110-89-4; 3-*p*-tolylpropionic acid, 1505-50-6; 2,3-diphenylpropionylpiperidide, 37112-06-4; 1-piperidino-1,3-diphenyl-2-propanone, 37112-07-5; 2,3,3-triphenylpropionylpiperidide, 37112-08-6; *trans*-2-phenylcyclopentanecarboxylic acid, 37108-09-1; methyl *trans*-2-phenylcyclopentanecarboxylate, 37108-10-4.

Favorskii Rearrangements. VIII.[1] Effects of Methyl Substitution and a Test for Internal Return from Enolate Ions

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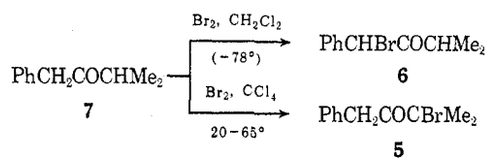
Tertiary bromide (or chloride) $C_6H_5CH_2COCMe_2X$ (**5**) reacted with 0.05 *M* NaOMe to give principally $C_6H_5CH_2COCMe_2OMe$ (**8**) plus a small yield of $C_6H_5CH_2CMe_2CO_2Me$ (**9**). With 1 *M* NaOMe the per cent of Favorskii ester (**9**) increased at the expense of α-methoxy ketone (**8**). The isomeric chloride $C_6H_5CHClCOCHMe_2$ (**6**) also gave **8** as the major product (plus minor amounts of **9**) with 0.05 *M* NaOMe, and again the formation of **9** was favored by increasing the methoxide concentration. On the other hand, bromide **6** gave principally $C_6H_5CHOHCOCHMe_2$ (presumably *via* an α-methoxyoxirane intermediate) and only small amounts of **8** and **9**. Rate studies showed that the rate of formation of **9** from chloride **6** and bromide **6** were identical, within experimental error. This contrasts with the results from the $C_6H_5CMeXCOCH_3$ system where $k^{Br}/k^{Cl} = 105$. Mechanistic interpretations are given. The rate of deuterium exchange for $C_6H_5CH_2COCHMe_2$ corresponded closely enough to the rate of halide loss from $C_6H_5CHXCOCHMe_2$ to show that little or no internal return occurs to the $C_6H_5CH_2(O^-)=CMe_2$ enolate ion during deuterium exchange in methanol.

In earlier papers we have shown that methyl substitution has a dramatic effect on the mode of reaction with bases of the isomeric aryl-α-chloro-2-propanones, $ArCH_2COCH_2Cl$ (**1**) and $ArCHClCOCH_3$ (**2**). Most 1-chloro-3-aryl-2-propanones (**1**) react with 0.05 *M* sodium methoxide in methanol at 0° to give quantitative yields of Favorskii esters, $ArCH_2CH_2CO_2Me$.[3] Methyl substitution α to the chlorine ($ArCH_2COCHMeCl$, **3**) changes the rate-limiting step of the Favorskii rearrangement and causes the formation of α-methoxy ketone by-products.[4] On the other hand, most 1-aryl-1-chloro-2-propanones (**2**) react with 0.05 *M* NaOMe in MeOH at 0° to give low yields of Favorskii esters (10–40%);[5] the major products are α-methoxyoxiranes, which are converted into α-hydroxy ketones during processing.[5] Here methyl substitution at the α′ position ($ArCHClCOCH_2Me$, **4**) eliminates the formation of α-methoxyoxiranes and leads to the formation of Favorskii esters and α-methoxy ketones, the relative amounts of which depend on the methoxide concentration. (With $PhCH_2COCHMeCl$ and 2 *M* NaOMe only ester is formed and with 0.0001 *M* NaOMe only α-methoxy ketone is formed.[4]) In order to continue the study of the effect of methyl substitution the reactions of the isomeric α-halo ketones $PhCH_2COCMe_2X$ (**5**) and $PhCHXCOCHMe_2$ (**6**) have now been examined. The reaction of **6** took on added interest with the observation that the rate of halide release from an analogous α-halo sulfone, $PhCHBrSO_2CHMe_2$, was over 500 times faster than the rate of base-catalyzed deuterium exchange of the tertiary hydrogen atom in the corresponding unhalogenated sulfone, $PhCH_2SO_2CHMe_2$, presumably because the internal return occurring in the exchange reaction was eliminated or decreased in the Ramberg–Bäcklund reaction.[6] Comparison of the rate of methoxide-induced chloride ion release from **6** with the rate of methoxide-catalyzed deuterium exchange for the corresponding ketone, $PhCH_2COCHMe_2$ (**7**), offered a way, then, to test for internal return from the enolate ion of **7**.

