Favorskii Rearrangements. III. Further Evidence for an Ionization–π-Participation Mechanism

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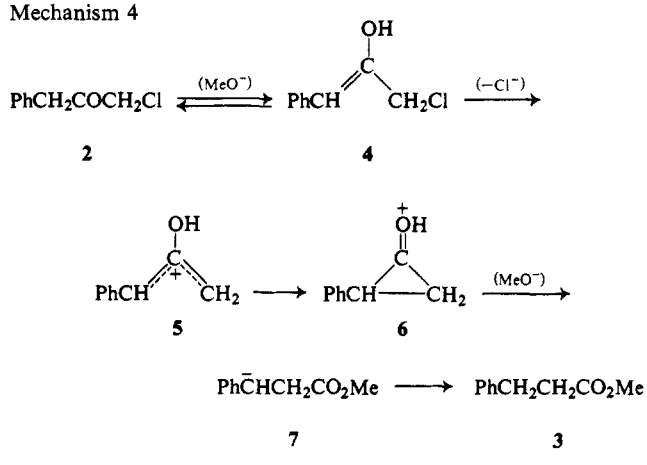
Abstract: From deuterium exchange and rate data it is shown that the conversion of $ArCH_2COCH_2Cl$ (**2**) to $ArCH_2CH_2CO_2Me$ with 0.05 *M* NaOMe in MeOH at 0° involves reversible carbanion formation, and that $\rho = -4.97$ for the first-order release of chloride ion from this carbanion. The rate of chloride ion release exhibits a positive salt effect, but no common ion effect. Dilution of the methanol with water gave an appreciable rate acceleration (Grunwald–Winstein $m = 0.647$). $ArCHClCOCH_3$ (**1**) compounds responded similarly to salt and solvent effects; evidence is presented to show that isomerization of **1** to **2** (or *vice versa*) does not precede rearrangement. The data allow exclusion of seven mechanisms for these reactions. The favored mechanism remaining is one involving ionization of the C–Cl bond aided by π participation on the part of the neighboring enolate ion.

The observation that the isomeric 1-phenylchloropropanones, $PhCHClCOCH_3$ (**1**) and $PhCH_2COCH_2Cl$ (**2**), reacted with sodium methoxide in methanol to give the same ester ($PhCH_2CH_2CO_2Me$ (**3**)) provided an important insight into the mechanism of the Favorskii reaction.[3] It allowed exclusion, at least for this system, of three "unsymmetrical" mechanisms.[4,5] These were: (1) Favorskii's rearrangement of an intermediate alkoxyoxirane (epoxy ether), (2) Richard's rearrangement *via* carbene and ketene intermediates, and (3) Tchoubar's semibenzilic rearrangement. The only reservation in this respect was that a prior rearrangement of the chloro ketone (**1** → **2** or **2** → **1**) was not excluded by the evidence. This possibility was ruled out by Loftfield in the α-chlorocyclohexanone system,[4] but this does not necessarily rule it out in other systems. In fact, such a rearrangement has been suggested (without evidence) to account for the lack of stereoselectivity in the reaction of 17α-bromo-3-α-acetoxypregnane-11,20-dione.[6] Evidence against isomerization of chlorine during rearrangement of 1-chloro-2-methylcyclohexyl methyl ketone has been presented,[7] but at the same time the difficulty of completely ruling out this possibility here and also in the 3-bromo-*trans*-2-decalone system has been emphasized.[7,8] We have now extended our study of the $ArCHClCOCH_3$ system (*meta*- and *para*-substituted **1**) to the $ArCH_2COCH_2Cl$ system (*meta*- and *para*-substituted **2**) in order to examine the question of prior rearrangement and other points pertinent to the mechanism.

The investigation of electronic effects in the $ArCH_2COCH_2Cl$ system was expected to reveal additional information concerning six other possible mechanisms. Loftfield excluded a fourth mechanism, McPhee and Klingsberg's solvolysis to a carbonium ion and isomerism to a new carbonium ion *via* an enol,[3] on the grounds that it gave no role to the base.[4,5] This mechanism can be revived in modified form, however. One could assume that the role of the base is to establish a ketone–enol equilibrium, and that the allylic enolic chloride **4** undergoes methanolysis to form a carbonium ion (**5**), which in turn gives a cyclopropanone, or the like (**6**), which gives **3**.[7]

Mechanism 4



This mechanism appears unlikely for reactions in strongly basic media, where the enol is converted largely to the enolate ion. As presented, it can be excluded for **1** and for a number of chlorocyclohexanones, since it predicts that the rate of loss of chloride ion will be independent of methoxide ion concentration, whereas experiment shows that these reactions are, in fact, first order in methoxide ion.[9] It was desirable, therefore, to determine the reaction order for **2**.

Information concerning mechanisms 5–8 was also expected to be forthcoming from the study.

Mechanism 5 is a concerted 1,3 elimination to give a cyclopropanone (**8**), which could then react with base to give Favorskii ester **3**. By analogy with the results of concerted 1,2 eliminations in systems like $ArCH_2CH_2X$ one would expect the Hammett ρ to be positive and of

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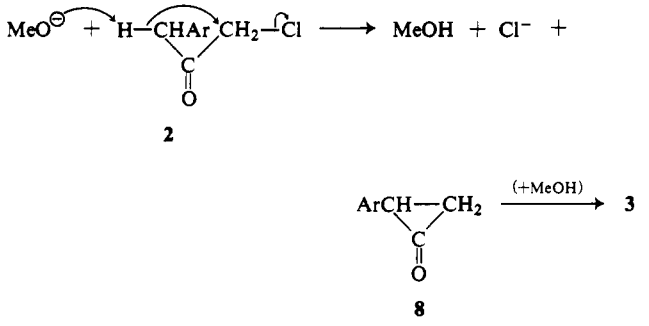
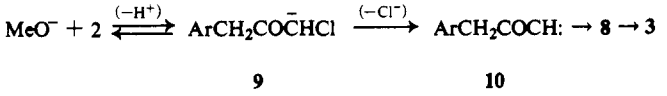
(3) W. D. McPhee and E. Klingsberg, *J. Amer. Chem. Soc.*, **66**, 1132 (1944).
(4) R. B. Loftfield, *ibid.*, **73**, 4707 (1951).
(5) A. S. Kende, "Organic Reactions," Vol. 11, John Wiley & Sons, Inc., New York, N. Y., 1960, Chapter 4.
(6) N. L. Wendler, R. P. Graber, and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).
(7) H. O. House and W. F. Gilmore, *J. Amer. Chem. Soc.*, **83**, 3980 (1961).
(8) E. E. Smissman, T. L. Lemke, and O. Kristiansen, *ibid.*, **88**, 334 (1966).
(9) (a) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *ibid.*, **89**, 6704 (1967); (b) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **90**, 6751 (1968).

