Favorskii Rearrangements. IV. Mechanistic Change on Methyl Substitution[1]

F. G. Bordwell and Merle W. Carlson

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received November 6, 1969*

Abstract: The structural change from $PhCH_2COCH_2Cl$ to $PhCH_2COCHClCH_3$ (**1**) caused (a) a 220-fold increase in rate of the Favorskii reaction with NaOMe–MeOH, (b) elimination of deuterium exchange prior to rearrangement, (c) elimination of a Br–Cl leaving group effect, (d) a change in ρ from -5.0 to $+1.4$, and (e) the formation of appreciable amounts of an α-methoxy ketone by-product. The latter became the exclusive product at low methoxide ion concentrations. For *meta*- and *para*-substituted derivatives of **1** the distribution of products between ester and α-methoxy ketone was found to depend on the nature of the substituent. These results are shown to be consistent with a mechanism in which proton removal from **1** is the slow, rate-limiting step. The product forming steps are loss of chloride ion from the resulting enolate ion (*via* a dipolar-ion-like transition state) leading to the ester and loss of chloride ion from the corresponding enol leading to the α-methoxy ketone. The behavior of $PhCH_2COCHClPh$ (**5**) with NaOMe–MeOH is similar to that of **1**. Methanolysis of **5** catalyzed by 2,6-lutidine or Lut–LutH$^+$ buffer gave exclusively the α-methoxy ketone. Evidence is presented to show that this product arises by methanolysis of an intermediate enol allylic chloride.

In the previous paper the reaction of a series of α-chloro ketones, $ArCH_2COCH_2Cl$, with sodium methoxide in methanol was shown to proceed by reversible enolate ion formation.[2] The large negative ρ (-5.0) for the step in which chloride ion dissociated from the enolate ion demonstrated the presence of a high degree of ionic character for the C–Cl bond in the transition state for this reaction. It was reasoned that substitution of a methyl group α to the chlorine atom (*i.e.*, to give $ArCH_2COCHClCH_3$) should stabilize the developing positive charge at that carbon atom, and should accelerate the reaction. This indeed proved to be the case. In fact, the rate acceleration was so large that it led to a change in the rate-determining step and in the nature of the products.[1] Whereas $PhCH_2COCH_2Cl$ gave an essentially quantitative yield of Favorskii ester ($PhCH_2CH_2CO_2Me$) with 0.05 *M* (or less concentrated) sodium methoxide in methanol, $PhCH_2COCHClCH_3$ gave 61% of Favorskii ester [$PhCH_2CH(CH_3)CO_2Me$, **2**] and 39% of an α-methoxy ketone [$PhCH_2COCH(OMe)CH_3$, **3**]. At low methoxide concentrations only the latter product was formed.

Formation of high yields of an α-methoxy ketone at low methoxide ion concentrations has been observed previously for the closely related α-chloro ketone $PhCH_2COCHClPh$,[3] and also with 6-tosyloxyisophorone.[4] It was suggested that these α-methoxy ketones arose by reaction of methanol with dipolar ion intermediates.[3,4] The present paper will show that methanolysis of enol allylic chloride intermediates is a much more likely source of these products.

Results

Effect of Methoxide Ion Concentration and the Reaction Conditions on Product Distribution. Reaction of 3-chloro-1-phenylbutan-2-one (**1**) with sodium methoxide in methanol yielded the Favorskii rearrangement product, methyl 2-methyl-3-phenylpropionate (**2**), together with 3-methoxy-1-phenylbutan-2-one (**3**).

$$\underset{\mathbf{1}}{PhCH_2COCHClCH_3} \xrightarrow[MeOH]{NaOMe} \underset{\mathbf{2}}{PhCH_2CH(CH_3)CO_2Me} + \underset{\mathbf{3}}{PhCH_2COCH(OMe)CH_3}$$

The distribution of products **2** and **3** was found to be dependent upon the concentration of sodium methoxide (Table I).

Table I. The Effect of Methoxide Ion Concentration on the Distribution of Products Formed from 3-Chloro-1-phenylbutan-2-one (**1**) at 0°

[MeO$^-$],[a] *M*	% Favorskii ester (**2**)	% methoxy ketone (**2**)
Low[b]	0	100
0.020	50	50
0.050	61	39
0.075	71	29
0.10	77	23
0.15	81	19
0.20	85	15
0.27	87	13
0.35	89	11
0.50	91	9
2.0	100	0

[a] Present in large excess relative to the concentration of **1** (*ca.* 10^{-3} *M*). [b] Slow addition of a 10% excess of 0.05 *M* sodium methoxide to a solution of chloro ketone ("inverse addition").

Except for the inverse addition experiment all runs shown in Table I were made using 1.0 g of α-chloro ketone and a reaction time of 2 hr. A plot of the yield ratio % ester/% methoxy ketone *vs.* the methoxide ion concentration from 0.020 to 0.20 *M* was linear [correlation coefficient (r) = 0.994]. At higher methoxide concentrations the plot curved; this is due to at least some degree to the difficulty in analyzing these mixtures, which contain only small amounts of methoxy ketones. For p-$MeOC_6H_4CH_2COCHClCH_3$ the yield of Favorskii ester increased with increasing methoxide ion

(1) For a preliminary account, see F. G. Bordwell, M. W. Carlson, and A. C. Knipe, *J. Am. Chem. Soc.*, 91, 3949 (1969).
(2) F. G. Bordwell, R. G. Scamehorn, and W. R. Springer, *ibid.*, 91, 2087 (1969).
(3) A. W. Fort, *ibid.*, 84, 2620 (1962).
(4) A. W. Fort, *ibid.*, 84, 2625 (1962).

concentration as follows: 0.037 *M* (18%); 0.15 *M* (33%); 0.87 *M* (61%); 2 *M* (*ca.* 100%). The yield of α-methoxy ketone decreased proportionally; no ester was detected in an inverse addition experiment. A plot of % ester/% methoxy ketone *vs.* [NaOMe] (average concentration used) was linear with a correlation coefficient (*r*) of 0.998. It is noteworthy here, where the per cent of α-methoxy ketone remains appreciable at relatively high methoxide concentrations (allowing a more accurate analysis), that the plot remains linear at high methoxide concentration.

The corresponding bromide, $PhCH_2COCHBrCH_3$, formed ester (**2**) and methoxy ketone (**3**) in the same yields as did **1** with 0.05 *M* sodium methoxide in methanol. Under inverse addition conditions (low methoxide ion concentration) the bromide gave only **3** and with 2.0 *M* NaOMe it gave only **2**.

No release of chloride ion from **1** in methanol was detected in 24 hr, showing that **3** does not arise by methanolysis of the α-chloro ketone. No reaction of **3** with 2 *M* NaOMe occurred in a 2-hr period, showing that **3** is not converted to **2** during the reaction.

At both 0 and 70° **1** with 0.05 *M* NaOMe produced the same product distribution of **2** and **3**. Addition of 2 *M* lithium perchlorate decreased the amount of **2** slightly (from 61 to 58%).

Deuterium Exchange and Kinetics. When the reaction of **1** with 2 *M* NaOMe was run in methanol-O-*d* only 1.06 deuterium atoms were incorporated into ester **2**. In a comparable experiment with $m\text{-}NO_2C_6H_4CH_2COCHClCH_3$ the ester produced showed the incorporation of 1.38 deuterium atoms.