Results

Preparation of Bromo and Chloro Ketones 5 and 6.—Bromination of 3-methyl-1-phenyl-2-butanone (**7**) at



low temperature gave 1-bromo-3-methyl-1-phenyl-2-butanone (**6**, X = Br) contaminated with small amount of the isomeric bromo ketone **5**. At room temperature **5** was the principal product. The isomers were separated by chromatography.

Chlorination with sulfuryl chloride gave chlorides **5** and **6**, but conditions decidedly favoring one isomer over the other were not easily realized, and chromatographic separation was more difficult than with the bromides. Pure samples of chloride **6** were obtained by removal of the more reactive tertiary chloride **5** by treatment with methanolic sodium methoxide. A pure sample of chloride **5** was obtained from bromide **5** by treatment with LiCl in DMF.

Reactions of Halo Ketones 5 and 6 with Sodium Methoxide in Methanol.—Reactions of mixtures of either bromides **5** and **6** or chlorides **5** and **6** with 0.05 *M* NaOMe in MeOH showed that the tertiary α-halo ketones **5** reacted completely to give essentially all α-methoxy ketone (**8**) before an appreciable reaction of the secondary α-halo ketones **6** had occurred. Experiments with pure bromide **5** at higher methoxide concentrations gave some Favorskii ester **9** at the expense of α-methoxy ketone (**8**).

(1) For part VII see F. G. Bordwell and J. Almy, *J. Org. Chem.*, **38**, 571 (1973).

(2) National Institutes of Health Postdoctoral Fellow, 1969–1971. This investigation was supported by Public Health Service Research Grant No. CA-50610 from the National Cancer Institute.

(3) F. G. Bordwell, R. G. Scamehorn, and W. R. Springer, *J. Amer. Chem. Soc.*, **91**, 2087 (1969).

(4) F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3370 (1970).

(5) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **90**, 6751 (1968).

(6) F. G. Bordwell and M. D. Wolfinger, *ibid.*, **93**, 6303 (1971).

$PhCH_2COCMe_2Br$
5

0.05 M NaOMe → $PhCH_2COCMe_2OMe$ 8(97%) + $PhCH_2CMe_2CO_2Me$ 9(3%)

1 M NaOMe → 8(60%) 9(35%)

Reaction of secondary chloride **6** with 0.05 M NaOMe gave α-methoxy ketone **8** as the major product (*ca.* 85%) accompanied by *ca.* 10% of Favorskii ester **9**. With 1 M NaOMe the percentage of **9** increased to *ca.* 45% at the expense of **8**.

$PhCHClCOCHMe_2$ (6) $\xrightarrow{1\ M\ NaOMe}$ $PhCH_2COCMe_2OMe$ **8** (55%) + $PhCH_2CMe_2CO_2Me$ **9** (45%)

Reaction of bromide **6** with 1 M NaOMe in MeOH at 0° gave *ca.* 65% of α-methoxyoxirane **10** (judging from

$PhCHBrCOCHMe_2$ (6) $\xrightarrow{1\ M\ NaOMe}$ PhCH(OCH$_3$)–CCHMe$_2$ (O) **10**(65%) + **8**(15%) + **9**(15%)

the amount of α-hydroxy ketone **11** formed on processing), 15% of α-methoxy ketone **8**, and 15% of Favorskii ester **9**.

Kinetic Results.—From the rate of bromide ion release recorded over a period of 250 sec from a mixture of bromides **5** and **6** it is estimated that the rate constant for bromide **5** lies between 0.5 and 3 M^{-1} sec^{-1} at 0° in MeOH. (Less than 1% of reaction of **6** occurs during this time interval.)

Rates of chloride ion release were measured for chloride **6** at 0° under pseudo-first-order conditions using sodium methoxide concentrations of 0.0232 and 0.0518 M. The average of second-order rate constants for three runs was in each instance $2.29 \pm 0.08 \times 10^{-3}$ M^{-1} sec^{-1}. Identical runs with bromide **6** gave $k_2 = 7.89 \pm 0.3 \times 10^{-3}$ M^{-1} sec^{-1} (average of three runs with 0.232 M NaOMe) and $k_2 = 7.95 \pm 0.3 \times 10^{-3}$ M^{-1} sec^{-1} (average of three runs with 0.0518 M NaOMe). It is evident from these data that the kinetics are in each instance cleanly first order in methoxide. Correcting the rates by multiplying k_{obsd} times the per cent of Favorskii ester formed gave the k^{Br}/k^{Cl} ratio for the Favorskii reaction as 1.5.

Rates of base-catalyzed deuterium exchange for ketone **7** were determined with NaOMe–MeOD at 0, 25, and 37.5° by observing the disappearance of the α-tertiary proton by nmr. The second-order rate constants for five runs were 1.6×10^{-2} and 1.2×10^{-2} (at 37.5°); 4.8×10^{-3} (at 25°); 4.7×10^{-4} and 5.3×10^{-4} M^{-1} sec^{-1} (at 0°); $E_a = 15 \pm 1$ kcal/mol ($r = 0.998$ for five points).