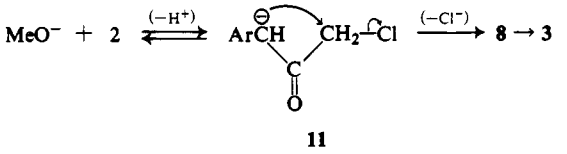
Mechanism 5



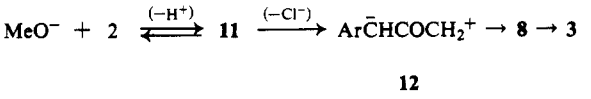
Mechanism 6



Mechanism 7



Mechanism 8

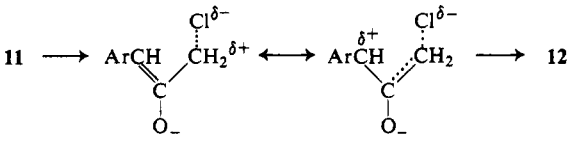


appreciable magnitude if mechanism 5 obtains.[10] On the other hand, in mechanism 6 the position of the **2** ⇄ **9** equilibrium and the rate of loss of chloride ion should be relatively insensitive to the nature of the substituents in the aryl group since the carbon atom holding the negative charge in **9** is insulated from the Ar group by a methylene group and a carbonyl group. Furthermore, the inductive effects of the groups will counteract one another, *e.g.*, electron-withdrawing groups will favor carbanion formation but will retard loss of chloride ion.

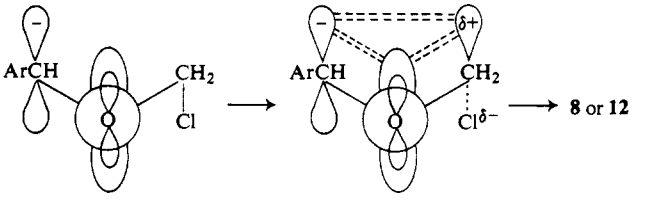
It is more difficult to anticipate the electronic effects in mechanisms 7 and 8. Mechanism 7 is an intramolecular SN2 type displacement. The best analogy appears to be the Ramberg–Bäcklund reaction of the corresponding sulfone system, $ArCH_2SO_2CH_2Br$.[11] Here the Hammett ρ value for the over-all reaction is +1.5.[11a] Using a value of ρ = +4.3 for the preequilibrium step,[12] gives ρ = −2.8 for the step in which the bromide ion is released. For the corresponding ketone system, $ArCH_2COCH_2Cl$, reacting by mechanism 7 both the position of the equilibrium and the loss of the halide ion would be expected to be less sensitive to substituent effects, and the corresponding ρ values should be smaller in each instance.

In mechanism 8 a considerable positive charge is developing at the α-carbon atom as the chloride ion dissociates from carbanion **11** to form dipolar ion **12**. This could be aided in the transition state (**13**) by electron donation from the ring. A larger negative ρ value might then be expected for the step in which the chloride ion is lost than was observed in the Ramberg–Bäcklund reaction. A similar result might be expected for mechanism 9, which has been suggested for halide release from the carbanion derived from **1**. Here ionization of the halide ion from the carbanion is believed to be aided by π participation.[9b]

Mechanism 8



Mechanism 9



(10) In 1,2 eliminations from analogous $ArCH_2CH_2X$ systems the ρ values range from +2.07 to +3.77, depending on the nature of X and the reaction conditions, see J. F. Bunnett, *Angew. Chem. Int. Ed. Engl.*, **1**, 225 (1962), for a review.

(11) (a) M. D. Wolfinger, Ph.D. dissertation, Northwestern University, 1968; (b) See F. G. Bordwell and J. M. Williams, Jr., *J. Amer. Chem. Soc.*, **90**, 435 (1968), and references cited therein for evidence concerning the mechanism of the Ramberg–Backlund reaction.

(12) This is the ρ value for the $ArCH_2SO_2CH_3$ + $DMOS^-$ ⇄ $ArC^-HSO_2CH_3$ + DMSO equilibrium, R. H. Imes, unpublished results.

Results

The series of benzyl chloromethyl ketones, $ArCH_2COCH_2Cl$, containing *p*-MeO, *p*-Me, *m*-Me, *m*-MeO, H, *m*-Cl, *m*-NO_2, and *p*-NO_2 substituents were prepared by the reaction of the arylacetyl chlorides with diazomethane by a slight modification of the procedure used previously.[3]

Deuterium Exchange. Deuterium exchange with methanol-O-d_1 catalyzed by sodium methoxide with the parent compound, $PhC_{\alpha'}H_2COC_\alpha H_2Cl$, gave $PhC_{\alpha'}H_2C_\alpha H_2CO_2Me$ (**3**) in which a total of 92.5% of the α- and α′-hydrogen atoms had been exchanged by deuterium (nmr analysis). Assuming that one deuterium is placed in the α′ position by deuteration of an intermediate carbanion, $PhC_{\alpha'}{}^-C_\alpha CO_2Me$, the nmr integration of the α′ and α positions in the ester indicates that 86% of exchange occurred at C-α′ and 93% at C-α prior to loss of chloride ion. In a comparable experiment run with 50% (v/v) D_2O–MeOD the extent of exchange at C-α was 94% and that at C-α′ was 29%. A similar experiment in CH_3OD with the corresponding bromide showed 34% exchange at C-α′ and 86% at C-α prior to halide loss.

Product Determinations. The yields of Favorskii ester **3** ($ArCH_2CH_2CO_2Me$) were essentially quantitative with the parent compound or its derivatives bearing electron-donating substituents (*p*-Me, *m*-Me, *p*-MeO, *m*-MeO) using excess 0.05 *M* sodium methoxide in methanol. Lower yields of **3** were obtained with the *m*-Cl and *m*-NO_2 compounds (62 and 26%, respectively) and no ester was obtained with *p*-$NO_2C_6H_4CH_2COCH_2Cl$. Slow addition of 10% excess of 0.05 *M* sodium methoxide to a methanol solution of the chloro ketone ("inverse addition") gave the same yields as were obtained by normal

Table I. Rate Constants for the Reaction of *m*- and *p*-$YC_6H_4CH_2COCH_2Cl$ with Sodium Methoxide (0.0460 *M*) in Methanol at 0°

Y	10^3k_{obsd}, M^{-1} sec^{-1}	10^3k_{Fav}, M^{-1} sec^{-1} [a]	k_2(rel)[b]
p-CH_3O	1350	1270	3.38×10^2
p-CH_3	143	143	1.76×10^1
m-CH_3	37.5	37.1	2.3
H	26.3	26.3	1.0
m-CH_3O	27.8	26.7	4.6×10^{-1}
m-Cl	7.04	4.36	1.26×10^{-2}
m-NO_2	2.56	0.666	1.88×10^{-4}
p-NO_2	0.462	0.0	...

