Favorskii Rearrangements. Evidence for Steric Control in the Fission of Crowded Cyclopropanone Intermediates

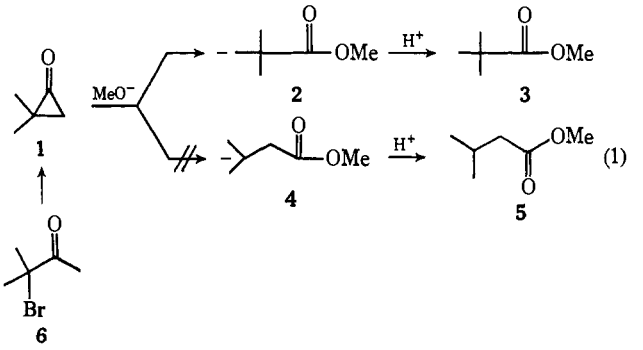
Christoffer Rappe,[1a] Leif Knutsson,[1a] Nicholas J. Turro,[1b] and Robert B. Gagosian[1b]

Contribution from the Institute of Chemistry, University of Uppsala, Uppsala 1, Sweden, and Department of Chemistry, Columbia University, New York, New York 10027. *Received September 15, 1969*

Abstract: The Favorskii rearrangements of four 2- and 4-halo-2-methyl-3-pentanones (**11–14**) were found to yield the same ratio of esters **9** and **10** using the same bases as for the ring opening of trimethylcyclopropanone (**20**) and its hemiketals (**21**). These results provide strong evidence that **20** and **21** are intermediates in the rearrangements. The experiments also demonstrate that steric factors, in addition to carbanion stability, determine the direction of the base-catalyzed ring opening of cyclopropanones. Studies of the Favorskii rearrangement with other related systems, **15–19**, are also reported.

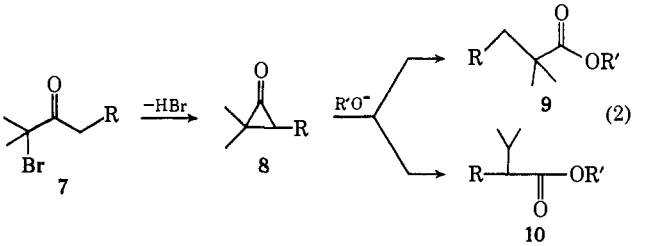
The base-induced rearrangement of α-halo ketones to carboxylic acid derivatives (Favorskii rearrangements)[2] is known to occur *via* at least two mechanisms.[3] Although the stereochemistry[4] and structure[5] of many Favorskii products are most reasonably explained in terms of a cyclopropanone intermediate, a "semibenzilic acid like" mechanism appears to obtain for certain ketone substrates.[6]

The direction of rearrangement, when a "semibenzilic acid like" mechanism operates, depends on the position of the α-halogen (for unsymmetrical starting ketones), while a cyclopropanone mechanism implies the structure of Favorskii products will be independent of whether an α or α' halogen is present in the starting ketone.[2] In general, it is thought that the direction of ring opening of cyclopropanones (and therefore the structure of Favorskii products when a cyclopropanone mechanism occurs) may be predicted by consideration of the stability of the most stable of the two possible carbanions[7] produced by base attack on the cyclopropanone.[5] In order to be useful, this proposal requires (a) that the transition state for the ring-opening step is very close to the carbanion along the reaction coordinate, (b) that proton transfer (required to form the isolated product) does not affect the direction of ring opening, (c) that ring opening is irreversible, and (d) that carbanion stability order is known. For example, treatment of 2,2-dimethylcyclopropanone (**1**) with sodium methoxide in CH_2Cl_2 or MeOH followed by hydrolysis leads to formation of methyl trimethylacetate (**3**) in quantitative yield[8] (eq 1). The absence (<0.5%) of methyl isopropylacetate (**5**)[9] is consistent with the hypothesis that the lower energy of transition state leading to **3** relative to **5** is related to the lower energy of primary carbanion **2** relative to **4**. This



(1)

rule has been used to predict the direction of base cleavage of α-halo ketones in Favorskii rearrangements, which can, but do not necessarily, proceed *via* a cyclopropanone intermediate.[2,3] The rearrangement of 3-bromo-3-methyl-2-butanone (**6**) with methoxide in ether resulted exclusively in formation of **3**.[10,11] The rearrangement of α-bromoisopropyl ketones (**7**), which can be assumed to proceed *via* the cyclopropanone **8**, yielded a mixture of esters **9** and **10** (eq 2).[11] Thus, in this case, the cleavage of the cyclopropanone must