The rate of chloride ion release from **1** was too rapid at 0° to be measured under the pseudo-first-order conditions used earlier.[2] Rates were determined therefore under second-order conditions. Variation of the methoxide ion concentration and the concentration of **1** showed that the reaction was first order in each.

Rate data for **1** and the corresponding bromide are compared in Table II with those for $PhCH_2COCH_2Cl$ (**4**) and $PhCH_2COCHClPh$ (**5**).

Table II. Rates of Reaction of $PhCH_2COCHXCH_3$ (**1**), $PhCH_2COCH_2X$ (**4**), and $PhCH_2COCHXPh$ (**5**) with Sodium Methoxide in Methanol at 0° [a]

Halo ketone	[Halo ketone], *M*	[$NaOCH_3$], *M*	k_2,[b] M^{-1} sec^{-1}
1 (X = Cl)	6.87×10^{-4}	11.2×10^{-3}	6.57[c]
1 (X = Cl)	7.32×10^{-4}	8.74×10^{-3}	6.75
1 (X = Br)	7.37×10^{-4}	8.89×10^{-3}	6.40
1 (X = Br)	7.05×10^{-4}	8.89×10^{-3}	6.14
4 (X = Cl)	7.50×10^{-3}	1.95×10^{-2}	(2.73×10^{-2})[d]
4 (X = Br)	7.50×10^{-3}	5.00×10^{-2}	1.67[d]
5 (X = Cl)	6.50×10^{-4}	8.24×10^{-4}	9.12[c]

[a] The rate of halide release was determined by withdrawal of aliquots and titrating with silver nitrate. [b] Second-order rate constants were determined from the slope of a plot of log $(b - x)/(a - x)$ *vs.* *t*. [c] Average of two runs. [d] From ref 2.

Note that for **1** the rates for the bromide and chloride are identical within experimental error ($k_{Br}/k_{Cl} \cong 1.0$), whereas for **4** $k_{Br}/k_{Cl} = 63$.

Substituent Effects. The *meta*- and *para*-substituted derivatives of **1** also reacted with methoxide ion to give mixtures of Favorskii esters and α-methoxy ketones.

Table III. Rates and Relative Yields[a] of Esters and Methoxy Ketones from Substituted 3-Chloro-1-phenylbutan-2-ones[b]

Substituent	% ester	% methoxy ketone	k_2, M^{-1} sec^{-1} [e]
p-CH_3O	19	81	3.48
p-CH_3	42	58	4.47
H	61	39	6.69
p-F	58	42	10.8
m-Cl	82	18	13.5
m-NO_2	67[c]	*d*	11.6[f]

[a] Only methoxy ketone and Favorskii ester were isolated; the relative yields were determined by vpc. [b] All reactions were run in 0.05 *M* $NaOCH_3$ (100% excess base) in methanol for 2 hr at 0°. [c] Approximately 33% of the material decomposed to tars during the reaction. [d] Gave 100% methoxy ketone under inverse addition conditions. [e] From two to five runs at 0°. [f] The corrected value is >19 (see text).

The distribution of these products and rates of reaction were found to depend on the nature of the substituent (Table III).

A plot of log k_2 (Table III) *vs.* ordinary Hammett σ constants omitting the *m*-NO_2 point gave $\rho = 0.95$ ($r = 0.948$). A comparable plot omitting both the *m*-Cl and *m*-NO_2 points (there is reason to expect a change in rate-limiting step for these derivatives—see Discussion) gave $\rho = 1.36$ ($r = 0.973$). This is probably the more reliable value. A Hammett plot of log (% ester/% methoxy ketone) *vs.* σ for the first five entries in Table III gave $\rho = 1.83$ ($r = 0.956$).

Reactions of $PhCH_2COCHClPh$ (5) with Methoxide Ion and with 2,6-Lutidine. Reaction of **5** with 0.05 *M* NaOMe in methanol gave 26% ester **6**, 36% α-methoxy ketone **7**, and *ca.* 40% unidentified product(s).

$$\underset{\mathbf{5}}{PhCH_2COCHClPh} \xrightarrow[MeOH]{NaOMe} \underset{\mathbf{6}}{PhCH_2CHPhCO_2Me} + \underset{\mathbf{7}}{PhCH_2COCHOMePh}$$

With 2 *M* NaOMe the yield of **6** increased to 39% and no **7** was formed. Under inverse addition conditions only **7** was formed.

Variation of the concentration of methoxide ion and of **5** showed the reaction to be first order in each. The rates were the same, within experimental error, for **5** and the corresponding bromide.

In the absence of acid or base catalysis methanolysis of **5** was too slow (24% in 25 hr at 25°) to account for the formation of any appreciable amount of **7**. Treatment of **7** with 2 *M* NaOMe–MeOH for 2 hr gave no **6**.

A study by Fort of the reaction of **5** with methanol catalyzed by 2,6-lutidine (2,6-dimethylpyridine) showed the product to be exclusively **7**, and the rate of reaction was found to be first order in 2,6-lutidine and first order in **5**.[3] We have confirmed and extended this result, and have also observed that the corresponding bromide reacts at an identical rate, within experimental error. The results are summarized in Table IV.

The investigation was extended to include studies with 2,6-lutidine–2,6-lutidinium ion buffers. When a large excess of Lut–LutH$^+$ buffer is used the concentrations of lutidine and of methoxide ion remain essentially constant throughout a run. If lutidine and methoxide ion are both acting as catalysts

$$k_{obsd} = k_2[\text{Lut}] + k_2'[\text{MeO}^-]$$

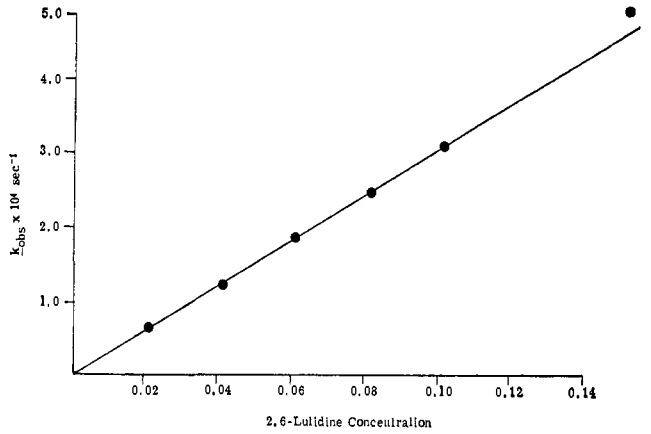


Figure 1. The effect of the concentration of 2,6-lutidine concentration on k_{obsd} in the methanolysis of $PhCH_2COCHClPh$ in Lut–LutH$^+$ buffers at 25°.

A plot of k_{obsd} *vs.* [Lut] should then give a line with a slope equal to k_2 and an intercept equal to k_2'[MeO$^-$]. In practice the line was found to go through the origin (Figure 1), which indicates that the reaction is being carried by lutidine alone. The data are summarized in Table V.

