# Favorskii Rearrangements. VII.[1] Formation of Amides from α-Halo α′-Aryl Ketones

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Reaction of *cis*-2-chloro-6-phenylcyclohexanone (1) with 0.05 *M* NaOMe in MeOH gave only *cis*- and *trans*-2-methoxy-6-phenylcyclohexanones. Observation of a small $k^{Br}/k^{Cl}$ rate ratio (*ca.* 4) for this reaction showed that the deprotonation step was rate limiting. Even 2 *M* NaOMe failed to produce Favorskii ester from 1, whereas piperidine in MeOH gave the Favorskii amide in high yield. Piperidine was also effective in giving a Favorskii product from 1-bromo-1,3,3-triphenyl-2-propanone whereas NaOMe was not. With 1-chloro-2-phenyl-2-propanone (5) piperidine gave a high yield of Favorskii amide. In the presence of 0.17 *M* piperidine and 0.17 *M* NaOMe in MeOH 5 gave 60% of amide and 40% of ester. It is suggested that the superiority of piperidine to methoxide ion in promoting Favorskii rearrangements in these systems is caused by its ability to form a Favorskii amide from an intermediate other than a cyclopropanone; enamine 19 is suggested as a likely intermediate. 1-Bromo-1,3-diphenyl-2-propanone reacted with piperidine in 50% ether–chloroform to give 60% of amide; no amide was formed in MeOH.

Reactions of α-halo ketones with alkoxide bases proceed by two principal pathways: (1) attack at the carbonyl group leading to α-alkoxy oxiranes and (on work-up) to α-hydroxy ketones or α-hydroxy ketals, and (2) enolate ion formation leading to Favorskii rearrangement products and α-alkoxy ketones. Enolate ion formation is strongly promoted by the presence of a phenyl group at the α′-carbon atom. For example, $PhCH_2COCH_2Cl$ reacts with 0.05 *M* NaOMe in MeOH to give a quantitative yield of Favorskii ester,[3a] whereas the isomeric $PhCHClCOCH_3$ gives only 13% yield under these conditions.[3b] We have now examined the effect of substitution of a phenyl group into the α′ position of 2-chlorocyclohexanone by studying the behavior of *cis*-2-chloro-6-phenylcyclohexanone toward NaOMe in MeOH and toward piperidine in MeOH. The investigation with secondary amines was extended to certain other α′-phenyl-substituted α-halo ketones.

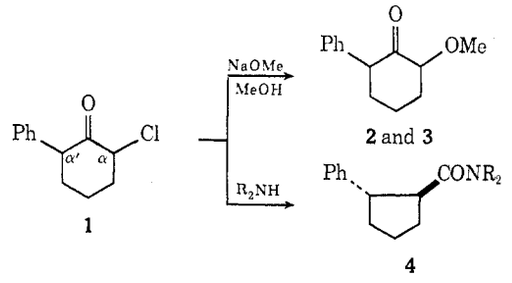
The reaction of secondary amines with α-halo ketones has generally been reported to give α-dialkylamino ketones as the primary product (SN2 reaction). In some instances small yields of Favorskii amides (20–30%) have been reported, however,[4] and two examples are known in which an amine derivative (an aminal) of a cyclopropanone was obtained in appreciable yield (37% from α-chlorocyclohexanone and 41% from α-chlorocycloheptanone).[5] In the present paper secondary amines have been found to produce Favorskii amides from several α′-phenyl α-halo ketones in high yields. The ability of piperidine to produce Favorskii products from two of these under conditions where methoxide ion is unable to do so is of synthetic and mechanistic significance.

## Results

**Reactions with Sodium Methoxide in Methanol.**—Reaction of *cis*-2-chloro-6-phenylcyclohexanone (1) with 0.05 *M* NaOMe in MeOH gave a nearly quantitative conversion into a mixture of *cis*- and *trans*-2-methoxy-6-phenylcyclohexanones (2 and 3, respectively); little or no Favorskii ester (methyl 2-phenylcyclopentanecarboxylate) was formed. Increasing the sodium methoxide concentration to 2.5 *M* gave essentially the same result. Reactions with NaOMe in aprotic solvents (DME, DMSO, $Et_2O$) also failed to produce ester.