(2)

a, R′ = Me
b, R′ = *t*-Bu

occur from both directions, indicating that either (a) the carbanion stabilities of the cleavage intermediates are comparable and/or (b) steric and other factors are

(1) (a) University of Uppsala. Favorskii Rearrangements. XVI. (b) Columbia University. This paper is Cyclopropanones. XV. Paper XIV: see N. J. Turro and R. B. Gagosian, *Chem. Commun.*, 949 (1969).

(2) A. Kende, *Org. Reactions*, **11**, 261 (1960).

(3) E. W. Warnhoff, C. M. Wong, and W. T. Tai, *J. Am. Chem. Soc.*, 90, 514 (1968).

(4) G. Stork and I. J. Borowitz, *ibid.*, **82**, 4307 (1960); H. O. House and F. A. Richey, Jr., *J. Org. Chem.*, **32**, 2151 (1967).

(5) N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).

(6) B. Tchoubar and O. Sackur, *Compt. Rend.*, **208**, 1020 (1939); C. L. Stevens and E. Farkas, *J. Am. Chem. Soc.*, **74**, 5352 (1952); A. C. Cope, M. E. Synerholm, and E. S. Graham, *ibid.*, **72**, 5228 (1950); **73**, 4702 (1951); C. Rappe and L. Knutsson, *Acta Chem. Scand.*, **21**, 163 (1967); J. M. Conia and J. L. Ripoll, *Bull. Soc. Chim. France*, **755**, 763 (1963); J. M. Conia and J. Salaun, *Tetrahedron Letters*, 1175 (1963).

(7) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 243.

(8) W. B. Hammond and N. J. Turro, *J. Am. Chem. Soc.*, **88**, 2880 (1966).

(9) R. B. Gagosian, unpublished results.

(10) N. J. Turro, R. B. Gagosian, C. Rappe, and L. Knutsson, *Chem. Commun.*, 270 (1969); J. G. Aston and R. B. Greenburg, *J. Am. Chem. Soc.*, **62**, 2590 (1940).

(11) C. Rappe and L. Knutsson, *Acta Chem. Scand.*, **21**, 2205 (1967).

Table I. Composition and Physical Data of the Esters from the Rearrangements (Solvent, Alcohol)

Halo ketone		Base	Yield, %	Composn (nmr), % 9	10	Composn (vpc), % 9	10	Bp (mm), °C	$n^{25}D$
$(CH_3)_2CBrCOC_2H_5$	11	MeONa	46	84[a]	16[a]	84	16	128–131 (760)	1.4032
	11	EtONa	65	88[a]	12[a]	82	18	90 (143)	1.4013
	11	*t*-BuOK	35	100[a]	0[a]	99	1	64 (67)	1.4030
$(CH_3)_2CClCOC_2H_5$	12	MeONa	63	84	16	74	26		1.4047
	12	*t*-BuOK	25	100	0	99	1	57 (20)	1.4026
$(CH_3)_2CHCOCHBrCH_3$[b]	13	MeONa	*c*	88	12	76	24	128–132 (760)	1.4069
$(CH_3)_2CHCOCHClCH_3$	14	MeONa	49	88	12	82	18		1.4059
	14	*t*-BuOK	20	100	0	99	1	58 (22)	1.4025
$(CH_3)_2CBrCOC_3H_7$	15	MeONa	52	66[a]	34[a]	68	32	64–66 (40)	1.4081
	15	*t*-BuOK	40	97[a]	3[a]	97	3	59 (15)	1.4059
$(CH_3)_2CClCOC_3H_7$	16	MeONa	60	68	32	65	35	53–54 (22)	1.4093
	16	*t*-BuOK	28	81	19	97	3	58–59 (15)	1.4072
$(CH_3)_2CHCOCHClC_2H_5$	17	MeONa	53	72	28	67	33	61 (29)	1.4087
	17	*t*-BuOK	*c*			96	4		
$CH_3CHClCOC_4H_9$	18	MeONa	57	*d*	*d*	80[e]	20[e]	54–55 (18)	1.4080
	18	*t*-BuOK	3	*d*	*d*	100	0		
$(CH_3)_2CHBrCOCH_2C_6H_5$	19	MeONa	28	100	0	100	0	109 (10)	1.5006
	19	*t*-BuOK	4	100	0	100	0	106 (0.5)	1.4950