Discussion

The formation of 97% α-methoxy ketone from tertiary chloride **5** and 0.05 M NaOMe continues the trend observed for $PhCH_2COCHMeCl$ (**3**) relative to $PhCH_2COCH_2Cl$ (**1**), where 39% of α-methoxy ketone was formed from **3** at the expense of Favorksii ester (the exclusive product with **1**).[3,4] The additional methyl substituent in **5** (compare **3**) evidently causes a further acceleration of the rate of methanolysis of the enol allylic chloride causing the α-methoxy ketone (**8**) to be

$PhCH_2COCMe_2X$ (5) + MeO^- ⇌ Ph(H)C=C(O$^-$)CMe$_2$X + MeOH ⇌ Ph(H)C=C(OH)CMe$_2$X + MeO^-

Ph(H)C=C(O$^-$)CMe$_2$X $\xrightarrow{-X^-}$ PhCH(C=O)CMe$_2$ $\xrightarrow[(MeO^-)]{MeOH}$ **9**

Ph(H)C=C(OH)CMe$_2$X $\xrightarrow{MeOH}$ $PhCH_2COCMe_2OMe$ **8**

the almost exclusive product at low (0.05 M) methoxide concentrations.

It is noteworthy that the formation of **8** was not accompanied by any of the isomeric methoxy ketone $PhCHOMeCOCHMe_2$, and that **8** was formed also from secondary bromide **6** and chloride **6**. This corresponds to the behavior of **3** and its isomer **4**.[4]

The shift in product toward Favorskii ester **9** at the expense of α-methoxy ketone **8** with increasing methoxide concentration is similar to the effect observed for **3**. It is believed to be caused by a shift in the enol ⇌ enolate equilibrium toward enolate ion with increasing methoxide concentration.[4]

The rate-limiting step changes from chloride ion release for **1** to proton abstraction for **3** because of the increased rate of ionization of chloride ion caused by the methyl substituent.[4] Ionization of chloride ion from the enol (or enolate ion) of **5** should be even faster than for **3**, and here too the rate of proton abstraction should be rate limiting. The rate estimated for bromide **5** is two to ten times slower than that for chloride **3**, which seems reasonable since the rate of abstraction of the benzylic proton in $PhCH_2COCXMe_2$ might be retarded to this extent by the presence of the extra methyl group (compare $PhCH_2COCHXMe$).

Rates for chlorides **2**, **4**, and **6** are summarized in Table I, along with those for $PhCMeXCOCH_3$ (**11**), an isomer of **4**.

For **2** and **11** the rate of ionization of the C–Cl bond enters into the rate-limiting step, as shown by the fact that extensive deuterium exchange has occurred in the resulting Favorskii ester (*e.g.*, a minimum of 84% prior to rearrangement for **11**[7]) and by large k^{Br}/k^{Cl} ratios (85 for **2** and 105 for **11**[7]). The approximately threefold slower rate for chloride **11** as compared to **2** is surprising, since methyl substitution should have a large accelerating effect on the rate of ionization of the chloride ion. [Note that $PhCH_2COCHClMe$ (**3**), an isomer of **11**, reacts at least 650 times as fast.] Apparently there are a number of retarding factors in the reaction of **11** which counteract the potential

(7) R. G. Scamehorn, Ph.D. Dissertation, Northwestern University, 1968.

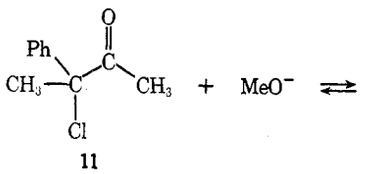
TABLE I
RATES OF FAVORSKII REARRANGEMENTS WITH 0.05 *M* SODIUM METHOXIDE IN METHANOL AT 0°

α-Chloro ketone	$10^3 k$,[a] M^{-1} sec^{-1}	Favorskii ester, %	Reference
$PhCHClCOCH_3$ (2)	0.40	13	5
$PhCHBrCOCH_3$ (2)	34	15	5
$PhCMeClCOCH_3$ (11)	0.124	49	7
$PhCMeBrCOCH_3$ (11)	13	56	7
$PhCHClCOCH_2Me$ (4)	80.5[b]	70	10
$PhCHClCOCHMe_2$ (6)	0.016[b]	7	*c*
$PhCHBrCOCHMe_2$ (6)	0.024[b]	3	*c*