[a] Corrected by multiplying k_{obsd} by the per cent yield of Favorskii ester. [b] Relative rate for the step in which chloride ion is released [calculated from $\log k_2 = \sigma\rho + \log k_0$ with $\rho = +3$, see text].

addition for $PhCH_2COCH_2Cl$ and *m*-$ClC_6H_4CH_2COCH_2Cl$. Increasing the methoxide concentration to 2 *M* raised the yields of ester for *m*-$NO_2C_6H_4CH_2COCH_2Cl$ somewhat, as was true in the $ArCHClCOCH_3$ system.[9b]

The by-products were not as readily isolated as in the isomeric $ArCHClCOCH_3$ series;[9b] apparently decomposition occurred on the silica gel column used for chromatography. The nmr spectra of the crude products from $ArCH_2COCH_2Cl$ with Ar = *m*-ClC_6H_4 and *m*-$NO_2C_6H_4$ were consistent with a mixture of ester and of the expected hydroxy methyl ketal, namely, $ArCH_2C(OMe)_2CH_2OH$. This assignment was confirmed by isolation of the hydroxy ketones, $ArCH_2COCH_2OH$, on hydrolysis. These hydroxy ketones differed from those obtained from **1**.

In two separate experiments the product formed from the reaction of $PhCH_2COCH_2Cl$ with excess 0.05 *M* alkali in 50% v/v aqueous methanol was found to be 95 and 98% of $PhCH_2CH_2CO_2Me$. In a comparable experiment with $PhCHClCOCH_3$ there was obtained 29% $PhCH_2CH_2CO_2Me$, 6% $PhCH_2CH_2CO_2H$, and 67% $PhCHOHCOCH_3$.

Reaction by the path $ArCHClCOCH_3$ (**1**) → $ArCH_2COCH_2Cl$ (**2**) → $ArCH_2CH_2CO_2Me$ (**3**) would require that by-products characteristic of **2** be formed from **1**, along with product **3**.[9b] The virtual absence of by-products from parent **2** or its *p*-Me, *m*-Me, *p*-MeO, or *m*-MeO derivatives precluded the application of this test to series **1** compounds with these substituents. An nmr analysis of the crude product from *m*-$ClC_6H_4CHClCOCH_3$ failed to reveal the presence of by-products characteristic of *m*-$ClC_6H_4CH_2COCH_2Cl$, but the low yield of **3** (*ca.* 5–10%) obtained from **1** reduced the significance of this experiment. It was repeated with *m*-$ClC_6H_4CHClCOCH_3$ (**1**) and with *m*-$ClC_6H_4CH_2COCH_2Cl$ (**2**) in 50% aqueous methanol. A substantial yield of ester was obtained from **1**, and peaks characteristic of the by-products from **2** were absent. Unfortunately, however, the yield of ester from **2** was now so high that the extent of by-product formation was low. These experiments are not in themselves very conclusive, but they are consistent with the evidence arrived at on the basis of medium changes and electronic effects (see below) showing that rearrangement of **1** → **2** does not occur to any appreciable extent prior to rearrangement.

Kinetics. The rates of halide ion release were determined under pseudo-first-order conditions, and the rate constants were obtained as described previously.[9]

For $PhCH_2COCH_2Cl$ the rate constants determined with 0.0195 *M*, 0.0460 *M*, and 0.0975 *M* methoxide were 2.73×10^{-2} M^{-1} sec^{-1}, 2.63×10^{-2} M^{-1} sec^{-1}, and 3.15×10^{-2} M^{-1} sec^{-1}, respectively. The first two values are within the experimental error of the measurements and show that the reaction is first order in methoxide ion. The 44% higher value obtained with 0.0975 *M* MeO^- suggests a positive salt effect. This was confirmed by carrying out runs with added salts under second-order conditions. These are collected in Table II along with runs made under pseudo-first-order conditions.

Table II. Salt Effects in the Reaction of $PhCH_2COCH_2Cl$ (0.0075 *M*) with Sodium Methoxide at 0°

[NaOMe], *M*	[Salt], *M*	10^2k_2, M^{-1} sec^{-1}	10^2k_{rel}
0.001	...	2.18	1.00
0.001	0.1 ($LiClO_4$)	2.69	1.23
0.001	0.1 (LiCl)	2.90	1.33
0.0195	...	2.73[a]	1.25
0.0460	...	2.63[a]	1.21
0.0975	...	3.15[a]	1.44
0.0465	0.1 ($LiClO_4$)	3.23[a]	1.48
0.0465	1.0 ($LiClO_4$)	5.42[a]	2.48

[a] Calculated from the pseudo-first-order constants.

Table III. Solvent Effect on the Rate of Reaction of $PhCH_2COCH_2Cl$ with Excess 0.05 *M* Base in Aqueous Methanol at 0°

Vol % H_2O	10^2k_2, M^{-1} sec^{-1}
0	2.63
5	6.23
10	13.1
25	50.3
50	289

Addition of water to the methanol caused an appreciable increase in the rate of reaction (Table III).

In 50% aqueous methanol the rate constant (k_{obsd}) for the reaction of $PhCHClCOCH_3$ (**1**) with 0.05 *M* base was 2.17×10^{-1} M^{-1} sec^{-1}, a 70.5-fold increase over $k_{obsd} = 3.09 \times 10^{-3}$ M^{-1} sec^{-1} in methanol.

The rate for $PhCH_2COCH_2Br$ with 0.05 *M* sodium methoxide in methanol at 0° was found to be 1.67 M^{-1} sec^{-1}. The k_{Br}/k_{Cl} ratio is 63.5.