[a] C. Rappe and L. Kuntsson, *Acta Chem. Scand.*, **21**, 2205 (1967). [b] Unstable, rearranges partly to the other α-halo isomer. [c] Very low yield. [d] Difficult to determine due to the complex nmr spectrum. [e] The main component was 2-ethylvaleric acid as determined by hydrolysis of the ester and preparation of crystalline derivatives: (a) W. D. McPhee and E. Klingsberg, *J. Am. Chem. Soc.*, **66** 1132 (1944); (b) J. G. Aston and J. D. Newkirk, *ibid.*, **73**, 3900, 3902 (1951). (c) Care must be taken in the use of this early data, since mixtures of esters would probably not have been detected by the techniques employed (distillation, boiling points, etc.). We have found that the vpc separations of the isomeric esters **9** and **10** are sometimes difficult, which suggests that the earlier work may well have been unable to differentiate between such isomers.

beginning to play a significant role in determining the energy of the transition state for cleavage.[11]

We present evidence here that (a) acyclic α-halo ketones undergo Favorskii rearrangements *via* cyclopropanone intermediates and (b) the direction of base induced ring opening is a function of the structure of the cyclopropanone and to a less significant extent on the structure of the attacking base.

Results

The yields and products from the treatment of a number of acyclic α-bromo and α-chloro ketones with alkoxides (the method has been described previously[11]) are given in Table I. The yields of esters are weighed isolated yields, and the ratio of type **9** and **10** esters were determined by nmr and vapor phase chromatography. The vpc analyses revealed that in the reaction with *t*-butoxide the yield was almost exclusively ester of type **9**, the error in the previous nmr analyses is due to overlapping of the methylene quartet at carbon 3 and the *t*-butyl group.[11] Control experiments, in which partially reacted halo ketone was recovered, demonstrated that no rearrangement of halogen from the α to α′ position occurs in the systems studied.

Yields and products from treatment of trimethylcyclopropanone (**20**) with alkoxides are given in Table II. The absolute yields of esters were determined by nmr and the relative yields were determined by vpc.

20 **21**

a, R = Me
b, R = *t*-Bu

The halo ketones **11–19** were prepared either *via* direct halogenation of the parent ketone using bromine or sulfuryl chloride or *via* diazo ketones.[12] The trimethylcyclopropanone **20** was prepared from dimethylketene and diazoethane.[13]

Table II. Cleavage of 2,2,3-Trimethylcyclopropanone and 2,2,3-Trimethylcyclopropanone Alkyl Hemiketals with Base

Molecule	Solvent	Base	Yield, %	Composn, % 9	10
20	CH_2Cl_2	MeONa	100	79	21
20	CH_2Cl_2	*t*-BuOK	90	>99	<1[a]
21a	CH_2Cl_2	MeONa	100	82	18
21a	MeOH	MeONa	100	82	18
21b	CH_2Cl_2	*t*-BuOK	90	>99	<1[a]
21b	*t*-BuOH	*t*-BuOK	90	>99	<1[a]

[a] Not detected by vpc.

Discussion

The fact that ketones **11–14** all yield essentially the same ratio of esters **9** and **10** (Table I) using the same base as trimethylcyclopropanone (**20**) and its hemiketal (**21**) (Table II) is compelling evidence that **20** and/or **21** is an intermediate in the Favorskii rearrangement of the ketones listed in Table I, since the ratio of esters **9** and **10** should be very sensitive to changes in mechanistic pathways. It is also interesting to note that a larger group than methyl in the ketone increases the relative amount of ester derived from the less stable carbanion, while *t*-butoxide as base almost exclusively yielded the ester derived from the most stable carbanion. These results are in harmony with the hypothesis that steric factors in addition to carbanion stability determine the direction of cleavage of cyclopropanones by base.