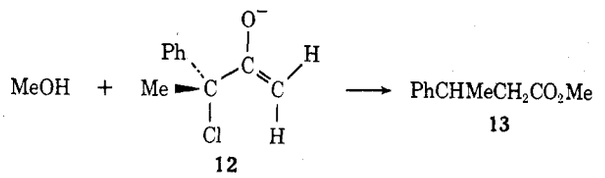
[a] Corrected by multiplying k_{obsd} by the fractional yield of Favorskii ester. [b] Minimum value for halide release (deprotonation is rate limiting). [c] Present study.

accelerating effect of methyl. Retarding factors could include a shift in equilibrium between **11** and its enolate ion (**12**) favoring **11**, due to increased steric hindrance in **12** caused by the methyl substituent (compare **12** with the enolate ion from **2**), and steric retardation of ionization of halide ion from **12** caused perhaps by crowding in the transition state wherein the C–X bond is parallel to the p orbitals in **12**.

It is noteworthy that the yield of Favorskii ester **13**



11



12

from **11** is almost four times as great as that from **2**, even though the Favorskii rate for **11** is over three times *slower*. Evidently formation of the α-methoxyoxirane by-product is regarded even more by α-methyl substitution than is halide ion release. The latter effect has been demonstrated since $PhCOCHMeBr$ has been shown to form an α-methoxyoxirane in a reaction with NaOMe in MeOH at a rate nine times slower than that for $PhCOCH_2Br$.[8] For chlorides **4** and **6** α-methoxyoxirane formation is not able to compete with α-methoxy ketone and Favorskii ester formation. This is a consequence of the strong accelerating effect that methyl substitution has on the release of halide ion from the allylic enol and enolate chlorides derived from **4** and from **6**. For bromide **6**, however, α-methoxyoxirane once more becomes the major product. This is surprising since it indicates that the second methyl substituent in **6** has nowhere near the maximum α-Me effect on the methanolysis of the allylic enol and enolate bromides from **6**.[9] Once again a steric retardation of halide ion release is indicated (compare **12**).

Deuterium exchange experiments show that the rate of proton abstraction is rate limiting for **4**.[10] The fact that $k^{Br}/k^{Cl} \cong 1$ for **6** shows that proton abstraction is also rate limiting in this reaction. The 35-fold faster rate for **4** than for **6** then must represent the retarding effect of methyl substitution on the proton abstraction rate (*secondary vs. tertiary* hydorgen atom).[11]

Comparison of the rate of proton abstraction from **6** by NaOMe in MeOH with the rate of abstraction of the tertiary proton from the corresponding ketone **7** with NaOMe in MeOD shows that k_{obsd} for **6** is *ca.* 5 times faster at 0°. Taking into account the solvent effect[12] increases the difference to *ca.* tenfold. This is the order of magnitude expected for the inductive effect of Cl or Br.[13] We conclude that little or no internal return occurs from the enolate ion of **7** during methoxide-catalyzed deuterium exchange in methanol solution. In one sense this is not surprising since the close agreement between rates of deuterioxide-catalyzed racemization and deuterium exchange for PhCOCHMeEt in dioxane–D_2O[16] excludes internal return during deuterium exchange as being important in this system under these conditions. On the other hand, the remarkably slow rate of base-catalyzed exchange of the tertiary proton in $PhCOCHMe_2$ relative to $PhCOCH_2Me$ in DMF[11b] and the evidence for internal return to the carbanion derived from abstraction of the tertiary proton in $PhCH_2SO_2CHMe_2$[6] made it seem advisable to test for internal return to the $PhCH_2C(O^-)=CMe_2$ enolate ion. Our failure to observe internal return is in agreement with the earlier results with the $PhC(O^-)=CMeEt$ enolate ion[16] and once again emphasizes the striking difference between carbanions derived from ketones as compared to those derived from sulfones.[17]

Experimental Section

3-Methyl-1-phenyl-2-butanone.—Benzylmagnesium chloride prepared by the method of Benkeser and Johnston[18] from 8.7 g (0.36 g-atom) of magnesium turnings, 22.8 g (0.18 mol) of benzyl chloride, and 600 ml of dry ether was added over 1 hr to an efficiently stirred solution of 50 ml (0.48 mol) of isobutyryl chloride in 400 ml of ether maintained under nitrogen at −78°. The mixture was stirred for an additional 2 hr at −78° and then poured over sulfuric acid and ice. The organic phase was washed three times with water, dried, and concentrated under reduced pressure to yield 30 g of oil which was distilled under 0.5-mm pressure. The first fraction, 14 g, boiling below 35° was isobutyric acid; the second, 15 g, boiling between 35 and 70° was chromatographed on 150 g of 90–200 mesh silica gel (Baker). Fractions eluted with 1–4% ether in hexane (7.6 g, 26%) contained 65–95% of product and were rechromatographed. Fractions eluted