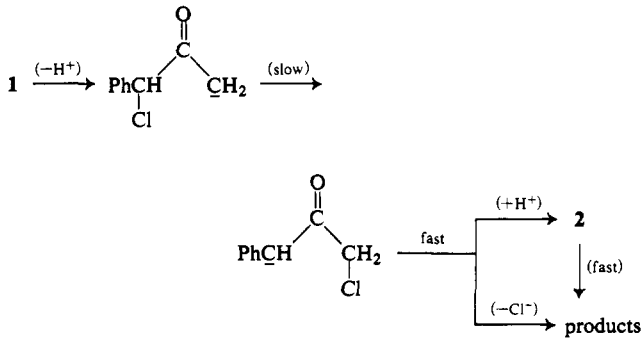
The rate constants for $PhCH_2COCH_2Cl$ at 10 and 15° were 1.18×10^{-1} M^{-1} sec^{-1} and 2.37×10^{-1} M^{-1} sec^{-1}, respectively. The activation energy obtained by a plot of log *k* *vs.* $1/T$ for three temperatures was 23 kcal/mol ($\Delta S^{\ddagger} = +16$ eu).

Discussion

The discussion will center around the significance of the results obtained with respect to the choice between mechanisms 4 and 9 presented above.

Lack of Isomerization of 1 to 2 or of 2 to 1. As discussed above, it is necessary to rule out prior interconversion of **1** and **2** before it is safe to conclude that the formation of a common product (**3**) excludes unsymmetrical mechanisms. At 0° with 0.05 *M* sodium methoxide **1** gave 13% of **3** as compared to 100% from **2**. This fact, together with the 66-fold faster k_{Fav} for the reaction of **2**, excludes the possibility that **2** is rearranging to **1** prior to reaction. On the other hand, it is conceivable that the 13% of **3** produced from **1** arises from a slow isomerization of **1** to **2** followed by a rapid conversion

to **3**. The presumed mechanism for such a rearrangement would be



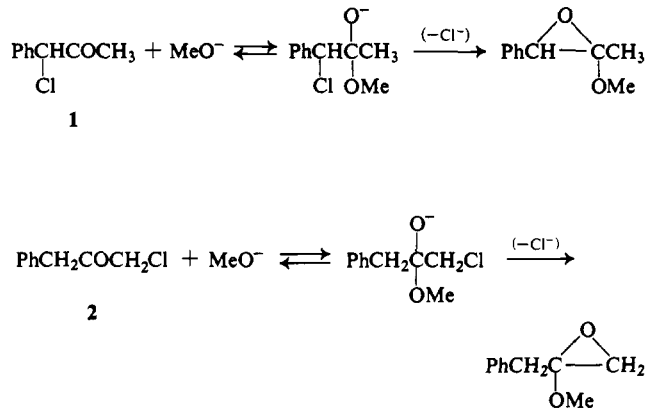
This mechanism can be ruled out since it predicts that the reaction will be accelerated by substitution of electron-withdrawing groups into the phenyl ring, whereas the opposite is true ($\rho = -2.37$[9b]). The 197-fold increase in rate for **1** on changing the medium from methanol to 50% v/v aqueous methanol is also inconsistent with this mechanism, but is readily understandable in terms of a mechanism wherein the C–Cl bond has appreciable ionic character in the transition state.[9b,13]

One might argue that rearrangement of **1** to **2** could occur by a mechanism whereby **1** ionizes to dipolar ion **12** followed by internal return of chloride ion to **12** giving **2**. But this is merely an elaboration of mechanism 8 or 9 and can be disregarded unless experimental evidence for it can be produced (Ockham's razor).

Additional evidence against the $ArCHClCOCH_3 \rightarrow ArCH_2COCH_2Cl \rightarrow ArCH_2CH_2CO_2Me$ path for system **1** is provided by the failure to detect by-products characteristic of m-$ClC_6H_4CH_2COCH_2Cl$ in the reaction of m-$ClC_6H_4CHClCOCH_3$.

The isomerism of **1** to **2** by a carbanion mechanism would appear to be particularly attractive inasmuch as the (benzylic) type halide is unusually labile and a more highly stabilized enolate ion would be formed. Since this does not occur, it would appear from these results, coupled with those of earlier investigators,[4,7] that prior isomerization of the halo ketone is unlikely to occur in the highly basic medium in which Favorskii reactions are ordinarily conducted.

Substituent Effects. Before considering substituent effects it is of interest to examine possible factors that contribute to the low yield (13%) of **3** from **1**, as compared to the high yield (100%) of **3** from **2** at 0° with 0.05 *M* NaOMe.[14] The increased yield from **2** is not likely to be due to a slower rate of by-product formation. The position of the equilibrium for addition of methoxide ion to the carbonyl group for **2** should be much the same as for **1**. The rate of methoxyoxirane formation from the adduct derived from **2** is no doubt slower than that derived from **1** (the phenyl group accelerates the latter rate) but



loss of chloride ion from carbanion **9** (from **1**) should also be faster than from **11**, for the same reason. Therefore, little difference in the relative amounts of ester and by-product from **1** and **2** would be expected.

The most important factor favoring the Favorskii reaction of **2**, relative to **1**, is the appreciable increase in carbanion (enolate ion) concentration (perhaps 1000-fold) brought about by the presence of the phenyl group. Electron-releasing substituents in **2** decrease the concentration of carbanion, but they also increase the rate of chloride ion release (the Hammett ρ obtained by plotting k_{Fav} in Table I *vs.* σ is -2.93). Electron-withdrawing substituents in **2** decrease the rate of the Favorskii reaction (Table I), and increase the tendency of methoxide ion to add to the carbonyl group.[9b] The progressive increase in by-product formation with m-Cl, m-NO_2, and p-NO_2 is a consequence of this.

The Enol Mechanism. The enol mechanism outlined above (mechanism 4) predicts that the rate of halide loss from **2** will be zero order in methoxide concentration. The observed first-order dependence rules out this possibility.[15]

Evidence Against a Concerted Mechanism. The extensive deuterium exchange occurring during the rearrangement of **2** demonstrates that carbanions are being formed reversibly. In our earlier papers it has been noted that extensive deuterium exchange is generally accompanied by a large Br/Cl leaving group effect. The coincidence of these phenomena constitutes an argument against a concerted mechanism.[9a] The relatively large $k_{Br}:k_{Cl}$ ratio observed for **2** (63:1) adds additional evidence on this score.