Rates of halide release at 0° in MeOH were determined under second-order conditions using varying concentrations at 1 (0.00106, 0.00108, 0.00121, and 0.00118 *M*) and of NaOMe (0.00951, 0.0698, 0.073, and 0.119 *M*). The average second-order rate constant was $9.0 \pm 2 \times 10^{-2}\ M^{-1}\ \text{sec}^{-1}$ ($r \cong 0.99$ for each run). The rate constant for the bromo analog of 1, determined in the same manner, was $3.67 \pm 0.23 \times 10^{-1}\ M^{-1}\ \text{sec}^{-1}$.

**Reactions with Secondary Amines.**—Reaction of chloride 1 with excess piperidine at 0° for 1 hr gave conversion in high yield into Favorskii amide (*trans*-2-phenylcyclopentanecarboxpiperidide, 4). Amides




were also produced in high yields using high concentrations of piperidine in methanol or 2.8 *M* dimethylamine in aqueous methanol. With low concentrations of piperidine in MeOH (0.10 to 0.33 *M*) mixtures of methoxy ketones (2 and 3) and amide 4 were obtained. For example, with 0.10 *M* piperidine in MeOH about 55% of methoxy ketones and 45% of amide were formed. Increasing the concentration of piperidine to 0.33 *M* increased the amount of amide, and an increase in amide relative to methoxy ketones was also observed on adding NaOMe (0.15 to 0.30 *M*).

(1) For part VI see F. G. Bordwell and R. G. Scamehorn, *J. Amer. Chem. Soc.*, **93**, 3410 (1971).

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

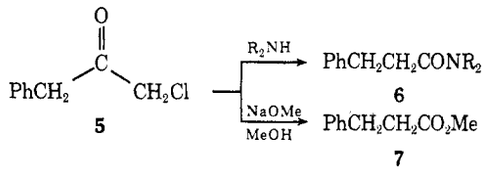
(4) A. S. Kende, *Org. React.*, **11**, 287 (1960); (b) E. L. May and E. Mosettig, *J. Amer. Chem. Soc.*, **70**, 1077 (1948); (c) R. M. Dodson, E. F. Morello, and W. G. Dauben, *ibid.*, **76**, 606 (1954); (d) J. Jullien and P. Fauche, *Bull. Soc. Chim. Fr.*, (5) **20**, 374 (1955); (e) C. L. Stevens, A. B. Ash, A. Thuillier, J. H. Amin, A. Balys, W. E. Dennis, J. P. Dickerson, R. P. Glinski, H. T. Hanson, M. J. Pillai, and J. W. Stoddard, *J. Org. Chem.*, **31**, 2593 (1966).

(5) J. Szmuszkovicz, E. Cerda, M. F. Grostic, and J. F. Zieserl, Jr., *Tetrahedron Lett.*, 3969 (1967); J. Szmuszkovicz, D. J. Duchamp, E. Cerda, and C. G. Chidester, *ibid.*, 1309 (1969).

Use of 0.33 $M$ 2,2,6,6-tetramethylpiperidine in methanol gave only methoxy ketones (**2** and **3**) and no amide.

Rates of reaction of piperidine (0.990 $M$) with **1**, and its bromo analog, in MeOH at 0° were determined conductometrically; for **1**, $k = 1.85 \pm 0.03 \times 10^{-3}$ $M^{-1}$ sec$^{-1}$ (average of three runs with $r = 0.999$ or better) and, for the bromo analog, $k = 3.99 \pm 0.09 \times 10^{-3}$ $M^{-1}$ sec$^{-1}$ (average of three runs with $r = 0.999$ or better).

Reaction of 1-chloro-3-phenyl-2-propanone (**5**) with 1 $M$ piperidine in methanol also gave Favorskii amide (**6**) as the principal product. With NaOMe present **5** gave both Favorskii amide (**6**) and Favorskii ester (**7**); for example, with **5** and 0.17 piperidine and 0.17 $M$ NaOMe 60% of amide **6** and 40% of ester **7** were formed. With 0.17 $M$ piperidine and 0.33 $M$ NaOMe 40% of amide **6** and 55% of ester **7** were formed. Reaction of 1-chloro-3-$p$-tolyl-2-propanone (**8**) with 2 $M$ piperidine gave the corresponding amide (**9**) along with *ca.* 30% of 1-piperidino-3-$p$-tolyl-2-propanone, **10** (SN2 product). Using 1 $M$ piperidine and 1 $M$ NaOMe in MeOH gave amide **9** and the corresponding ester (**11**), but no **10**.