(8) V. S. Karavan and T. I. Temnikova, *Zh. Org. Khim.*, **2**, 1417 (1966).
(9) For solvolysis of an alkyl halide the maximum α-CH_3 effect is *ca.* 10^8; see J. F. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2540 (1970).
(10) F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3377 (1970).
(11) (a) R. P. Bell and H. C. Louguet-Higgins, *J. Chem. Soc.*, 636 (1946), found that the rate ratio of deprotonation by hydroxide ion in water for $(MeCH_2)_2C{=}O$ *vs.* $(Me_2CH)_2C{=}O$ was 18 to 1.0. (b) H. Shechter, M. J. Collis, R. Dessy, Y. Okuzumi, and A. Chen, *J. Amer. Chem. Soc.*, **84**, 2905 (1962), found that the rate ratio for deprotonation of $PhCOCH_2Me$ *vs.* $PhCOCHMe_2$ with Et_3N in D_2O–DMF was 700:1.0.
(12) Judging from deuterium exchanges of comparable rates for carbon acids $k^{MeOD}/k^{MeOH} \cong 2$; see S. Andreades, *ibid.*, **86**, 2003 (1964); W. T. Ford, E. W. Graham, and D. J. Cram, *ibid.*, **89**, 4604 (1967); J. N. Roitman and D. J. Cram, *ibid.*, **93**, 2225 (1971).
(13) A tenfold rate enchancement would require a ρ^* value of *ca.* 2.8; for acetate ion catalyzed bromination of ketones $\rho^* = 1.59$[14] and for methoxide ion catalyzed deuterium exchange of the α-hydrogen atoms in esters $\rho^* = 1.78$.[15]
(14) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. Newman, Ed., Wiley, New York, N. Y., 1956, p 608.
(15) J. Hine, L. G. Mahone, and C. L. Liotta, *J. Amer. Chem. Soc.*, **79**, 5911 (1957).
(16) S. K. Hsu, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 78 (1938).
(17) See D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapters II and III, for a discussion.
(18) R. A. Benkeser and T. E. Johnston, *J. Amer. Chem. Soc.*, **88**, 2220 (1966).

TABLE II

PROPERTIES OF 1-PHENYL-2-BUTANONE DERIVATIVES AND METHYL 2,2-DIMETHYL-3-PHENYLPROPIONATE

Compound	Registry no.	$\delta_{TMS}^{CDCl_3}$ [a] $C(CH_3)_2$	$CH(CH_3)_2$	CHPh	Ph	OCH_3	Calcd, % C	Calcd, % H	Found, % [a] C	Found, % [a] H
$PhCH_2COCH(CH_3)_2$	2893-05-2	1.08[b]	2.68[b]	3.70						
$PhCHBrCOCH(CH_3)_2$	37112-23-5	1.05[c]	2.93[b]	5.57	7.27		54.79	5.43	54.69	5.45
$PhCHClCOCH(CH_3)_2$	37112-24-6	0.82[c]	2.75[b]	5.40	7.30		67.13	6.67	67.16	6.64
$PhCH(OH)COCH(CH_3)_2$	37112-25-7	0.90[d]	2.60[b]	5.15	7.30	4.30[e]				
$PhCH_2COC(CH_3)_2OCH_3$	37112-26-8	1.25		3.90	7.25	3.20	74.96	8.39	74.90	8.36
$PhCH_2COCBr(CH_3)_2$	29443-17-2	1.87		4.07	7.27		54.79	5.43	55.06	5.50
$PhCH_2COCCl(CH_3)_2$	37112-28-0	1.70		4.03	7.10					
$PhCH_2C(CH_3)_2CH_3$[e]	14248-22-7	1.12		2.80	7.15	3.60				

[a] Spectra were taken on a Varian T-60 spectrometer. Microanalyses were performed at Microtech Laboratories, Skokie, Ill. Samples were purified by evaporative distillation prior to analysis. [b] $J = 7$ Hz. [c] Doublet of doublets, $J = 7$ Hz; signal separation 3 Hz. [d] Doublet of doublets, $J = 7$ Hz; signal separation 18 Hz. [e] Signal for hydroxyl proton.

with 5–7% ether in hexane (4.1 g, 14%) contained pure 3-methyl-1-phenyl-2-butanone.[19]

3-Bromo-3-methyl-1-phenyl-2-butanone (5-Br).—To 700 mg (0.00432 mol) of 3-methyl-1-phenyl-2-butanone in 5 ml of carbon tetrachloride and 5 ml of ether was added 0.284 ml (0.80 g, 0.0050 mol) of bromine in 2 ml of carbon tetrachloride. The mixture was stirred and refluxed until the bromine color disappeared. The solution was dried with magnesium sulfate and saturated with anhydrous hydrogen bromide. The mixture was maintained for several hours at room temperature during which more HBr was added; the bromination and subsequent isomerization reaction was followed by examining filtered and evaporated aliquots by nmr. After 3 hr 71% of 3-bromo-3-methyl-1-phenyl-2-butanone and 10% of 1-bromo-3-methyl-1-phenyl-2-butanone were present. The total reaction mixture was filtered and evaporated to yield 746 mg of pale yellow oil, which was chromatographed on 20 g of silica gel. Fractions (20 ml) 12 and 13 (0.5% v/v) ether in hexane) yielded 60 and 35 mg of pure tertiary bromide. Intermediate fractions were combined and rechromatographed.