Table IV. Rates of Reaction of $PhCH_2COCHClPh$ and $PhCH_2COCHBrPh$ with 2,6-Lutidine in Methanol

Halide[a]	[Lut], *M*	Temp, °C	10^4k_{obsd}, sec^{-1}	10^3k_2,[b] M^{-1} sec^{-1}
Cl	0.250	25	5.70	2.28[c]
Cl	0.200	25	4.60	2.30
Cl	0.150	25	3.63	2.42
Cl	0.100	25	2.38	2.38[d]
Cl	0.258	0	0.855	0.342[c,e]
Br	0.258	0	0.88	0.34
Cl[f]	0.258	0	0.913	0.354
Cl[g]	0.258	0	1.19	0.460

[a] Halo ketone concentrations were 6.00–7.00 × 10^{-4} *M*. [b] k_2 was calculated from k_{obsd} by dividing by the concentration of lutidine. [c] k_2 is the average of two determinations. [d] Average value of k_2 at 25° is 2.34 × 10^{-3} M^{-1} sec^{-1}. [e] E_a calculated for the reaction of **5** (X = Cl) and lutidine in methanol using two rate constants, k_2 = 3.42 × 10^{-4} at 0° and k_2 = 2.38 × 10^{-3} at 25°, is 12 kcal/mol. [f] [$LiClO_4$] = 0.0413 *M*. [g] [$LiClO_4$] = 0.413 *M*.

Table V. Methanolysis of 1-Chloro-1,3-diphenylpropan-2-one[a] (**5**) in Lut–LutH$^+$ Buffer Solutions[b] at 25°

[Lut] = [LutH$^+$],[c] *M*	10^4k_{obsd}, sec^{-1}	10^3k_2,[d] M^{-1} sec^{-1}
0.150	4.91	3.27
0.100	3.08	3.08[e]
0.0800	2.44	3.05
0.0600	1.84	3.06[e]
0.0400	1.19	2.98
0.0200	0.628	3.14
0.0200	0.605	3.02[e,f]
		3.09[g]

[a] Halo ketone concentrations were 6.00–7.00 × 10^{-4} *M*. [b] The slightly higher values for k_2 here are presumably due to a salt effect (for example see last two entries in Table IV). [c] The lutidine–lutidinium *p*-toluenesulfonate buffer was prepared by adding 0.5 equiv of *p*-toluenesulfonic acid ($TsOH\cdot H_2O$) to lutidine. [d] k_2 was calculated from k_{obsd} by dividing by the concentration of lutidine. [e] k_2 is the average of two determinations. [f] With [H_2O] = 0.150 *M* (to test for the effect of small concentrations of water from $TsOH\cdot H_2O$). [g] Determined from the slope of a plot of $k_{obsd} = k_2$[Lut]; see Figure 1.

Discussion

Accelerating Effect of Methyl and of Phenyl Substitution. There is abundant evidence to indicate that substitution of a methyl group or phenyl group into the α position of $PhCH_2COCH_2Cl$ (**4**) to give $PhCH_2COCHClCH_3$ (**1**) or $PhCH_2COCHClPh$ (**5**) brings about an abrupt change in the rate-determining step for the reaction with sodium methoxide in methanol. For **4** a large negative ρ (−5.0) and a large k_{Br}/k_{Cl} leaving group effect (63/1) indicate extensive ionization of the C–X bond in the rate-determining step. In sharp contrast the rate of halide loss from **1** has a positive ρ (+1.36) and a k_{Br}/k_{Cl} ratio near unity (0.9/1). The k_{Br}/k_{Cl} leaving group effect for **5** is also near unity. These and other pertinent data are summarized in Table VI.

The marked increase in the rate of chloride ion release for **1** and for **5**, as compared to **4** (Table VI), must be the cause of the striking changes in deuterium exchange, Br/Cl leaving group effects, substituent effects, and product distribution. For **1** and **5** the rate of proton abstraction by methoxide ion must be the rate-limiting step. This explains the absence of deuterium exchange, the absence of a Br/Cl leaving group effect, and the positive ρ value.[5] The relatively small effect for **5**, as compared to **4**, of adding salt or water to the methanol solvent is also consistent with this interpretation.

The rates for **1** and **5** are not strictly comparable to that for **4** since the rate-limiting steps are different. The 220-fold and 330-fold rate increases represent *minimum* values for the increase in the rate of chloride ion release. They are large enough, however, to provide strong support for the idea that the high degree of positive charge developing on the α carbon in the transition state can be effectively stabilized by methyl or by phenyl substitution.[7]

The 1.4-fold higher rate of chloride ion release from **5** relative to **1** no doubt corresponds to the difference in inductive effects on the rate of proton removal resulting from the replacement of a methyl group by a phenyl group at a β position. The mechanism for the reaction of **1** or **5** with sodium methoxide in methanol can be represented as[8]

$$PhCH_2COCHClR + MeO^- \underset{}{\overset{\text{slow}}{\rightleftharpoons}}$$

1 or **5**

$$MeOH + PhCH{=}C(O^-)(CHR\,Cl) \xrightarrow{\text{fast}} \text{products}$$

Methanolysis of Enol Allylic Chlorides as a Possible Source of α-Methoxy Ketones. The product distribu-

(5) The small size of this ρ value is of particular interest since one might have expected appreciable conjugation in the transition state between the developing carbanion (enolate ion) and the aryl group. On the other hand, there is some precedent for a small ρ value in systems of this type since the ρ value for deprotonation of $ArCHMeNO_2$ by hydroxide ion in 50% (v/v) H_2O–MeOH at 15° is +1.44.[6]

(6) W. J. Boyle, Jr., unpublished results.

(7) The maximum acceleration possible would be the 10^6 value for methyl substitution at carbonium ion centers in limiting solvolysis reactions. See A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 74.

(8) The 6% deuterium exchange in **1** indicates a partition of about 15:1 for product formation *vs.* reprotonation for the enolate ion.

Table VI. Effect of Methyl and of Phenyl Substitution on the Reaction of $ArCH_2COCH_2X$ with Sodium Methoxide in Methanol at 0°

	$ArCH_2COCH_2X$ (4)[a]	$ArCH_2COCHXMe$ (1)	$ArCH_2COCHXPh$ (5)
Relative rates (X = Cl)[b]	1.0	>250[c]	>330[c]
Deuterium exchange[d]	*Ca.* 80%	*Ca.* 6%	
k_{Br}/k_{Cl}	63	0.9	1.0
Hammett ρ	−5.0	1.4	
Salt effect rate increase[e]	25–30%		7%
k(50% H_2O–MeOH)/ k(MeOH)	110		6
Products with			
2 *M* NaOMe	100% ester	100% ester (2)	39% ester (6)[f]
0.05 *M* NaOMe	100% ester	2 and 3	6 and 7
Ca. 10^{-5} *M* NaOMe[g]	100% ester	100% 3	100% 7

[a] See ref 2. [b] For chloride ion release. [c] This is a minimum value; a change in the rate-limiting step precludes an exact determination (see Discussion). [d] Exchange prior to chloride ion loss. [e] 0.1 *M* salt. [f] Plus an unidentified product; no 7 is present. [g] Inverse addition.

tion for $PhCH_2COCHClCH_3$ (1) and $PhCH_2COCHClPh$ (5) is strongly dependent on the methoxide ion concentration. At high methoxide ion concentrations 1 gave only ester (2). At low methoxide ion concentrations 1 and 5 gave only α-methoxy ketones (3 and 7, respectively). This behavior contrasts sharply with that of $PhCH_2COCH_2Cl$ (4), which gave high yields of Favorskii ester at either high or low methoxide ion concentrations. Presumably the ester in this latter reaction arises from a cyclopropanone, dipolar ion, or like intermediate. It is possible that the difference in sensitivity of 1 and 5, on the one hand, and 4 on the other to methoxide ion is due to a change in the reactivity of the intermediate due to the presence of the methyl or phenyl group, but this seems unlikely. The alternative view that the presence of these groups has encouraged competition from an unrelated side reaction appears much more probable. Methanolysis of an intermediate enol allylic chloride in competition with its enolate ion is an attractive possibility since this scheme could accommodate the effect of methoxide ion on the product distribution.[9]