Reaction of 1-bromo-1,3-diphenyl-2-propanone (**12**) with 0.1 $M$ piperidine in MeOH gave SN2 product, 1-piperidino-1,3-diphenyl-2-propanone, plus a small amount of methoxy ketone; no amide was formed. With 0.5 $M$ piperidine in 50% (v/v) ether–chloroform 40% of the amino ketone and 60% of amide were obtained.

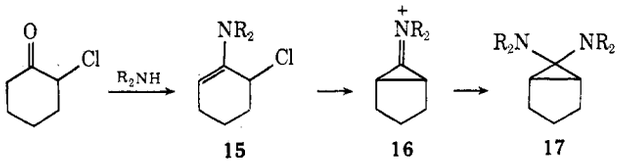
Reaction of 1-bromo-1,3,3-triphenyl-2-propanone (**13**) with neat piperidine or with 7 $M$ piperidine in MeOH gave Favorskii amide as the principal product. With 1 $M$ piperidine in MeOH only *ca.* 10% of amide was formed, together with *ca.* 35% of 1,3-diphenylindanone[1] and *ca.* 10% of 1-methoxy-1,1,3-triphenyl-2-propanone.[6] [1,3-Diphenylindanone did not react with (neat) piperidine to form the amide under the experimental conditions.]

## Discussion

Formation of $\alpha$-methoxy ketones **2** and **3** from the reaction of *cis*-2-chloro-6-phenylcyclohexanone (**1**) with low concentrations (0.05 $M$) of NaOMe in MeOH is expected by analogy with the behavior of 2-chlorocyclohexanone[7a] and of $PhCH_2COCHMeCl$ (**14**).[7b] The behavior of **1** differs, however, in that no Favorskii ester is produced even at high concentrations (2 $M$) of NaOMe. (With 2 $M$ NaOMe 2-chlorocyclohexanone gives 49% of Favorskii ester and 47% of hydroxy ketal,[7a] and **14** gives 100% of Favorskii ester.[7b]) Substitution of a phenyl group into the $\alpha'$ position of 2-chlorocyclohexanone greatly enhances the rate of enolate ion formation relative to attack at the carbonyl group in **1**; production of $\alpha$-methoxy ketones (by methanolysis of the enol allylic chloride) and of Favorskii ester is thereby favored over hydroxy ketal formation.[3,4,7] The presence of an additional $\alpha'$-alkyl (ring) substituent in **1**, as compared to **14**, would be expected to enhance the methanolysis rate,[8] which accounts for the formation of $\alpha$-methoxy ketones in preference to Favorskii ester even in the presence of high concentrations of NaOMe.

The rate of chloride ion release from **1** with NaOMe in MeOH at 0° is *ca.* 22 times faster than from 2-chlorocyclohexanone. The rate acceleration can be attributed to the presence of the phenyl substituent in **1**, but the rates are not strictly comparable because preequilibrium carbanion–enolate ion formation is appreciable for 2-chlorocyclohexanone,[9] whereas for **1** the relatively small $k^{Br}/k^{Cl}$ rate ratio (*ca.* 4; compare with 63 for $PhCH_2COCH_2X$) shows that proton removal is largely rate limiting. In this respect the behavior of **1** resembles that of **14** ($k^{Br}/k^{Cl} = 0.9$).[7b] The 73-fold slower rate for chloride ion release for **1** as compared to **14** is no doubt due primarily to retardation of the deprotonation rate caused by the presence of an additional $\alpha'$-alkyl (ring) substituent in **1**.