3-Chloro-3-methyl-1-phenyl-2-butanone (5-Cl).—To 35 mg (0.145 mmol) of 3-bromo-3-methyl-1-phenyl-2-butanone in 10 ml of dimethylformamide freshly distilled from lime was added 60 mg of fused lithium chloride. The mixture was stirred 8 hr at room temperature and poured into a separatory funnel containing carbon tetrachloride and water. The organic phase was washed five times with water, dried, and concentrated under reduced pressure to give 27 mg (95%) of 3-chloro-2-methyl-1-phenyl-2-butanone.

1-Chloro-3-methyl-1-phenyl-2-butanone (6-Cl).—To 857 mg (0.053 mol) of 3-methyl-1-phenyl-2-butanone in a 20 × 200 mm test tube was added 20 ml of dichloromethane. The solution was cooled to −20° with a Dry Ice–acetone–water slush and saturated with chlorine gas. A trace of anhydrous hydrogen chloride was added, and the tube was capped and maintained at −20° for 16 hr. Excess chlorine and hydrogen chloride were then removed under a stream of nitrogen, and the cold mixture was poured into aqueous saturated sodium bicarbonate. The organic layer was washed twice with water, dried, and concentrated to give 1.1 g of pale yellow oil which was chromatographed on 50 g of silica gel. Fractions eluted with 0.75% ether in hexane contained 0.907 mg (86%) of 1-chloro-3-methyl-1-phenyl-2-butanone.

1-Bromo-3-methyl-1-phenyl-2-butanone (6-Br).—Into a 20 × 200 mm test tube was placed 714 mg of 3-methyl-1-phenyl-2-butanone, 20 ml of dichloromethane, and 1 g of anhydrous magnesium sulfate. The test tube was cooled to −78°, and a solution of 0.25 ml of bromine in 5 ml of dichloromethane was added dropwise over 10 min. The mixture was saturated with anhydrous hydrogen bromide, capped, and kept at −78° for 24 hr, after which excess bromine and hydrogen bromide were removed in a stream of dry nitrogen. The pale yellow solution was poured into a separatory funnel, washed with saturated aqueous sodium bicarbonate solution, and then washed twice with water. The organic layer was dried with anhydrous magnesium sulfate; evaporation under partial pressure left 900 mg of a pale yellow oil whose analysis by nmr showed 67% 1-bromo-3-methyl-1-phenyl-2-butanone, 4% 3-bromo-3-methyl-1-phenyl-2-butanone, and 27% 3-methyl-1-phenyl-2-butanone. The products were partially separated by elution on 40 g of silica gel. Fractions eluted with 0.25% ether in hexane contained pure 1-bromo-3-methyl-1-phenyl-2-butanone. Fractions eluted with 0.50% or greater ether in hexane contained traces of isomeric bromo ketone and unbrominated ketone and were rechromatographed.

Product Distribution Runs.—The halo ketone (40–50 mg) was dissolved in a cooled solution of sodium methoxide–methanol of appropriate strength. The reactions were neutralized (phenolphthalein) with cold, dilute hydrochloric acid, concentrated below 25° when necessary, and shaken in ether–water mixtures. The organic phase was washed twice with water, dried, and concentrated under reduced pressure and analyzed by nmr. Product determinations were made by comparison of the integrals for one or more lines unique for a product (Table II) *vs.* that for the phenyl region. All weighed yields represent greater than 90% recovery. Pure products, isolated and analyzed, are described below.

3-Methoxy-3-methyl-1-phenyl-2-butanone and Methyl 2,2-Dimethyl-3-phenylpropionate.—To 3.16 g of 3-bromo-3-methyl-1-phenyl-2-butanone was added 100 ml of 2.0 *M* sodium methoxide in methanol at 0°. The mixture was maintained at 0° for 7 min and neutralized slowly while cooled with concentrated hydrochloric acid. The solution was concentrated to 10% of its volume and shaken with ether–water. The organic phase was washed twice with water, concentrated, and chromatographed on 120 g of silica gel. Fractions eluted with 1.5% ether in hexane contained 336 mg(13.5%) of pure methyl 2,2-dimethyl-3-phenylpropionate, a colorless oil. The methyl ester was hydrolyzed by boiling 1 hr with 12 ml of water, 12 ml of methanol, and 1 g of sodium hydroxide to the known[20] acid, mp 56–57° (ether–hexane).