Fort considered the possibility of methanolysis of the enol as a mechanism for the formation of α-methoxy ketone 7 from 5 in the reaction with 2,6-lutidine.[3] He rejected it because methanolysis in acidic medium, which should involve the enol, was slow, and because the reaction showed no indication of being accelerated by the lutidinium ion produced in later stages of the reaction. We have confirmed the much slower rate of methanolysis in acidic medium, but this does not rule out the enol mechanism for basic media since the rates would be expected to be different.[10] With regard to the second point, it is true that the enolization might be subject to simultaneous general acid and general base catalysis, but this is not a *requirement*. Examination of Table V shows that doubling the Lut–LutH$^+$ buffer concentration doubles k_{obsd} but does not quadruple the rate as would be required if both Lut and LutH$^+$ were catalyzing the reaction. The reaction appears to be catalyzed by 2,6-lutidine alone.[11]

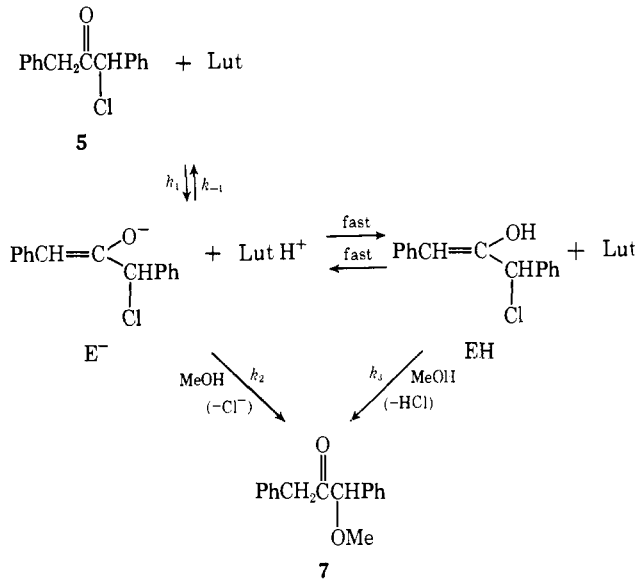
(9) We are indebted to Dr. A. C. Knipe for calling our attention to this possibility.

(10) In the acid-catalyzed reaction the rate-determining step is proton abstraction by a methanol molecule from the ketone conjugate acid. Evidently this reaction is appreciably slower than proton abstraction by methoxide ion from the ketone.

(11) Figure 1 indicates no catalysis by methoxide ion. Since Lut + MeOH = LutH$^+$ + MeO$^-$, the possibility that the reaction is carried by MeO$^-$ and LutH$^+$ is not ruled out, but appears highly unlikely.

Mechanistic possibilities can be discussed conveniently with the aid of Scheme I.

Scheme I



The rate of chloride ion release from 5 to form 7 will be first order in lutidine under the following circumstances: (a) reaction occurs *via* enolate ion (E$^-$) with $k_2 \gg k_{-1}$ (k_1 rate limiting), (b) reaction occurs *via* E$^-$ with $k_2 \ll k_{-1}$ (k_2 rate limiting), and (c) reaction occurs *via* enol (EH) with $k_3 \gg k_{-1}$ (k_1 rate limiting). A fourth possibility, reaction occurring *via* EH with $k_3 \ll k_{-1}$ (k_3 rate-limiting), can be excluded since in this case the rate would be zero order in 2,6-lutidine.

The absence of a k_{Br}/k_{Cl} leaving group effect for 5 in this reaction rules out the possibility that k_2 is rate limiting (mechanism b). Rate-limiting proton removal followed by formation of 7 through rapid methanolysis of the enolate ion (E$^-$) or enol (EH) remain as possibilities. Evidently loss of chloride ion from one (or both) of these species is much more rapid than protonation of the enolate ion *on carbon*. On the other hand, protonation of the enolate ion *on oxygen* by lutidinium ion is no doubt essentially diffusion controlled and protonation of the enolate ion on oxygen by methanol is very rapid.[12] For this reason an equi-

(12) Note, for example, that the rate of protonation of methoxide ion by methanol in 90% methanol is 10^7 M^{-1} sec^{-1}.[13]

(13) Z. Luz, D. Gill, and S. Meiboom, *J. Chem. Phys.*, 30, 1540 (1959).

librium between enolate ion (E^-) and enol (EH) is certain to be established under these conditions.

Loss of chloride ion from E^- would be expected to be more rapid than from EH by about two or three orders of magnitude. In order for methanolysis of EH to compete with that of E^- it would appear necessary, therefore, that EH be favored in the equilibrium by a factor of, say, 100 to 1. For the reaction

$$E^- + MeOH \rightleftharpoons EH + MeO^-$$

$$K_{eq} = \frac{[EH][MeO^-]}{[E^-][MeOH]} = \frac{K_{MeOH}}{K_{EH}}$$

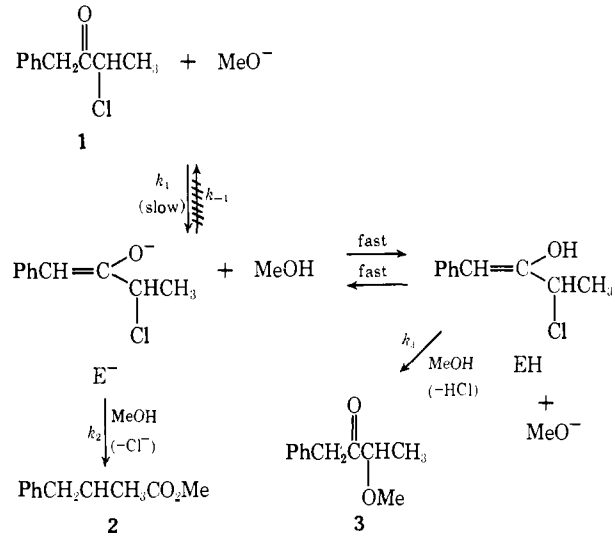
or

$$[EH]/[E^-] \times [MeO^-] = K^{auto}_{MeOH}/K_{EH}$$

Since the autoprotolysis constant of methanol is $10^{-16.7}$, K_{EH} would have to be *ca.* $10^{-17.4}$ in methanol in order that the EH/E^- ratio be 100/1 in 0.05 *M* NaOMe. The pK_a of acetone in water is *ca.* 20,[14] and the fraction of enol is below 2×10^{-6}.[15] This places the pK_a of acetone enol in water at *ca.* 14.3. The enols from **1** and **5** are probably about 1.5 pK_a units more acidic because of the presence of the chlorine atom.[16] Thus a pK_a of about 13 in water appears to be a reasonable estimate. In methanol the pK_a should be about four units higher,[19] which places the pK_a's of the enols of **1** and **5** in methanol at *ca.* 17.

The methoxide ion concentration in a 1 *M* solution of 2,6-lutidine in methanol is 7×10^{-5} *M*, assuming pK_b for 2,6-lutidine in methanol is 9.7.[21] Assuming that the pK_a of the enol in methanol is 17, the EH/E^- ratio in a 1 *M* solution of 2,6-lutidine in methanol will be *ca.* 3×10^4. In the Lut–LutH$^+$ buffer $[MeO^-] \cong 2 \times 10^{-10}$ *M* and EH/$E^- \cong 10^{10}$. Under inverse addition conditions the methoxide ion concentration is estimated to be *ca.* 10^{-5} *M*, and EH/$E^- \cong 2 \times 10^5$. These calculations leave no doubt that methanolysis of enol allylic chlorides is a likely reaction path under these conditions.