The ability of secondary amines to produce high yields of Favorskii amide from **1** in light of the failure of even high concentrations of methoxide ion to produce Favorskii esters suggests that the amide is being formed by a route not available for ester formation. One possibility is reaction *via* an enamine allylic chloride in a route similar to that suggested by Szmuszkovicz and coworkers[6] for the conversion of 2-chlorocyclohexanone with piperidine into the aminal of the Favorskii cyclopropanone (**17**).




An alternative pathway for the formation of **17**, which does not appear to have been ruled out, is reaction of piperidine with an intermediate cyclopropanone. (Conversions of cyclopropanones into aminals are known to occur readily.[10]) The behavior of **1** toward piperidine (relative to methoxide ion) described above is accounted for much more readily by postulating an enamine intermediate, however, and the formation of Favorskii amides from 1-chloro-3-phenyl-2-propanone (**5**) and from 1-bromo-1,3,3-triphenyl-2-propanone (**13**) can also be accommodated best by this mechanism. There is persuasive evidence to favor an enamine intermediate over a cyclopropanone intermediate in the case of **5**. Here we have good reason to believe that the nearly quantitative yield of Favorskii ester formed from **5** and NaOMe–MeOH is derived from a cyclopropanone intermediate.[3] One would not expect piperidine to be able to compete with methoxide ion for this intermediate since the carbonyl group is ordinarily much

(6) The indanone and methoxy ketone are the principal products formed with sodium methoxide in methanol; see ref 1.

(7) (a) F. G. Bordwell and J. G. Strong, *J. Org. Chem.*, **38**, 579 (1973). (b) F. G. Bordwell and M. W. Carlson, *J. Amer. Chem. Soc.*, **92**, 3370 (1970).

(8) The ethanolysis rate of $Me_2C{=}CHCH_2Cl$ is *ca.* 65 times that of $MeCH{=}CHCH_2Cl$: C. A. Vernon, *J. Chem. Soc.*, 423, 4462 (1954).

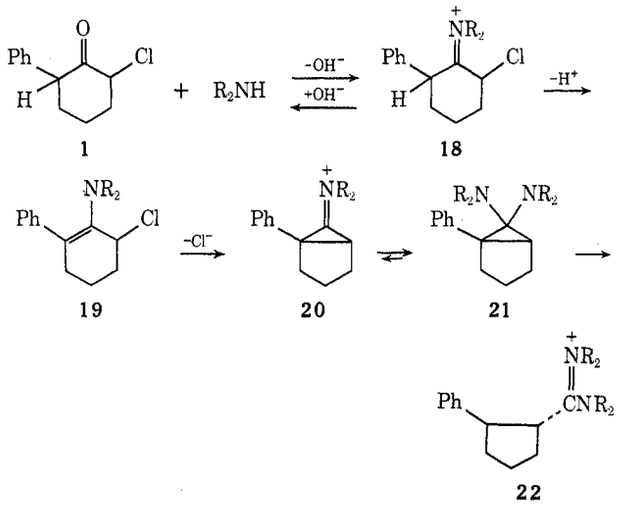
(9) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967).

(10) W. J. M. Van Tilborg, S. E. Schaafsma, H. Steinger, and T. J. de Boer, *Rec. Trav. Chem. Pays-Bas*, **86**, 417 (1967).

more receptive to attack by methoxide ion.[11] Formation of a *higher* yield of amide than ester from **5** on treatment with equivalent amounts of piperidine and methoxide ion is, therefore, inconsistent with the generation of both the amide and ester from a cyclopropanone intermediate. It seems more likely that the amide is derived from an enamine intermediate (comparable to **15**) and that the ester is derived from a cyclopropanone intermediate. If this explanation is correct, enamine formation must be a rapid reaction since the second-order rate constant for the reaction of **5** with methoxide ion is $2.6 \times 10^{-1}\ M^{-1}\ \text{sec}^{-1}$ at 0°.[3] Loss of bromide ion from **13** in the reaction with NaOMe–OH to form 1,3-diphenylindanone is *ca.* 10 times faster,[1] which may explain the inability of amide formation (presumably *via* the enamine) to compete with 1,3-diphenylindanone formation (presumably *via* a dipolar ion) except at high concentrations of amine. The rate of loss of halide ion from **1**, or its bromo analog, with NaOMe–MeOH is of the same order of magnitude as for **5** (see above). Enamine formation can be reasonably expected to compete favorably, therefore, with formation of the α-methoxy ketone from **1**, as observed.