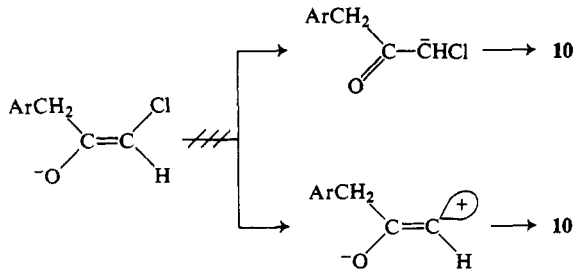
For the $ArCH_2COCH_2Cl$ system the concerted mechanism predicts a sizable positive Hammett ρ by analogy with 1,2 eliminations from $ArCH_2CH_2X$ systems (see above).[10] Inasmuch as the observed over-all ρ obtained by plotting k_{Fav} *vs.* σ is a sizable negative value ($\rho = -2.93$, standard deviation = 0.419, correlation coefficient = 0.952) the concerted mechanism can be definitely excluded in this instance.

The Carbene Mechanism. As discussed above, loss of chloride ion from a $ArCH_2COC^-HCl$ carbanion should be relatively insensitive to substituent effects. The large ρ value observed appears to be inconsistent with this mechanism. Furthermore, the anion is really an enolate

(13) The yield of **3** from **1** is increased from 13 to 36% by this medium change. The yield is evidently kept from going even higher by a corresponding increase of *ca.* 45-fold in the rate of formation of the methoxyoxirane by-product. This is not surprising since C. L. McCabe and J. C. Warner, *J. Amer. Chem. Soc.*, **70**, 4031 (1948), observed a 22-fold increase in the rate of base-initiated oxirane formation in changing from methanol to 50% aqueous methanol.

(14) With 2 *M* NaOMe (or $LiClO_4$) at 65° the yield of **3** from **1** is *ca.* 65–70%.[3] This increase is the result of a higher activation energy for the Favorskii reaction, relative to methoxyoxirane formation, and a greater sensitivity to salt effects.[9b]

(15) If methanolysis of the enol is much faster than protonation of the enolate ion to give ketone, the ketone ⇄ enol equilibrium will not be established, and the enol mechanism would not be excluded by the kinetics. A mechanism of this type is, however, highly unlikely in strongly basic medium because of the low concentration of enol.



ion, and ionization of the chloride ion to form a carbene would require rehybridization or formation of a vinyl carbonium ion. Neither of these possibilities appears very attractive.

Finally, as will be shown in the next section, a much better Hammett correlation for the reaction of **2** is obtained when the reaction is considered as occurring in two steps, one of which involves formation of an α′ carbanion rather than an α carbanion.

Mechanism of Halide Ion Loss. We have seen that plotting k_{Fav} against σ, as would be the correct procedure for a concerted mechanism, led to a poor fit of the data with $\rho = -2.93$. [Note, for example, that the rate for *m*-$MeOC_6H_4CH_2COCH_2Cl$ is slightly *faster* than that of the parent compound; with a negative ρ the *m*-MeO group ($\sigma = +0.115$) should be retarding the rate, not accelerating it.] A much better fit of the data in obtained by assuming that the methoxide ion initiated loss of chloride ion from $ArCH_2COCH_2Cl$ occurs in two steps: (a) reversible carbanion formation, and (b) loss of chloride ion from the ArC^-HCOCH_2Cl carbanion. The substituent effects can then be analyzed in terms of a modified Hammett equation.[9b]

$$\log k/k_0 = \sigma\rho_a + \sigma\rho_b$$

In this equation ρ_a refers to step a and ρ_b refers to step b. The ρ value for the equilibrium step is not yet known, but a value $\rho_a = +3$ should be of about the right order of magnitude.[16] The k_2(rel) values calculated from this equation are shown in Table I. These values, which reflect the sensitivity of chloride ion loss to changes in substituents, show a spread of over six powers of ten from *m*-NO_2 to *p*-MeO. Plotting $\log k_2$(rel) *vs.* σ (using $\sigma^+_{p\text{-Me}}$ and $\sigma^+_{p\text{-MeO}}$) gave $\rho_b = -4.23$ (standard deviation, 0.35; correlation coefficient = 0.983). A plot excluding the *p*-MeO point, which clearly deviated from the line, gave $\rho_b = -4.97$ (standard deviation, 0.26; correlation coefficient = 0.995). Fitting the *p*-MeO point on this line gave $\sigma^+_{p\text{-MeO}} = -0.516$, a value intermediate to the "normal" σ (−0.268) and σ^+ (−0.778).[17]

The high negative value for ρ shows that chloride ion loss from ArC^-HCOCH_2Cl (carbanion **11**) is even more favored by the presence of electron-donating substituents than is true for $ArCHClCOCH_2^-$ ($\rho = -2.37$[9b]). It is evident that an appreciable positive charge is being developed on the carbon holding the chlorine in **11** as ionization occurs, and that this positive charge is being effectively delocalized by electron-releasing substituents. This is the result expected in mechanism 8 leading to zwitterion **12** *via* transition state **13** or in mechanism 9 where **14** is the transition state. It is less consistent with mechanism 7, the intramolecular SN2 mechanism, since in the model series $ArC^-HSO_2CH_2Br$ for this type of mechanism ρ has a *smaller* negative value (*ca.* −2.8)[11a] instead of the larger value expected.

The 20–30% increase in rate caused by the presence of 0.1 *M* $LiClO_4$ or LiCl also suggests that considerable ionic character is developing in the transition state for chloride ion loss from **2**. This is comparable to the effects observed with *t*-BuBr in 90% aqueous acetone and Ph_2CHCl in 80% aqueous acetone.[18] It contrasts with the latter system in that LiCl failed to produce a (rate-retarding) common ion effect. A positive salt effect was deduced previously for the Favorskii reaction of **1** from the marked increase in the yield of Favorskii ester *vs.* methoxyoxirane obtained at high NaOMe or $LiClO_4$ concentrations.[9b] This interpretation is supported by the results with **2**. The 100% increase in rate observed with **2** in the presence of 1 *M* $LiClO_4$ would be sufficient to account for the yield changes with **1**, assuming a comparable salt effect for the Favorskii reaction of **1** and a negligible salt effect for methoxyoxirane formation.[19]

The marked acceleration of the rate of reaction for **2** on dilution of the methanol solvent with water (Table III) provides additional evidence for appreciable ionic character for the C–Cl bond in the transition state for halide release. Part of this acceleration could come from a shift in the preequilibrium to give more carbanion. If this were the sole cause of the rate acceleration there should be no change in the amount of deuterium exchange. In practice, the extent of deuterium exchange at C-α′ was found to decrease from 86 to 29% when the reaction was run in 50% D_2O–MeOD. This shows that there has been a substantial increase in the rate of chloride ion release relative to protonation of the enolate ion, and indicates that the solvent effect is being exerted principally on the step wherein chloride ion dissociates from the enolate ion.