Mechanism for the Formation of α-Methoxy Ketones. In the previous section the mechanism of methanolysis of **5** to form **7** catalyzed by 2,6-lutidine was shown to involve a rate-limiting deprotonation followed by a rapid loss of chloride ion from the enol (or possibly the enolate ion). The absence of deuterium exchange, the absence of a Br/Cl leaving group effect, and the positive ρ value for the conversion of **1** to **2** and **3** by NaOMe–MeOH require a similar mechanism for the methoxide catalyzed reaction.



In the mechanistic scheme it is assumed that **2** arises from the enolate ion (E^-) and that **3** arises from the enol (EH). The rate-limiting step is k_1; the relative magnitudes of k_2 and k_3 and the position of the equilibrium determine the product composition.

This scheme requires that % **2**/% **3** vary linearly with the methoxide ion concentration, and this was observed (see Results). At high methoxide concentrations the product is exclusively **2** because the concentration of E^- is high, whereas at low methoxide concentration the product is exclusively **3** because the concentration of EH is high. If we accept the estimate made earlier of $K_{EH} \cong 10^{-17}$ for **1** as well as **5**, the k_2/k_3 ratio calculated from the data in Table I is *ca.* 60/1, which seems about the right order of magnitude. (In 0.05 *M* NaOMe EH/$E^- \cong$ 40/1.)

A decrease in yield of ester **2** and an increase in yield of α-methoxy ketone **3** was observed with substitution of *p*-MeO and *p*-Me groups into **1** (Table III). This is at first sight surprising inasmuch as these groups accelerate the reaction to give ester in the series $ArCHClCOCH_3$[24] and $ArCH_2COCH_2Cl$[2] (the ρ values are −2.4 and −5.0, respectively). A plot of log (% **2**/% **3**) *vs.* σ gave ρ = 1.83 (r = 0.953); by using σ^+ values for *p*-MeO, *p*-F, and *p*-Me the correlation coefficient was improved to 0.999 (ρ = 1.12). The use of σ^+ values is consistent with the postulate that the product-determining step in the formation of *both* **2** and **3** is solvolysis of an allylic chloride (enolate ion or enol) conjugated to the aryl group. In other words, a plot of log (% **2**/% **3**) is equivalent to a plot of log (k_2/k_3). The increased yield of methoxy ketone observed on substitution of the electron-releasing *p*-MeO, *p*-F, and *p*-Me could then be caused by a greater sensitivity to substituent effects of methanolysis of the enol allylic chloride (EH) than of the enolate allylic chloride (E^-). ρ for the latter reaction should be about −5 by analogy with the $ArCH_2COCH_2Cl$ system.[2] Analogy for methanolysis of EH can perhaps be found in the ρ −6.08 value obtained for acid-catalyzed rearrangement of $ArCH(OH)CH{=}CHCH_3$ to $ArCH{=}CHCH(OH)$-

(14) R. P. Bell, *Trans. Faraday Soc.*, **39**, 253 (1943).
(15) R. P. Bell and P. W. Smith, *J. Chem. Soc., B*, 241 (1966).
(16) The phenyl groups should have very little effect as judged from analogous systems. For example, an *o*-phenyl group lowers the pK_a of phenol by only 0.1 pK_a unit,[17] a *m*-phenyl lowers it by 0.3 pK_a unit,[17] and substitution of a phenyl group in the 3 position of 2-hydroxynaphthoquinone raises the pK_a slightly.[18] On the other hand, the correction for the inductive effect of the chlorine atom is *ca.* 1.5 pK_a units.[17]
(17) G. B. Barlin and D. D. Perrin, *Quart. Rev.* (London), **20**, 75 (1966).
(18) M. Charton, *J. Org. Chem.*, **30**, 974 (1965).
(19) The average increase in pK_a's for a series of phenols in going from water to methanol is *ca.* four.[20]
(20) B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mae, and A. J. Parker, *J. Am. Chem. Soc.*, 88, 1911 (1966).
(21) The pK_b's for pyridine, α-methylpyridine, and 2,4,6-trimethylpyridine are increased by 2.39, 2.41, and 2.43 units in changing from water to methanol.[22] An average of these values was added to the pK_b of 2,6-lutidine in water (7.28)[23] to arrive at 9.7.
(22) N. A. Izmilov and T. V. Mozharova, *Zh. Fiz. Khim.*, **34**, 1709 (1960).
(23) N. Ikelkawa, Y. Sato, and T. Maeda, *Chem. Pharm. Bull.* (Tokyo), **2**, 205 (1954); *Chem. Abstr.*, **50**, 994 (1956).
(24) F. G. Bordwell and R. G. Scamehorn, *J. Am. Chem. Soc.*, **90**, 6751 (1968).

CH_3.[25] The ratio of these ρ's is 1.2. Alternatively, the positive ρ of 1.12 can be accounted for as representing the value for the enolate–enol equilibrium. (The ρ for substituted benzoic acids in methanol is 1.54.[25])

An acceptable Hammett plot (ρ = 1.36, r = 0.973) was obtained for the rate of chloride ion release for the $ArCH_2COCHClMe$ system for p-CH_3O, p-CH_3, H, p-F, m-Cl, and m-NO_2 substituents (Table III) only by omitting the m-Cl and m-NO_2 points. This ρ relates to the rate of deprotonation, since this is the rate-limiting step. The poorer correlation observed when the m-Cl point is included (ρ = 0.95, r = 0.948) is no doubt caused by k_1 being not strictly rate limiting in this instance. The m-Cl and m-NO_2 substituents should bring about a sharp decrease in k_2 and k_3, which might cause these rates to be of the same order of magnitude as k_{-1}[MeOH]. If so, k_{obsd} would no longer be equal to k_1 but instead to $k_1/(k_1[MeOH] + k_2)$. If this interpretation is correct some deuterium exchange would be expected. Nmr analysis showed that 38% deuterium exchange had indeed occurred at the α' carbon atom for m-$NO_2C_6H_4CH_2COCHClMe$ as compared to only 6% exchange for the parent compound. The k_{obsd} for the m-NO_2 derivative can be corrected for this exchange since $k_{-1}[MeOH] \cong (38/62)k_2$. Although the corrected rate of *ca.* 19 M^{-1} sec^{-1} represents only a minimum value, it brings the m-NO_2 point much closer to the line.

The success of the mechanistic scheme in accommodating the results strongly suggests that α-methoxy ketones are arising from **1** and from **5** by methanolysis of intermediate enol allylic chlorides rather than from a dipolar ion intermediate.[3,4] (Additional evidence on this point will be provided in the next paper in this series.) At the same time the marked rate accelerations observed for **1** and **5**, as compared to **4**, provides additional support for a high degree of ionic character in the transition state for the dissociation of chloride ion from the enolate ion. The transition state must certainly be dipolar ion like and formation of a dipolar ion intermediate is not unreasonable. On the other hand, collapse of the dipolar-ion-like transition state to a cyclopropanone is equally probable.[24] In any event the formation of α-methoxy ketones at low methoxide ion concentrations can no longer be construed as evidence for a dipolar ion intermediate.