Intermediate fractions (2% ether) contained ester and unidentified impurities. Fractions eluted with 2.5% ether in hexane contained 258 mg (10%) of 3-methoxy-3-methyl-1-phenyl-2-butanone, a colorless oil.

1-Hydroxy-3-methyl-1-phenyl-2-butanone.—Combined products (150 mg) of several product determination runs of 1-bromo-3-methyl-1-phenyl-2-butanone with base were chromatographed on 20 g of silica gel. Fractions eluted with 5% ether in hexane contained 45 mg of 1-hydroxy-3-methyl-1-phenyl-2-butanone. The semicarbazone derivative melted at 158–160° (lit.[21] mp 158–159°).

Kinetic Procedure. Rate of Halide Ion Release from 6 at 0°.—The rate of halide ion release was determined by analysis of aliquots withdrawn at timed intervals from a solution of halo ketone (0.001 *M*) and sodium methoxide (0.023 and 0.052 *M*) in methanol. The aliquots were quenched immediately in excess nitric acid and titrated potentiometrically using a Sargent Model D recording titrator equipped with a constant rate buret and platinum electrodes. The end point was determined from the first derivative of the titration curve.

Typically, 20.0 ml of 0.0251 *M* sodium methoxide in methanol and 80 ml of 0.0013 *M* ahlo ketone in MeOH (both equilibrated at 0° for 30 min) were combined rapidly, swirled, and maintained in an ice–water bath. Aliquots of 5.0 ml were withdrawn. The base concentration was corrected for cubic concentration upon cooling to 0°. The data were analyzed by the usual first-order

(19) This ketone was prepared in 66% yield from isobutyryl chloride and sodium phenyl(halomagnesio)acetate: D. Ivanoff and N. I. Nicoloff, *Bull. Soc. Chim. Fr.*, **4**, 1331 (1932).

(20) B. E. Hudson, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **62**, 2457 (1940), report mp 58°.

(21) M. Tiffeneau and J. Levy, *Bull. Soc. Chim. Fr.*, **37**, 1247 (1965). The hydroxy ketone was prepared from ethylmagnesium bromide and madelamide.

treatment (no aliquots were taken after 2 half-lives). Of the 15 kinetic points taken, one or two were rejected after a hand plot. Three infinity points were averaged. The correlation coefficient, slope, and least-squares standard deviation were calculated as before.[1]

Kinetics of Exchange of 3-Methyl-1-phenyl-2-butanone (7).—To a clean, dry 5-mm nmr tube was added approximately 30 mg of 3-methyl-1-phenyl-2-butanone and a measured amount of methanol-*O*-*d* (Diaprep, minimum 99% isotopic purity). The solution was analyzed at the appropriate temperature by a Varian A-60 nmr spectrometer equipped with a V-6040 variable temperature attachment. The probe was cooled with either an ice–water bath or Dry Ice–acetone bath, and temperature was checked periodically by lowering a calibrated thermometer into the probe to sample level. Temperature 25 and 0° were held to within 0.2° throughout all runs. After tuning, a full spectrum was taken and several additional scans were made on the dimethyl doublet 135 Hz upfield from the methyl resonance of the solvent. The tube was removed and the correct amount of 2.2 *M* sodium methoxide in methanol-*O*-*d* was added to achieve the desired base concentration and a total volume of 0.500 ml. The tube was capped, shaken, and replaced in the probe. After temperature equilibration, repetitive scans were taken on the upfield dimethyl signal. The instrument was periodically retuned and calibration samples (see below) were run.

Analysis of the scans of the dimethyl group for the amount of deuterium incorporation in the methine position was carried out by measuring line lengths of the two peaks of the doublet, together with that of the inner triplet (displayed as a broad singlet), correcting for the lack of base line separation for the doublet of the protio component, correcting for the relative widths of the individual peaks, and calibrating the corrected peak heights with three known standard mixtures (see below). These base line and line width corrections on the standard mixtures gave calibration curves which were nearly linear and had a slope of near unity. The mole fraction of unexchanged material before calibration is expressed as

$$[\mathrm{H}] = \frac{L_1 + L_2}{(L_1 + L_2)(1 - a) + L_3 b}$$

where L_1, L_2, L_3 refer to the line lengths of the low- and high-field lines of the doublet for the protio and inner triplet for the deuterio compounds, respectively, a is $L_3/L_1 + L_2$ prior to introduction of base, and b is $(2WH_3/L_3)/(WH_1/L_1 + WH_2/L_2)$. WH is the width at half-height measured for a given peak. Both a and b are constant throughout a run; b is calculated from data on lines 1 and 2 at $t = 0$ and line 3 at $t = \infty$. The infinity value of [H] was calculated from the equilibrium amounts of H in three positions in the ketone and one position in the solvent (1% H present originally). This treatment was adequate for all runs taken; the value $(L_1 + L_2)(1 - a) + L_3 b$ was uniform throughout a run indicating that the six-proton signal remained at a constant overall intensity despite changes in line shape. No runs was carried out to more than 2 half-lives beyond which L_1 and L_2 would be uncorrected for contributions from line 3.