A plot of log *k* *vs.* Grunwald–Winstein Y values[20] gave an excellent fit (standard deviation, 0.037; correlation coefficient = 0.995) with a slope (*m* value) of 0.647. The *m* value for **1** must be even larger since a change from methanol to 50% aqueous methanol causes a rate acceleration of *ca.* 197-fold as compared to 110-fold for **2**. The rate acceleration with a comparable solvent change in model intramolecular SN2-type displacements is much less. In the Ramberg–Bäcklund reaction of $PhCH_2SO_2CHBrPh$ the increase is fivefold,[11a] and for oxirane formation from $ClCH_2CH_2OH$ it is 22-fold.[13] Judging from *m* values, chloride ion loss from **2** or **1** is more sensitive to solvent effects than *i*-PrBr (*m* = 0.544), $PhCH_2Cl$ (*m* = 0.425), or $CH_2{=}CHCH_2Cl$ (*m* = 0.40).

The formation of the ester **3**, to the exclusion of the acid, in 50% aqueous methanol, where the mole fraction of water is *ca.* 0.7 is worthy of comment. If the relative acidities of 2.9 and 1.8 for methanol and water, respectively, determined for water[21] are accepted for 50%

(16) This value was chosen because it is about midway between that found for the equilibrium for the weaker carbon acid series $ArCH_2SO_2CH_3$ (ρ = +4.32, R. H. Imes, unpublished results) and the stronger carbon acids series $ArCH(CH_3)NO_2$ (ρ = +1.0, W. J. Boyle, Jr., unpublished results).

(17) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(18) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 365.

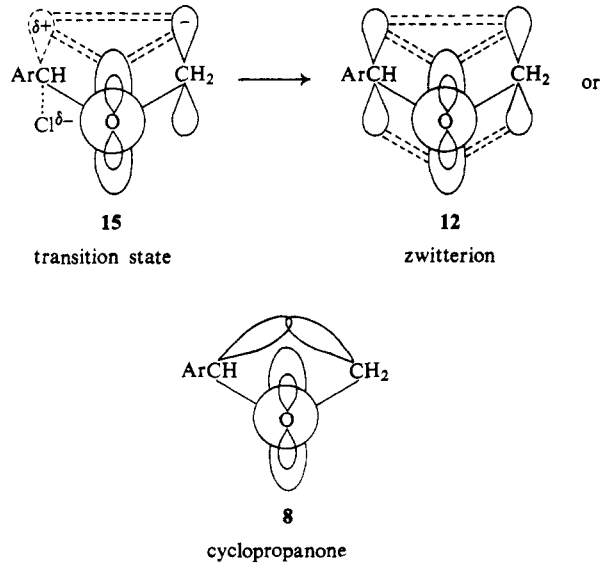
(19) The salt effect for oxirane formation from the reaction of hydroxide with $ClCH_2CH_2OH$ has been found to be zero, L. O. Winstrom and J. C. Warner, *J. Amer. Chem. Soc.*, **61**, 1205 (1939), and that for phenyloxirane formation from $PhCHBrCH_2OH$ has been found to be small (A. C. Knipe, unpublished results).

(20) E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, **70**, 846 (1948); S. Winstein, E. Grunwald, and H. W. Jones, *ibid.*, **73**, 2700 (1951).

aqueous methanol, the $[HO^-]/[MeO^-]$ ratio is *ca.* 1.4:1 in this medium. This places the relative nucleophilicities of MeO^- and HO^- toward the intermediate giving rise to **3** at over 140 to 1, assuming that methoxide ion is the reactive species. Relative MeO^-/HO^- nucleophilicities of the order of 10^2 have been observed previously with active ester substrates and the selectivity has been observed to increase with the substrate activity.[22]

The observed rate constant (k_{Fav}) for the parent compound in the $ArCH_2COCH_2Cl$ series is 66 times that in the $ArCHClCOCH_3$. The lesser sensitivity of the latter series to substituent changes increases this ratio to 245-fold in the case of the *p*-MeO substituent (and decreases it for electron-withdrawing substituents). Nevertheless, the rate constant for chloride ion release from the ArC^-HCOCH_2Cl carbanion (k_2) is probably *less* than that from the $ArCHClCOCH_2^-$ carbanion in every instance. The faster observed rate arises because $k_{Fav} = Kk_2$, and the equilibrium constant (K) is larger in the $ArCH_2COCH_2Cl$ series. For example, if it is assumed that the pK_a for $PhCH_2COCH_2Cl$ is about 3 units lower than that for $PhCHClCOCH_3$, this would make the rate of chloride loss 15-fold faster from the $PhCHClCOCH_2^-$ carbanion.[23] In terms of mechanism 9 this could be due to the greater degree of bond breaking in transition state **15**, as compared to that in **14**, to a greater nucleophilicity of the $COCH_2^-$ group as compared to the PhC^-HCO group, or both.

We know from the large negative ρ (-2.37) for the reaction of $ArCHClCOCH_3$ that the C–Cl bond must be appreciably broken in transition state **15**.[9b] The degree of bond breaking is probably greater in transition state **15** than **14** (benzyl-type halide *vs.* primary halide). At the same time participation by the enolate ion grouping has been shown to provide an important driving force for chloride ion release from the enolate ion $ArCHClCOCH_2^-$ (it provides about 10^5 more driving force than does the $-CO_2^-$ group in a comparable position).[9b] Both factors would be expected, therefore, to promote chloride ion release for $ArCHClCOCH_2^-$ relative to ArC^-HCOCH_2Cl. Indeed it is surprising to find that chloride ion release from the former is not *more* than an order of magnitude faster. That it is not is probably a consequence of both the stabilization provided by delocalization of the positive charge to the aryl group in **14** and the increased nucleophilicity of C-α′ allowed by electron release from the aryl group. The importance of the latter factor is attested to by the observation of a negative ρ value for bromide ion release from $ArC^-HSO_2CH_2Br$ (ρ = *ca.* -2.8).[11a] Here it is highly unlikely that any of the positive charge on carbon released by ionization of the C–Br bond can be delocalized to the aryl group. The high sensitivity of the reaction to substituent effects must then reflect a sensitivity to changes in the nucleophilicity at C-α′. A similar effect would be expected for halide ion release from the enolate ion ArC^-HCOCH_2X. The greater sensitivity of the Favorskii reaction of $ArCH_2COCH_2Cl$ than the Ramberg–Bäcklund reaction of $ArCH_2SO_2CH_2Br$ to substituent effects (ρ = -4.97 and -2.8, respectively) can then be explained as a combination of increased carbanion nucleophilicity and of stabilization of transition state **14** by charge delocalization. The separation of the latter two effects is no doubt artificial, and it is perhaps better to say simply that ionization aided by π participation is more sensitive to substituent effects than σ participation.