Experimental Section

Materials. The substituted phenylacetic acids were purchased from Aldrich Chemical Co. Baker analyzed methanol was used in kinetics experiments without further purification. Benzyl α-chlorobenzyl ketone (**5**) was prepared according to the method described by Fort[3] and benzyl α-bromobenzyl ketone was obtained from Richard G. Scamehorn.

Kinetic Procedure. The rate of halide release was determined by withdrawal of aliquots at timed intervals from a solution of the halo ketone and base, quenching with nitric acid, and titrating with silver nitrate solution. The titration of halide ion was carried out potentiometrically using a Sargent recording titrator, Model D, equipped with a constant rate buret and platinum electrodes. The end point was determined by the first derivative of the titration curve.

In a typical second-order run 100 ml of a 10^{-3} M halo ketone and 50 ml of 4×10^{-3} M sodium methoxide in methanol solution (both equilibrated at 0° for 30 min) were combined rapidly and the flask was swirled to mix the reactants. The temperature was maintained at 0.00 ± 0.03° by use of an Aminco Model 4-8600 constant-temperature bath. Aliquots of 5.00 ml were withdrawn at various intervals with an automatic pipet, delivered into a quenching solution of 2 ml of acetone and 0.5 ml of 3 M nitric acid, and then titrated. The initial concentration of the halo ketone was determined from titrated infinity aliquots taken after a minimum of ten half-lives. The initial methoxide concentration was calculated from its known concentration prior to dilution and was corrected for changes resulting from cubic concentration upon cooling to 0°. The second-order rate constants were determined from the slope of a plot of $\log (b - x)/(a - x)]$ *vs.* t. The reactions were followed until two to four half-lives. The rate constants were reproducible to within 5%.

For the kinetics runs in which 2,6-lutidine (0.01–1.0 M) was the base a pseudo-first-order kinetics procedure was followed. Enough nitric acid was added to the quenching solution to neutralize completely the lutidine and leave the solution slightly acidic for titration. The observed rate constants were calculated from plots of $\log [a/(a - x)]$ *vs.* t, and the second-order rate constants were found by dividing the observed rate constants by the concentrations of lutidine.

Deuterium Isotopic Analysis. The isotopic distributions were estimated from parent peaks in the mass spectra on a Consolidated Electrodynamics Corp. instrument, Model 21-104. The analyses were performed by Mr. Dan Netzel, Northwestern University.

3-Chloro-1-phenylbutan-2-one (1). A 600-ml solution of *ca.* 0.12 mol of diazoethane[26] in anhydrous ether contained in a 1-l. three-necked round-bottomed flask was cooled to −20° in a Dry Ice–acetone–water bath. Over a period of 15 min a solution of 10 g (0.06 mol) of phenylacetyl chloride in 50 ml of anhydrous ether was added with constant stirring. After an additional 0.5 hr anhydrous hydrogen chloride was slowly bubbled through the solution of diazo ketone for about 2 hr. During this time the temperature was maintained at −20° and stirring was continued. Water (200 ml) was added cautiously and the solution was placed in a separatory funnel. The ether layer was washed twice with 200 ml of 5% potassium carbonate solution and dried over magnesium sulfate. The solvent was removed by rotary evaporation and the residue was chromatographed on a 2.5 × 60 cm silica gel column using 2% ether in hexane as eluent. Fractions (250 ml) 6–9 yielded 8.3 g (70%) of **1**: λ_{max}^{film} 5.78 μ (C=O), 8.62 (C=O), 13.40 (Ph), 13.75 (C-Cl), 14.36 (Ph); $\delta_{TMS}^{CDCl_3}$ 1.40 (d, 3, CH_3, J = 7.0 Hz), 3.79 (2, CH_2), 4.29 (q, 1, CH, J = 6.5 Hz), 7.15 (5, Ph); $n^{25}D$ 1.5204.

Anal. Calcd for $C_{10}H_{11}ClO$: C, 65.75; H, 6.07. Found: C, 65.63; H, 6.12.

Substituted 3-Chloro-1-arylbutan-2-ones. A series of *meta*- and *para*-substituted 3-chloro-1-arylbutan-2-ones were prepared similarly to **1** using substituted phenylacetic acids. The yields and physical constants for these compounds are given in Table VII.

3-Bromo-1-phenylbutan-2-one. The preparation was similar to that of **1** except that anhydrous hydrogen bromide was used in place of hydrogen chloride. The yield from 3.3 g (0.02 mol) of phenylacetyl chloride was 2.9 g (60%). Analysis showed λ_{max}^{film} 5.79 μ (C=O); $\delta_{TMS}^{CDCl_4}$ 1.52 (d, 3, CH_3, J = 7.0 Hz), 3.80 (2, CH_2), 4.35 (q, 1, CH, J = 6.5 Hz), 7.15 (5, Ph); $n^{25}D$ 1.5395.

Anal. Calcd for $C_{10}H_{11}BrO$: C, 52.88; H, 4.88. Found: C, 52.63; H, 4.78.

Favorskii Reaction Procedures for the Reaction of 3-Chloro-1-phenylbutan-2-one (1) with Sodium Methoxide in Methanol at 0°. A. With 0.05 M Sodium Methoxide. A 1.00-g (5.48 mmol) sample of **1** dissolved in 1 ml of methanol was added rapidly to 220 ml of 0.05 M (11.0 mmol) sodium methoxide in absolute methanol at 0°. After 2 hr of stirring at 0° the solution was neutralized (phenolphthalein) with acetic acid and rotary evaporated below 25° to a volume of 2 ml. Water (250 ml) was added and the mixture was extracted with three 250-ml portions of ether. The combined organic fractions were washed with sodium bicarbonate solution and dried over magnesium sulfate. Rotary evaporation of the ethereal extract below 25° gave 0.97 g of yellow oil. Chromatography on a 1.5 × 25 cm silica gel column using 3% ether in hexane as eluent gave 0.56 g (58%) of methyl 2-methyl-3-phenylpropionate (**2**) from 250-ml fractions 3 and 4: λ_{max}^{film} 5.75 μ (C=O), 8.55 (C–O), 13.38 and 14.29 (Ph); $\delta_{TMS}^{CCl_4}$ 1.08 (d, 3, CH_3, J = 6.5 Hz), 2.4–3.2 (m, 3, CH and CH_2), 3.47 (3, OCH_3), 7.15 (5, Ph); $n^{25}D$ 1.5204.

After fraction 5 the ether content in the eluent was increased to 15% and fractions 7–9 yielded 0.37 g (38%) of 3-methoxy-1-phenylbutan-2-one (**3**); λ_{max}^{film} 5.80 μ (C=O), 8.96 (C=O) 13.62 and 14.32

(25) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(26) Prepared from ethyl N-nitroso-N-ethylurethan according to the method described by A. J. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, **13**, 763 (1948).

