1 g, 5.37 mmol; Ar = *p*-FPh), treated as above, gave 104 mg (0.572 mmol, 10.7%) of methyl 3-*p*-fluorophenylpropionate: λ_{max}^{film} 5.76 (CO), 8.15, and 8.60 μ; $\delta_{TMS}^{CDCl_3}$ 6.8–7.4 (m, 4, Ar), 3.64 (s, 3, CH_3O), and 2.4–3.1 (m, 4, CH_2). The ester (isolated by preparative glpc) upon treatment with sodium hydroxide solution gave *p*-fluorohydrocinnamic acid: mp 87.5–88.5° (lit.[52] mp 91°); $\delta_{TMS}^{CDCl_3}$ 12.0 (s, 1, CO_2H), 6.8–7.4 (m, 4, Ar), and 2.4–3.1 (m, 4, CH_2).

The yield of 1-hydroxy-1-*p*-fluorophenyl-2-propanone methyl ketal was 743 mg (3.47 mmol, 65%): λ_{max}^{film} 2.85 (OH), 8.20, 8.82, 9.33, and 9.60 μ; $\delta_{TMS}^{CDCl_3}$ 6.8–7.6 (m, 4, Ar), 4.80 (s, 1, CH), 3.32, 3.24 (s, 6, CH_3O), 2.77 (s, 1, OH), and 1.02 (s, 3, CH_3). Treatment with 2% hydrochloric acid in methanol for 2–3 min gave the corresponding ketol: λ_{max} 2.92 (OH), 5.82 (CO), 8.13, and 9.25 μ; $\delta_{TMS}^{CDCl_3}$ 6.9–7.5 (m, 4, Ar), 5.09 (CH, partially resolved doublet), 4.41 (OH, partially resolved doublet), and 2.03 (s, 3, CH_3); $n^{22}D$ 1.5078 (lit.[53] $n^{20}D$ 1.5095). The semicarbazone derivative had mp 184–184.5°.

Anal. Calcd for $C_{10}H_{12}FN_3O_2$: C, 53.33; H, 5.37. Found: C, 53.34; H, 5.39.

Favorskii Reaction of 1-Chloro-1-*p*-tolyl-2-propanone. **4** (1 g, 5.45 mmol; Ar = *p*-CH_3Ph) gave 241 mg (1.36 mmol, 25%) of methyl 3-*p*-tolylpropionate: mp 35–36° (lit.[54] mp 39°); λ_{max}^{film} 5.78 (CO), 8.4, and 8.7 μ; $\delta_{TMS}^{CCl_4}$ 7.03 (s, 4, Ar), 3.62 (s, 3, CH_3O), and 2.4–3.1 (m, 4, CH_2). The yield of 1-hydroxy-1-*p*-tolyl-2-propanone methyl ketal was 640 mg (3.05 mmol, 56%): λ_{max}^{film} 2.86 (OH), 8.55, 8.84, 9.33, and 9.61 μ; $\delta_{TMS}^{CDCl_3}$ 7.23 (m, 4, Ar), 4.78 (s, 1, CH), 3.31, 3.23 (s, 6, CH_3O), 2.74 (s, 1, OH), 2.32 (s, 3, $ArCH_3$), and 1.05 (s, 3, CH_3). Treatment with 2% hydrochloric acid in methanol for 2–3 min gave the corresponding hydroxy ketone: λ_{max}^{film} 2.92 (OH), 5.84 (CO), and 9.23 μ; $\delta_{TMS}^{CDCl_3}$ 7.19 (s, 4, Ar), 5.04 (CH partially resolved doublet), 4.45 (OH partially resolved doublet), 2.32 (s, 3, $ArCH_3$), and 2.02 (s, 3, CH_3). The semicarbazone derivative has mp 190–191° (lit.[55] mp 189–190°).

The Reaction of 4 (Ar = *p*-NO_2Ph) with Sodium Methoxide in Methanol. Sodium (0.648 g, 0.0282 mol) was dissolved in 50 ml of methanol and cooled to 0°. 1-Chloro-1-*p*-nitrophenyl-2-propanone (2.4 g, 0.0112 mol) was added dropwise over a 30-min period. After stirring for 4 hr, the solution was poured into ether and water, and the aqueous layer was extracted twice more with ether. The combined ether fractions were washed with saturated sodium chloride solution, dried, and concentrated. The resulting yellow oil was adsorbed onto a silica gel column (90 g) packed with 6% ether in hexane. The first 375 ml of eluent gave 147 mg (0.857 mmol, 8%) of *p*-nitrobenzyl chloride (mp 70–72°) as a white solid. Elution with 20% ether in hexane gave 176 mg of material which contained 88 mg (5%) of *p*-nitrobenzyl methyl ether, and also contained some methyl *p*-nitrobenzoate. Elution with pure ether gave 1.67 g (6.93 mmol, 62%) of 1-hydroxy-1-*p*-nitrophenyl-2-propanone methyl ketal: mp 127.5–128°; λ_{max}^{KBr} 2.89 (OH), 6.60 and 7.42 (NO_2), 8.43, 9.18, and 9.65 μ; $\delta_{TMS}^{CDCl_3}$ 7.93 (q, 4, Ar), 4.92 (s, 1, CH), 3.37, 3.29 (s, 6, CH_3O), 2.87 (s, 1, OH), and 1.02 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27. Found: C, 54.89; H, 6.18.

The aqueous solution above was acidified and extracted with three 50-ml portions of ether and the combined ether layers were washed with sodium chloride solution and dried over sodium sulfate. The solvent was removed and the remaining yellow solid (mp 240°) was treated with diazomethane in ether. The ether was removed and the resulting material was adsorbed onto a silica gel column (20 g) and eluted with 5% ether in hexane to give 82 mg (0.454 mmol, 4%) of methyl *p*-nitrobenzoate, mp 94–95°.

Kinetic Procedure. The apparatus used in this study has been described.[2] In a typical run, 90 ml of a 10^{-3} *M* halo ketone solution and 50 ml of a 3.5×10^{-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. Aliquots (5 ml) were withdrawn at various intervals and delivered into a quenching solution of 2 ml of acetone and 4 ml of 0.25 *N* nitric acid, and then titrated for halide ion. The initial concentration of halo ketone was determined from titrated infinity aliquots taken after ten half-lives, and the 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 rate constants were calculated from plots of log $(a - x)$ *vs.* *t*. The reactions were followed for two to four half-lives and the experimental values presented are averages of at least two runs. The data were reproducible to within 5%.

Acknowledgment. We are indebted to Seymour Meyerson for the mass spectral analyses. This investigation was supported by Public Health Service Research Grant No. CA-07351 from the National Cancer Institute.

(52) K. Kindler, *Ber.*, **74B**, 321 (1941).
(53) J. Weichet, J. Hodrova, and L. Balaka, *Collect. Czech. Chem. Commun.*, **26**, 2040 (1961).
(54) G. R. Ramage, *J. Chem. Soc.*, 397 (1938).
(55) T. I. Temnikova and L. A. Petrova, *Zh. Obshch. Khim.*, **21**, 667 (1951).