Calibration samples were prepared by individually weighing pure protio and 97.5% isotopically pure trideuterio ketone (see below) into a single pan of a Cahn Model M-10 electrobalance. The mixtures were each dissolved in methanol and placed in separate nmr tubes. The mixtures contained 0.253, 0.397, and 0.672 of three atoms of deuterium after correction for the protio impurity in the deuterio component and the molecular weight difference between the components. A calibration curve was constructed for each run.

The calibrated mole fractions for protio ketone were used in the usual first-order treatment. A least-squares slope and standard deviations were obtained from a program[22] on a Wang 700 calculator.

The two runs each at 37.5 and 0° were at substantially different methoxide ion concentrations, showing that the reaction was first order in base.

3-Methyl-1-phenyl-1,1,3-trideuterio-2-butanone.—To 200 mg of partially deuterated 3-methyl-1-phenyl-2-butanone was added 1 ml of methanol-*O*-*d* and 0.02 ml of methanol-*O*-*d*–2.2 *M* sodium methoxide. The mixture was capped and left 10 hr at room temperature, then concentrated under reduced pressure. Fresh methanol-*O*-*d* was added, and the mixture was allowed to stand for an additional 10 hr. An equivalent amount of acetic acid-*O*-*d* was added, and the product was chromatographed after concentration under reduced pressure. Fractions eluted with 0.5–1.0% ether in hexane (120 mg, 60%) were analyzed by nmr in 0.022 *M* dichloromethane in carbon tetrachloride. Integration of the benzyl protons of the pure ketone *vs.* the dichloromethane showed 97.5% deuterium incorporation.

(22) This program was kindly supplied by Dr. T. G. Mecca.

Favorskii Rearrangements. IX. Stereochemistry of the Reaction with 2-Bromo-4-methyl-4-phenylcyclohexanone

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In the reaction of 2-chlorocyclohexanone or 2-bromo-5-methyl-5-phenylcyclohexanone (cis or trans) with NaOMe in MeOH the yield of Favorskii ester has been found to increase markedly at the expense of α-methoxyoxirane and α-methoxy ketone products on increasing the methoxide concentration. 2-Chloro- and 2-bromo-4-methyl-4-phenylcyclohexanones (**6**) are much less subject to this concentration effect, 40% yield of Favorskii ester being obtained even at low ($\sim 10^{-5}$ *M*) methoxide concentrations. The ratio of stereoisomeric esters formed from **6** was found to be *reversed* in going from low to high (2 *M*) methoxide concentrations. This result is rationalized in terms of equilibrating dipolar ion and cyclopropanone intermediates.

Previous papers in this series have provided evidence which points to the following mechanism for the Favorskii rearrangement, as applied to the $ArCH_2COCHXR$ (**1**) system with NaOMe in MeOH.[2]

The reversibility of the first step in the reaction sequence (*i.e.*, $k_{-1} \gg k_2$) was demonstrated for **1** with Ar = Ph and R = H by deuterium exchange and a large k^{Br}/k^{Cl} leaving group effect.[2c] (Similar evidence was also obtained for reversible carbanion formation in 2-halo-4,4-disubstituted cyclohexanones.[2a]) Ionization of the halogen from enolate ion **2** to form dipolar ion **3** was indicated by a large negative ρ (*ca.* −5) for this step with R = H, a sizable positive salt effect, and a strong rate acceleration by increasing the ionizing power of the solvent,[2b,c] Furthermore, a change in R from H to Me caused a marked rate acceleration, as expected in an ionization mechanism.[2d] In fact, the increase in k_2 was large enough to change the mecha-

(1) Abstracted in part from Ph.D. Dissertation of J. G. Strong, Northwestern University, 1968.

(2) (a) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967); (b) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **90**, 6751 (1968); (c) F. G. Bordwell, R. G. Scamehorn, and W. R. Springer, *ibid.*, **91**, 2087 (1969); (d) F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3370 (1970); (e) F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3377 (1970); (f) F. G. Bordwell and R. G. Scamehorn, *ibid.*, **93**, 3410 (1971); (g) F. G. Bordwell and J. Almy, *J. Org. Chem.*, **38**, 575 (1973).