15 transition state — **12** zwitterion

8 cyclopropanone

The evidence for appreciable ionic character in the C–Cl bond for the reaction of **2** deduced from salt and solvent effects and for the reaction of **1** deduced from salt effects, solvent effects, and a high negative ρ value can, of course, also be interpreted on the basis of mechanism 8, which postulates ionization to form dipolar ion **12** as an intermediate preceding formation of cyclopropanone (**8**). Mechanism 9 describes the reaction in terms of a dipolar-ion-like *transition state* in which the stereochemistry for ionization and participation are defined (see **14** or **15**). This transition state could lead to dipolar ion **12**, in which event mechanisms 8 and 9 would become identical. On the other hand, transition states **14** and **15** could lead (by disrotation) directly to cyclopropanone (**8**). The question of the nature of the intermediate (**8** or **12**) remains unanswered. Whatever its nature, the lack of isomerism of **1** to **2** (or *vice versa*) and the absence of a common ion effect indicates that recombination with chloride ion (external return) does not occur.

Experimental Section[24]

Materials. The substituted phenylacetic acids were purchased from Aldrich Chemical Co. Compounds of the series $ArCH_2COCH_2Cl$ were made using the procedure of McPhee and Klingsberg,[3] except that the diazomethane was made *via* the nitrosomethylurea and was not distilled. The preparation of 1-chloro-3-(*m*-tolyl)-2-propanone is given in detail below. A similar procedure was used for the others in the series; the results are summarized in Table IV.

1-Chloro-3-(*m*-tolyl)-2-propanone. To a dried solution containing *ca.* 0.11 mol of diazomethane contained in an ice-cooled 500-ml, three-necked, round-bottomed flask there was added, dropwise over a 15-min period with stirring, a solution of 8.41 g (0.05 mol) of *m*-tolylacetyl chloride dissolved in 10 ml of ether. The solution was stirred for 2 hr while warming to 20°. Dry hydrogen chloride was then bubbled through the solution for about 30 min. The

(21) P. Ballinger and F. A. Long, *ibid.*, **82**, 795 (1960).

(22) (a) W. P. Jencks and M. Gilchrist, *ibid.*, **84**, 2910 (1962); (b) M. L. Bender, G. E. Clement, C. R. Gunter, and F. J. Kezdy, *ibid.*, 3697 (1964); (c) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968).

(23) Assuming relative pK_a's of 14.7 and 17.7,[9b] for example, the (first order) rate constants calculated from $k_2 = k_{Fav}K_{MeOH}/K_{HA}$ would be 2.6×10^{-4} sec^{-1} and 4×10^{-3} sec^{-1}, respectively, at 0.°

(24) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analyses were preformed by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were taken on a Perkin–Elmer IR 137 spectrophotometer. Nmr spectra were measured on a Varian Associates A-60 or T-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 detector and a Disc Chart Integrator Model 227.

Table IV. Preparation and Properties of Some *meta*- and *para*-Substituted Chloromethyl Benzyl Ketones, $YC_6H_4CH_2COCH_2Cl$

Y	Mp or Bp, °C (mm)	Yield, %	$n^{31}D$	λ_{max}^{film}(C=O)[f]	Nmr $\delta_{TMS}^{CDCl_3}$ Ar	CH_2 α′	CH_2 α	Other	Calcd,[d] % C	Calcd,[d] % H	Found, % C	Found, % H
m-CH_3	127–130 (7)	65	1.5303	5.77	7.00–7.08	3.72	4.05	2.27(CH_3)	65.76	6.07	66.09	6.18
p-CH_3	56.5–58[e]	57	...	5.78*	7.11	3.82	4.07	2.32(CH_3)	65.76	6.07	65.94	5.88
m-NO_2	107–108[e]	33	...	5.82*	7.50–8.10	4.06	4.19		50.60[a]	3.78	50.15	3.51
p-NO_2	89–91 (Lit.[b] 91–92)	19	...	5.81*	7.64–8.64	4.25	4.37					
m-CH_3O	129–131 (0.3)	47	1.5325	5.79	6.92–7.76	3.83	4.28	3.89(CH_3O)	60.46	5.58	60.71	5.59
p-CH_3O	41–41.5[e]	48	...	5.80*	6.76–7.20	3.75	4.09	3.75(CH_3O)	60.46	5.58	60.65	5.46
m-Cl	32–35[e]	61	...	5.77*	7.24	3.86	4.10		53.24	3.97	53.24	3.76
H	77–78 (0.3) [Lit.[c] 133–135 (19)]	70	1.5364	5.77	7.27	3.81	4.08					

[a] % N, calcd: 6.57; found: 6.44. [b] K. Kaji, H. Nagashima, N. Ninoi, and T. Honada, *J. Pharm. Soc. Jap.*, **15**, 438 (1955). [c] W. D. McPhee and E. Klingsberg, *Org. Syn.*, **26**, 13 (1946). [d] Analytical samples were prepared by chromatographing the distilled or recrystallized product. [e] Crystallized from carbon tetrachloride. [f] Asterisks indicate in CCl_4.

solution was placed in a separatory funnel and successive small portions of water were added cautiously. The ether layer was washed twice with 50-ml portions of 5% sodium carbonate solution and dried over anhydrous magnesium sulfate. The solvent was stripped and the residue vacuum distilled to give the chloro ketone (Table IV).

1-Bromo-3-phenyl-2-propanone. The procedure was that for the chloro compound, substituting hydrogen bromide in place of hydrogen chloride. A 65% yield of light orange liquid, bp 121–124° at 4 mm; $n^{31}D$ 1.5571; λ_{max}^{film} 5.78 μ (CO); $\delta_{TMS}^{CDCl_3}$ 3.78, 3.83 (s, 2, CH_2), 7.21 (s, 5, Ph) was obtained.

Anal. Calcd for C_9H_8OBr: Br, 37.5. Found: Br, 37.3.