Table VII. Properties[a] of 3-Chloro-1-arylbutan-2-ones, $YC_6H_4CH_2COCHClCH_3$

Y	Yield,[b] %	$n^{25}D$	$\delta_{TMS}^{CDCl_3}$ CH_3(d)	CH_2(s)	CH(q)	Ar	Calcd, % C	H	Found, % C	H
p-CH_3O[c]	33		1.42	3.70	4.29	6.81 (q)	62.12	6.16		
p-CH_3[d]	67	1.5178	1.40	3.73	4.26	7.00 (s)	67.17	6.66	67.02	6.95
p-F	62	1.5035	1.47	3.80	4.34	6.8–7.2 (m)	59.86	5.02	59.33	4.85
m-Cl	41	1.5352	1.42	3.79	4.31	6.9–7.3 (m)	55.32	4.64	55.04	4.79
m-NO_2	52	1.5497	1.62	4.11	4.60	7.70 (d)	52.76	4.43	52.90	4.37
H	70	1.5204	1.20	3.20	3.77	7.22 (s)	65.75	6.07	65.35	6.12

[a] The ir λ_{max}^{film} (C=O) range was 5.76–5.78 μ for the chloro ketones listed. [b] Yield from preparation beginning with substituted phenylacetyl chloride using the standard synthesis as described for 3-chloro-1-phenylbutan-2-one (**1**). [c] Decomposed upon standing (no analysis made); other nmr δ 3.53 (CH_3O). [d] Other nmr δ 2.20 (CH_3Ar).

Table VIII. Properties[a] of Methyl 2-Methyl-2-arylpropionates, $YC_6H_4CH_2CH(CH_3)CO_2CH_3$

Y	Yield,[b] %	$n^{25}D$	$\delta_{TMS}^{CDCl_3}$ CH_3 (d)	$CH + CH_2$(m)	CH_3O (s)	Ar	Calcd, % C	H	Found, % C	H
p-CH_3O[c]	19	1.5057	1.12	2.4–3.0	3.54	6.85 (q)	69.21	7.75	69.08	7.78
p-CH_3[d]	48	1.4929	1.07	2.3–3.0	3.45	6.88 (s)	74.96	8.39	74.87	8.36
p-F	58	1.4769	1.08	2.4–3.0	3.49	6.6–7.1 (m)	67.33	7.19	67.09	7.00
m-Cl	77	1.5090	1.08	2.4–3.1	3.47	6.8–7.2 (m)	62.12	6.16	63.35	6.26
m-NO_2	67[e]	1.5221	1.21	2.5–3.2	3.68	7.89 (d)	59.18	5.87	59.09	6.18
H	62	1.4945	1.12	2.4–3.1	3.55	7.19 (s)	74.13	7.92	74.18	7.99

[a] The ir λ_{max}^{film} (C=O) range was 5.74–5.76 μ and λ_{max}^{film} (C—O) 8.54–8.57 μ for the esters listed. [b] Yields from the standard Favorskii reaction using 0.05 *M* methoxide (2 equiv) in methanol. [c] Other nmr δ 3.67 (CH_3O). [d] Other nmr δ 2.18 (CH_2Ar). [e] 33% of product was decomposed material which could not be identified.

Table IX. Properties[a] of 3-Methoxy-1-arylbutan-2-ones, $YC_6H_4CH_2COCH(OCH_3)CH_3$

Y	Yield,[b] %	$n^{25}D$	$\delta_{TMS}^{CDCl_3}$ CH_3 (d)	CH_3O (s)	CH (q)	CH_2 (s)	Ar	Calcd, % C	H	Found, % C	H
p-CH_3O[c]	83	1.5090	1.16	3.15	3.64	3.64	6.84 (q)	69.21	7.75	67.96	7.67
p-CH_3[d]	52	1.5018	1.15	3.13	3.62	3.64	6.92 (s)	74.96	8.39		
p-F	42	1.4865	1.23	3.22	3.68	3.73	6.6–7.2 (m)	67.33	7.19		
m-Cl	23	1.5092	1.23	3.23	3.71	3.72	6.9–7.2 (m)	62.12	6.16	61.88	6.09
m-NO_2[e]	0	1.5092	1.25	3.43	3.97	4.09	7.86 (d)	59.18	5.87	59.31	5.78
H	38	1.5003	1.20	3.20	3.60	3.77	7.20 (s)	74.13	7.92		

[a] The ir λ_{max}^{film} (C=O) range was 5.79–5.80 μ and λ_{max}^{film} (C–O) 8.96–9.00 μ for the methoxy ketones listed. [b] Yields from the standard Favorskii reaction using 0.05 *M* methoxide (2 equiv) in methanol. [c] Other nmr δ 3.56 (CH_3O). [d] Other nmr δ 2.19 (CH_3Ar). [e] No methoxy ketone was formed during Favorskii reaction; however, inverse addition of methoxide gave a quantitative yield of the methoxy ketone.

(Ph); $\delta_{TMS}^{CCl_4}$ 1.20 (d, 3, CH_3, J = 7.0 Hz), 3.20 (3, OCH_3), 3.60 (q, 1, CH, J = 7.0 Hz), 3.77 (2, CH_2), 7.21 (5, Ph); $n^{25}D$ 1.5003.

Identical weights of **2** and **3** (same molecular weights) gave vpc peaks with identical integration. Vpc analysis indicated that the oil before chromatography consisted of 61% ester (**2**) and 39% methoxy ketone (**3**).

B. With Substituted 3-Chloro-1-arylbutan-2-ones. The reactions of 1.00 g of *meta*- and *para*-substituted 3-chloro-1-arylbutan-2-ones with 0.05 *M* methanolic sodium methoxide were carried out as described in part A. Yields and physical properties of substituted methyl 2-methyl-3-arylpropionates are listed in Table VIII and those of substituted 3-methoxy-1-arylbutan-2-ones are given in Table IX.

C. With 2 *M* Sodium Methoxide. The reaction of 1.00 g (5.48 mmol) of **1** with 50 ml of 2 *M* sodium methoxide in methanol was carried out as in part A, except that the reaction time was cut to 15 min. Analysis of the 0.93 g of crude reaction product by vpc peak enhancement, ir, and nmr identified the product as the ester **2**. The yield was 96%.

D. With 0.05 *M* Sodium Methoxide, Inverse Addition Procedure. A 0.05 *M* solution of sodium methoxide in methanol (120 ml, 6.1 mmol) was added dropwise with stirring over a period of 7 hr to a solution of 1.00 g (5.48 mmol) of **1** in 50 ml of methanol at 0°. After neutralizing with acetic acid[27] the work-up was performed as in part A. Analysis of the 0.97 g of crude product by vpc peak enhancement, ir, and nmr identified the product as the methoxy ketone **3**. The yield was quantitative.

E. With Methoxide at a Constant Concentration of 0.02 *M* throughout Reaction. (See Table I for results at concentrations of methoxide from 0.02 to 0.50 *M*.) The reaction of 0.02 g of **1** with 1 l. of 0.020 *M* sodium methoxide in methanol was carried out as in part A. A 0.19-g sample of crude product was taken up in chloroform and analyzed by vpc. The product distribution was found to be 50% ester **2** and 50% methoxy ketone **3** by integration of peak heights and comparison of retention times to the authentic samples. (At the conclusion of the reaction the methoxide concentration had only decreased to 0.019 *M*.)

F. With 0.05 *M* Sodium Methoxide, 2 *M* Lithium Perchlorate. The reaction of **1** (0.25 g, 1.37 mmol) in 55 ml of methanol 0.05 *M* in sodium methoxide and 2 *M* in lithium perchlorate was carried out as described in part A. Work-up yielded 0.23 g of product which analyzed to be 42% methoxy ketone **3** and 58% ester **2** by vpc peak enhancement, nmr, and ir. The yield was 94%.

G. With Sodium Methoxide in Methanol-O-*d*. A 2.0 *M* solution of methoxide was prepared by dissolving 0.69 g of sodium in 15 ml of methanol-O-*d*. After cooling the mixture to 0°, 1.00 g (5.48 mmol) of **1** was added and stirred for 3 min. Dilute hydrochloric acid was added and the reaction mixture was processed and chromatographed as described in part A. The 0.92 g of product (93% yield) was found to be identical with **2**, except that the nmr spectrum showed an integral of the multiplet from δ 2.4 to 3.2 to be only 2.0 instead of 3.0. Isotopic analysis showed 1.06 ± 0.03 atoms of deuterium incorporated (three analyses).