In the case of cleavage of **20**, the intermediate anion **22**, which is presumably the intermediate precursor to

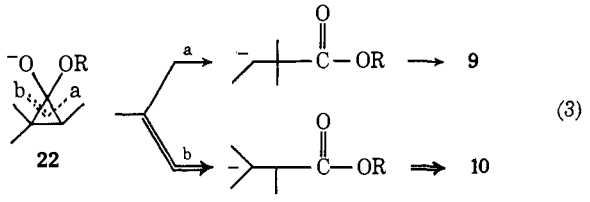
(12) (a) C. Rappe, *Arkiv Kemi*, **21**, 503 (1963); C. Rappe, *Acta Univ. Uppsal.*, 58 (1965); (b) D. P. Wyman and P. R. Kaufman, *J. Org. Chem.*, **29**, 1956 (1964); (c) W. E. Bachmann and W. S. Struve, *Org. Reactions*, **1**, 38 (1942).

(13) N. J. Turro and R. B. Gagosian, *J. Am. Chem. Soc.*, **92**, 2036 (1970).

ring opening, suffers from greater steric congestion than the analogous intermediate from 2,2-dimethylcyclopropanone (**23**). Furthermore, since the energy difference in carbanion stability between a secondary and

22 **23**

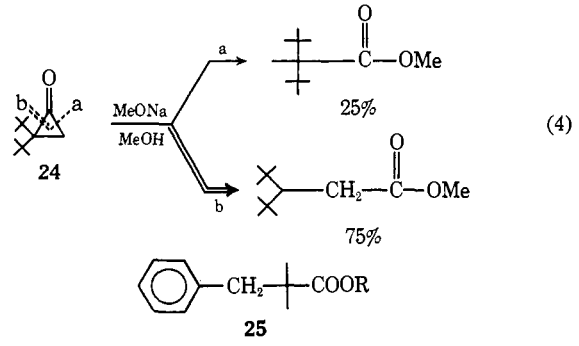
tertiary carbanion is not as large as between a primary and tertiary carbanion,[7] the additional strain energy released by breaking bond b is probably sufficient to allow cleavage of this bond to become somewhat competitive with cleavage of bond a (eq 3).



(3)

22

An extreme example of steric effects on ring opening is provided by the methoxide cleavage of 2,2-di-*t*-butylcyclopropanone (**24**) in which the predominant product is derived from the cleavage of the more highly congested bond (b), and not of the bond which produces the more stable carbanion (a) (eq 4).[14] Since **19** yields only **25**, it must be concluded that the carbanion generated from cleavage of the less substituted bond is stabilized by the phenyl group, as anticipated.



(4)

24 **25**

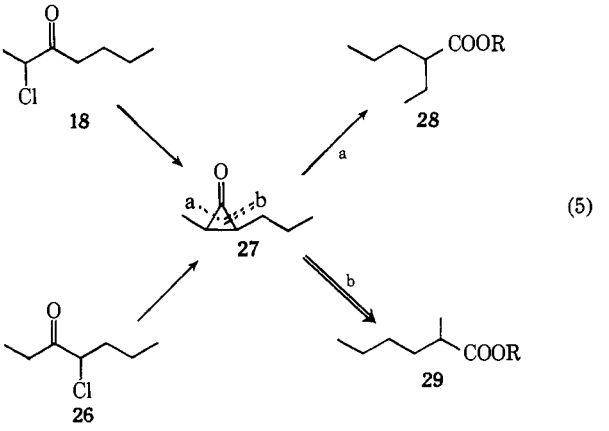
It has been suggested that opening of cyclopropoxides toward a secondary or tertiary position does not occur until attack is initiated by a proton or proton source.[15] In order to obtain information concerning the role of proton delivery in the base-induced ring openings of cyclopropanones, we attempted to attack the cyclopropanone with base in the absence of a proton source.

Trimethylcyclopropanone (**20**) was treated in CH_2Cl_2 under heterogeneous conditions with NaOMe. Although an nmr was taken immediately, there was no detectable difference between the nmr and an nmr taken after addition of water. Perhaps more careful exclusion of water in the preparation of **20** would make it possible to see anion **22** in the heterogeneous reaction. So far, attempts to rigorously dry methylene chloride solutions of **20** have led to rapid deterioration of the ketone.

The isomeric α- and α'-halo ketones **15–17** were found to give the same relative amounts of esters **9** and **10**, in perfect agreement with the formation of intermediate cyclopropanones.

It should be pointed out that the intermediates **21** and **22** may exist as two stereoisomers, which may or may not cleave to yield the same ratio of **9** and **10**. The fact that *t*-BuOK yields a greater amount of the more stable carbanion product is interesting and may result from preferential attack on the less hindered face of the cyclopropanone **20** followed by a specific bond cleavage. Another possibility is that proton delivery is more important in the ring opening of cyclopropanones by bulky bases.