Reaction of Benzyl Chloromethyl Ketone with 0.05 *M* Sodium Methoxide in Methanol at 0°. A 1.021-g (6.1 mmol) sample of chloro ketone dissolved in *ca.* 5 ml of methanol was added rapidly to 180 ml of 0.05 *M* sodium methoxide in methanol at 0°. After 2 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 dried ($MgSO_4$). Concentration gave a yellow oil which was absorbed onto a 50-g silica gel column packed with 5% ether in hexane. The first three fractions yielded 1.020 g (6.1 mmol, 100%) of methyl 3-phenylpropionate, identified by comparison of ir and nmr spectra and glpc retention times with those of an authentic sample.[9b] The results of similar experiments with *meta*- and *para*-substituted benzyl chloromethyl ketones are summarized in Table V.

Reaction of 1-Chloro-3-phenyl-2-propanone with 0.05 *M* Sodium Methoxide in 50% Water in Methanol. To a solution of 4 ml of 1 *M* sodium methoxide in methanol solution in 40 ml of water and 36 ml of methanol cooled to 0° was added with stirring 0.4971 g (2.98 mmol) of 1-chloro-3-phenyl-2-propanone. The solution was allowed to react for 10 min and then neutralized with acetic acid. The solution was extracted two times from saturated brine with ether and once with hexane. The combined organic layers were washed with bicarbonate solution, dried, and concentrated to give 0.48 g (2.89 mmol, 98%) of methyl 3-phenylpropionate with no other identifiable product (nmr analysis). (Extraction of the bicarbonate wash yielded only a trace of material.)

Reaction of 1-Chloro-1-phenyl-2-propanone with 0.05 *M* Sodium Methoxide in 50% Water in Methanol. As above 1.0050 g (5.92 mmol) of 1-chloro-1-phenyl-2-propanone dissolved in 5 ml of methanol was allowed to react at 0° with a solution of 8 ml (8.00 mmol) of 1 *M* sodium methoxide, 67 ml of methanol, and 80 ml of water. The crude product from the work-up was placed onto a 50-g silica gel column packed with 10% ether in hexane. The fractions yielded 0.278 g (1.69 mmol, 29%) of methyl 3-phenylpropionate; increasing the ether content to 40% yielded 0.594 g (3.96 mmol, 67%) of 1-hydroxy-1-phenyl-2-propanone identified by comparison of ir and nmr with an authentic sample. Acidification of the bicarbonate wash and extraction with ether yielded 0.0643 g (0.43 mmol, 7%) of hydrocinnamic acid.

3-(*m*-Nitrophenyl)-2-propanon-1-ol. The crude reaction product of 1-chloro-3-(*m*-nitrophenyl)-2-propanone with sodium methoxide was dissolved in a little methanol and refluxed with 25 ml of 5% sodium hydroxide solution for 15 min. The resulting solution was extracted three times with ether, dried, and concentrated to give 1-chloro-3-(*m*-nitrophenyl)-2-propanoic methyl ketal: λ_{max}^{film} 2.84 μ (OH); $\delta_{TMS}^{CDCl_3}$ 7.4–8.2 (m, 4, Ph), 3.34 (s, 2, CH_2), 3.29 (s, 6, CH_3O), 3.07 (s, 2, CH_2), 1.19 (triplet, 1, OH). Heating the ketal in 2% HCl with enough methanol to assure dissolution gave 3-(*m*-nitrophenyl)-2-propanon-1-ol, mp 88–89°; λ_{max}^{KBr} 2.95 (OH), 5.80 (CO), 9.13; $\delta_{TMS}^{CDCl_3}$ 7.2–8.2 (m, 4, Ph), 4.31 (s, 2, CH_2), 3.82 (s, 2, CH_2), 3.31 (partially resolved triplet, 1, OH).

Anal. Calcd for $C_9H_9O_4N$: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.12; H, 4.63; N, 7.06.

3-(*m*-Chlorophenyl)-2-propanon-1-ol. As above, 1-hydroxy-3-(*m*-chlorophenyl)-2-propanone methyl ketal was isolated: λ_{max}^{film} 2.82 μ (OH); $\delta_{TMS}^{CDCl_4}$ 7.04 (m, 4, Ph), 3.24 (s, 2, CH_2), 3.20 (s, 6, CH_3O), 2.83 (s, 2, CH_2), 1.14 (triplet, 1, OH). Treatment with 2% HCl gave the hydroxy ketone; λ_{max}^{film} 2.93 (OH), 5.81 (CO), and 9.13 μ; $\delta_{TMS}^{CDCl_3}$ 7.12 (m, 4, Ph), 4.08 (s, 2, CH_2), 3.79 (s, 2, CH_2), 3.20 (partially resolved triplet, 1, OH).

Anal. Calcd for $C_9H_9O_2Cl$: C, 58.55; H, 4.91. Found: C, 58.33; H, 4.86.

Pseudo-First-Order Kinetics. The method described earlier was used.[9b]

Second-Order Kinetics. In a typical second-order run, 50 ml of 3.11×10^{-3} *M* sodium methoxide was added by means of a rapid delivery pipet to 100 ml of 1.13×10^{-3} *M* halo ketone, both solutions having been cooled to 0° in a thermostated bath. At known intervals 5-ml aliquots were taken and the base neutralized with 1 ml of 6.54×10^{-3} *M* hydrochloric acid. The acid was then back-titrated with 3.11×10^{-3} *M* sodium methoxide with an automatic titrator. All concentrations were corrected for dilution and cubic contraction upon cooling. Rate constants were obtained from plots of $\log (b - x)/(a - x)$ *vs.* *t* and are the average of two runs. The data were reproducible to within 5%.

Table V. Yields of Products from the Reaction of *meta*- and *para*-Substituted Benzyl Chloromethyl Ketones, $YC_6H_4CH_2COCH_2Cl$, with 0.05 *M* Sodium Methoxide in Methanol at 0°

Y	$ArCH_2CH_2CO_2Me$, %	Mp, °C		Ref
H	100 (96[a])	(Liquid)	(Liquid)	9b
p-MeO	94	33–35	36–37	9b
m-MeO	96	27–28	28	9b
m-Me	99	42–44[c]	44[c]	9b
m-Cl	62 (64[a])	71–72[c]	72–73[c]	[d]
m-NO_2	26[b]	114–115[c]	116–117[c]	[e]

[a] By slow addition (12–24 hr) of a solution of 0.05 *M* NaOMe to a methanol solution of chloro ketone (inverse addition). [b] Nmr analysis indicated the presence of 73% of *m*-$NO_2C_6H_4CH_2COCH_2OH$. [c] Melting point of $ArCH_2CH_2CO_2H$. [d] R. Huisgen and H. Koenig, *Chem. Ber.*, **92**, 203 (1959). [e] M. Walter, H. Besendorf, and O. Schnider, *Helv. Chim. Acta*, **44**, 1546 (1961).

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