Favorskii Reaction of 3-Chloro-1-(*m*-nitrophenyl)butan-2-one with Sodium Methoxide in Methanol-O-*d*. The reaction of 0.40 g of the chloro ketone with 2.0 *M* sodium methoxide was run follow-

(27) Although there appears to be no evidence for methoxy ketones arising from epoxy ethers during a mildly acidic work-up, the inverse addition procedure was repeated without neutralizing with acid to eliminate this possibility.[28] Again **3** was found to be the only product and no epoxy ether could be detected.

(28) N. J. Turro, R. B. Gagosian, C. Rappe, and L. Knutsson, *Chem. Commun.*, 270 (1969).

ing the procedure in part G of the standard Favorskii reaction conditions. After chromatography 0.20 g of product was shown by vpc peak enhancement, ir, and nmr to be identical with methyl 2-methyl-3-(*m*-nitrophenyl)propionate except tha tthe nmr spectrum showed the integral of the multiplet from δ 2.5 to 3.2 to be 1.6 instead of 3.0 protons. Isotopic analysis showed 1.38 ± 0.04 atoms of deuterium incorporated (two analyses).

Reaction of 1-Chloro-1,3-diphenylpropan-2-one (5) in 0.05 *M* Sodium Methoxide in Methanol. The reaction of 1.00 g (4.09 mmol) of **5** in 164 ml (8.18 mmol) of 0.05 *M* sodium methoxide was carried out as previously described in part A of the standard Favorskii reaction conditions. A 0.95-g of sample of crude products was chromatographed on a 2 × 30 cm column of silica gel using 3% ether in hexane as eluent. Fractions (250 ml) 4–8 yielded 0.25 g (26%) of methyl 2,3-diphenylpropionate (**6**): λ_{max}^{film} 5.77 μ (C=O) 8.59 (C—O), 13.30 and 14.30 (Ph); $\delta_{TMS}^{CCl_4}$ 3.08 (d, 2, CH_2, J = 6.5 Hz), 3.43 (3, OCH_3), 3.76 (t, 1, CH, J = 7.0 Hz), 7.17 (m, 5, Ph), 7.27 (m, 5, OPh); $n^{25}D$ 1.5508.

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.84; H, 6.77.

Fractions 10–15 gave 0.35 g (36%) of 1-methoxy-1,3-diphenylpropan-2-one (**7**): λ_{max}^{film} 5.80 μ (C=O), 9.12 (C—O), 13.15 and 14.30 (Ph); $\delta_{TMS}^{CDCl_3}$ 3.21 (3, OCH_3), 3.68 (2, CH_2), 4.63 (1, CH), 7.12 (m, 5, Ph); 7.30 (m, 5, OPh); $n^{25}D$ 1.5509.

After fraction 17 the ether content was gradually increased to 50%. Fractions 25–32 yielded 0.35 g of a solid (mp 125–132°) which was not identified.[29]

Reaction of 1-Chloro-1,3-diphenylpropan-2-one (5) with 2.0 *M* Sodium Methoxide in Methanol. The reaction of 1.00 g (4.09 mmol) of **5** with 25 ml of 2.0 *M* sodium methoxide solution was carried out as described in part C of the Favorskii reaction procedure. After work-up the 1.00 g of crude product was chromatographed on a 1 × 30 cm silica gel column eluted with 3% ether in hexane. The first seven 250-ml fractions contained 3% ether in hexane and thereafter the ether content was increased to 20%. Fractions 5–7 contained 0.38 g (39%) of oil identified by nmr, ir, and vpc peak enhancement as methyl ester **6**. Fractions 12–16 yielded 0.60 g of solid which could not be identified. No methoxy ketone **7** was present.

Reaction of 1-Chloro-1,3-diphenylpropan-2-one (5) with 0.05 *M* Sodium Methoxide, Inverse Addition Procedure. A 0.05 *M* solution of sodium methoxide in methanol (100 ml, 4.2 mmol) was added dropwise over a period of 8 hr to 1.00 g (4.09 mmol) of **5** in 100 ml of methanol following the directions in part D of the Favorskii reaction procedure. After work-up the 0.98 g of product was identified by ir, nmr, and vpc peak enhancement as the methoxy ketone **7**. The yield was quantitative.

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(29) The product probably rearranges during chromatography. The nmr of the recrystallized solid contained several peaks not present in the nmr of the crude reaction products prior to chromatography.

Favorskii Rearrangements. V. Mechanisms for α-Alkoxy Ketone Formation[1]

F. G. Bordwell and M. W. Carlson

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received November 6, 1969*

Abstract: Reaction of $PhCHClCOCH_2CH_3$ (**7**) with 0.05 *M* NaOMe–MeOH gave the same products and nearly the same distribution of products, $PhCH_2CH(CH_3)CO_2Me$ (**10**, 70%) and $PhCH_2COCH(OMe)CH_3$ (**11**, 30%), as was obtained earlier[3] from its isomer, $PhCH_2COCHClCH_3$ (**8**). The following parallelisms were noted for acid-catalyzed and base-catalyzed solvolyses of **7**, **8**, and $PhCH_2COCHClPh$ (**9**): (a) **7** formed the same (rearranged) methoxy ketone (**11**) in either acid-catalyzed or base-catalyzed methanolysis, (b) **8** formed **11** in either acid-catalyzed or base-catalyzed solvolyses in 50% (v/v) H_2O–MeOH to the exclusion of the corresponding hydroxy compound (**12**), despite the presence of 70 mole % water, (c) **8** formed a nearly constant ratio of **11** (*ca.* 75%) and **12** (*ca.* 25%) for acid-catalyzed and a variety of base-catalyzed solvolyses in 75% (v/v) H_2O–MeOH (Table I), (d) **9** gave methoxy ketone [$PhCH_2COCH(OMe)Ph$] to the exclusion of the corresponding hydroxy ketone in acid-catalyzed and base-catalyzed solvolyses in 50% (v/v) H_2O–MeOH, and (e) **9** gave the same ratio of ethoxy and hydroxy ketones (70:30) in acid-catalyzed and base-catalyzed solvolyses in 50% (v/v) H_2O–EtOH. It is proposed that both the acid-catalyzed and base-catalyzed solvolyses proceed by the same mechanism, solvolysis of an intermediate enol allylic chloride. A striking and unprecedented selectivity for reaction with methanol or ethanol, rather than with water, is exhibited during these reactions. Reactions of sodium phenoxide in methanol were consistent with the proposed mechanism. It is suggested that the alkoxy ketones formed as by-products in many Favorskii rearrangement reactions are derived from solvolysis of enol allylic chlorides.

Alkoxy ketones are common by-products in Favorskii rearrangements. With certain α-halo ketones they can become the predominant or even exclusive product.[2,3] At least eight mechanisms have been suggested to account for their formation. These include: (1) SN1, (2) SN2,[4] (3) SN2′,[5] (4) cleavage of an allene oxide,[6] (5) rearrangement of an epoxy ether,[4a-c,6a] (6) reaction of a dipolar ion[7] or (7) cyclopropanone[6,7c] intermediate with (alcohol) solvent, and (8) alcoholysis

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