Some time ago[16] it was reported that the rearrangement of both 2-chloro-3-heptanone (**18**) and 4-chloro-3-heptanone (**26**) by sodium methoxide yields only one ester, namely **28**, a puzzling result, in view of the above discussion. It is difficult to understand why cleavage of bond a to give a methylsubstituted carbanion should be highly favored relative to cleavage of bond b, which yields a propyl-substituted carbanion. Repeating the experiment with pure **18** followed by vpc analyses of the ester fraction indicated the existence of two esters, **28** and **29**, in the ratio 4:1, respectively (eq 5). Vpc



(5)

18 **28** **27** **29** **26**

analyses of the product from treatment of **18** with *t*-butoxide revealed only one component, but the yield of product is too low to allow meaningful discussion about mechanistic implications.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 137 spectrometer. Nuclear magnetic resonance spectra were taken on a Varian A-60 or A60A analytical high-resolution nmr spectrometer. Chemical shifts are reported in δ (parts per million) from internal tetramethylsilane (δ 0.00) or from internal methylene chloride (δ 5.30) unless specified. Mass spectra were taken on a Hitachi Perkin-Elmer RMU-6D mass spectrometer. The vpc analyses given in Table I and Table III were performed on a Pye M 84 gas chromatograph using a 10% Peg 20 M on Diatomite C (100–120 mesh) column. The vpc analyses given in Table II were performed on an Aerograph Model 90P or Model 1200 gas chromatograph. The following liquid phase was used: 1,2,3-tris(2-cyanoethoxy)propane ($\beta\beta\beta$). Chromosorb P (Chrom P) was used as solid support. Unless specified, yields are based on nmr integrations of product absorption *vs.* methylene chloride. All commercial chemicals used were of reagent quality, or purified before use.

Preparation of the Halo ketones. General Procedure. A. Sulfuryl chloride (1.0 mole) was added dropwise and under stirring to the parent ketone (1.0 mole) at such a rate that the temperature was maintained at about 40°. Stirring was continued for 1 more hr after complete addition of sulfuryl chloride. The crude product was crudely distilled without prior washing and drying. The distillate was redistilled on a Büchi spinning band distillation column

(14) J. K. Crandall and W. H. Machleder, *J. Am. Chem. Soc.*, **90**, 7347 (1968).

(15) C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

(16) See Table I, footnote *e*.

Table III. Preparation and Data for the Halo Ketones

Halo ketone[a]	Method	Yield,[b] %	Bp (mm), °C	$n^{20}D$	Calcd, % C	Calcd, % H	Found, % C	Found, % H
12	A	17	63.4–64.4 (54)	1.4232	53.54	8.24	52.72	8.13
13	B[c]		75–80 (40)					
14	B[d]	21	67.0–67.5 (47)	1.4225	53.54	8.24	54.10	8.40
16	A	44	88.1–88.6 (75)	1.4266	56.57	8.82	56.63	8.94
17	A	11	71.5 (21)	1.4321	56.57	8.82	55.81	8.63
18	B	38	82.5 (31)	1.4335	56.57	8.82	56.78	8.83

[a] The halo ketones **11** and **15** were prepared by bromination with N-bromosuccinimide, see ref 11. [b] Counted on pure redistilled product. [c] This ketone could not be obtained absolutely pure due to halogen migration during the distillation.

in order to separate the isomeric monohalo ketones and the small amount of dihalogenated product.

B. Diazomethane was prepared from N-nitroso-N-methylurea,[17] and diazoethane from N-nitroso-N-ethylurethan.[18] The ethereal solution of the diazoalkane was dried with solid potassium hydroxide for at least 3 hr. Acid halide (0.2 mole) dissolved in ether (200 ml) was added dropwise to the diazoalkane solution (0.5 mole). The stirring was continued for an additional 2 hr, after which aqueous hydrogen chloride (37%) or hydrogen bromide (20%) was added dropwise until the evolution of nitrogen ceased. The reaction mixture was washed repeatedly with water until neutral. The ether was distilled through a Vidmer column and the crude product rapidly through a Vigreux column. The distillate was purified as under A.

The method used for the preparation, the yields, and the physical constants of the halo ketones are collected in Table III. The halo ketones were analyzed by nmr and vpc and found to be completely pure if not otherwise stated.

3-Bromo-1-phenyl-3-methyl-2-butanone. Bromine (0.05 mole) was added dropwise and under stirring to a solution of 1-phenyl-3-methyl-2-butanone (0.05 mole) in 48% aqueous hydrogen bromide (5 ml). The stirring was continued for 2 hr and then the mixture was stored at 0° for 36 hr. The organic phase was evaporated with an oil pump for 1 hr, and the crude product was found to be pure by nmr. The product could not be distilled at 0.1 mm due to decomposition, yield 82%, mp 15°.

Rearrangement of the Halo Ketones. General Procedure. A 0.05-mole sample of the halo ketone was added dropwise during 1 hr to an ethereal suspension (50 ml of ether) of 0.07 mole of sodium methoxide, sodium ethoxide, or potassium *t*-butoxide. The mixture was refluxed for 3 hr, water was added, and the organic layer extracted with water. The ethereal phase was dried ($MgSO_4$), the solvent distilled off, and the residue distilled *in vacuo* and analyzed by nmr. The results of the different runs are given in Table I.

2,2,3-Trimethylcyclopropanone (20) and 2,2,3-trimethylcyclopropanone methyl hemiketal (21a) were prepared as discussed in ref 13.

2,2,3-Trimethylcyclopropanone *t*-butyl hemiketal (21b) was prepared by the same method as for **21a** using *t*-butyl alcohol.

Reaction of 2,2,3-Trimethylcyclopropanone (20) and 2,2,3-Trimethylcyclopropanone Methyl Hemiketal (21a) with Sodium Methoxide. 2,2,3-Trimethylcyclopropanone (**20**) or its methyl hemiketal, **21a** (25 ml, 0.7 *M* in CH_2Cl_2), were allowed to stir with an equimolar amount of sodium methoxide for 7 hr. The solution was then treated with 5 ml of a saturated salt solution. The water layer was washed with two 5-ml portions of ether. The extracts were combined, dried over $MgSO_4$, and concentrated on a short column condenser (10 cm). The products were collected by vpc (6 ft × 0.25 in., 20% $\beta\beta\beta$, Chrom P, 100°, 60 cc of He/min). Two esters, methyl α,α-dimethylbutyrate (**9a**) and methyl α,β-dimethylbutyrate (**10a**) were found in the ratio of 79:21 in approximately 100% yield determined by vpc and nmr.

21a reacted under identical conditions with 5 ml of MeOH as cosolvent. Esters **9a** and **10a** were found in the ratio of 82:18 in approximately 100% yield as determined by vpc and nmr.

Reaction of 2,2,3-Trimethylcyclopropanone (20) and 2,2,3-Trimethylcyclopropanone *t*-Butyl Hemiketal (21b) with Potassium *t*-Butoxide. 2,2,3-Trimethylcyclopropanone (**20**) or its *t*-butyl hemiketal (**21b**) (25 ml, 0.7 *M* in CH_2Cl_2) were allowed to stir with an equimolar amount of sodium methoxide for 7 hr. The solution was then treated with 5 ml of a saturated salt solution. The water layer was washed with two 5-ml portions of ether. The extracts were combined, dried over $MgSO_4$, and concentrated on a short column condenser (10 cm). The products were collected by vpc (6 ft × 0.25 in., 20% $\beta\beta\beta$, Chrom P, 100°, 60 cc of He/min). One ester, *t*-butyl α,α-dimethylbutyrate (**9b**), was found to be the only product in over 90% yield as determined by nmr and vpc. **21b** was allowed to react under identical conditions with 5 ml of *t*-butyl alcohol as cosolvent. One ester, **9b**, was found to be the only product in over 90% yield determined by nmr and vpc.

Acknowledgment. The authors at Uppsala acknowledge the support from the Swedish Natural Science Research Council, the assistance of Dr. K. Andersson in the vpc analyses and of Mrs. E. Almlof and of Miss A.-C. Ternstrom in the preparation of α-halo ketones. The authors at Columbia wish to thank the Air Force Office of Scientific Research (Grant AFOSR-68-1381) for their generous support of this work. A gift from the Upjohn Co. is also gratefully acknowledged.

(17) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1961, p 165.

(18) A. L. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, 13, 763 (1948).