Comparison of the behavior of **1** and 2-chlorocyclohexanone[6] toward piperidine shows that the presence of the phenyl group promotes enamine formation at the expense of the SN2 reaction, and causes formation of Favorskii amide in place of the aminal. The phenyl group no doubt promotes enamine formation by facilitating deprotonation of an intermediate, such as **18**. The effect of methoxide ion in increasing the yield of amide can be explained as facilitating this deprotonation.

The phenyl group would also be expected to promote cleavage of aminal **21** to amidinium ion **22**. The latter




would be hydrolyzed to amide on work-up or by the mole of water released in converting **1** into **19**.

Cleavage of the C–X bond is not involved in the rate-limiting step of enamine formation, judging from the small (~4) $k^{Br}/k^{Cl}$ leaving group effect observed for the reaction of **1** and its bromo analog with 1 *M* piperidine in MeOH. According to the scheme shown, deprotonation of **18** will be rate limiting.[13] The smaller amount of amide *vs.* SN2 product formed from the *p*-methyl derivative of **5** can be accounted for by retardation of the deprotonation step in the reaction leading to amide. Work designed to gain additional information concerning the details of the mechanistic scheme shown for **1** is in progress.

## Experimental Section

*cis*- and *trans*-**2-Methoxy-6-phenylcyclohexanone (2 and 3).**—To 200 ml of 0.05 *N* sodium methoxide in methanol at 0° (prepared with 10 mmol of dry sodium methoxide, Matheson-equivalent weight 100 by titration) was added 0.97 g (0.0048 mol) of *cis*-2-chloro-6-phenylcyclohexanone (**1**), mp 122–123°.[14] The solution was stirred for 2 hr at 0° and then neutralized (phenolphthalein) with glacial acetic acid, concentrated under reduced pressure to 10% of its original volume, and shaken with water and ether. The organic phase was washed with brine and then water, dried, and concentrated to yield 0.90 g (99%) of a solid, mp 47–53°. Analysis of the crude material by nmr indicated that two methoxy ketones accounted for 70 and 30% of the product (by comparison of integrals of sharp singlets at δ 3.2–3.4 and a multiplet at 7.0–7.4 (see below)). Fractional crystallization from ether–hexane gave 0.356 g (36%, three crystallizations) of pure *cis*-2-methoxy-6-phenylcyclohexanone: mp 74–75°; nmr $\delta_{TMS}^{CCl_4}$ 1.4–2.3 (broad multiplet, 6, $CH_2$), 3.32 (s, 3, $OCH_3$), 3.40–4.0 (multiplet, 2, CH), 7.00–7.40 (multiplet, 5, Ph); ir $\lambda_{max}^{KBr}$ 3.40, 5.81, 6.90. The structure was based on equilibration data (see below).

*Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.49; H, 8.07.

Chromatography of combined mother liquors from the crystallizations described above yielded a second (trans) methoxy ketone from fractions eluted with 8% ether in hexane: $\delta_{TMS}^{CCl_4}$ 1.4–2.4 (m, $CH_2$, 6), 3.28 (s, 3, $OCH_3$), 3.40–4.00 (m, 2, CH), 7.0–7.4 (m, 5, Ph). The cis isomer was eluted with pure ether. Both the cis and trans isomers were subjected to equilibration conditions (0.1 *M* sodium methoxide in methanol. 0°, 44 hr or 0.5 *M* methoxide, 0°, 24 hr). The cis isomer predominated in each instance by a factor of *ca.* 4:1 (nmr analysis); unidentified products accounted for 3% of the total product.

**Product Distribution Runs for Reactions of 2-Chloro-6-phenylcyclohexanone (1) with Metal Alkoxides in Methanol, *tert*-Butyl Alcohol, Dimethoxyethane, Dimethyl Sulfoxide, Ether, and Dichloromethane.**—The solvent and base were combined and brought to the predetermined temperature. In the case of concentrated methoxide solutions, sodium or potassium was introduced to the alcohol solvent. The substrate was then introduced, and the solution was maintained at temperature for the prescribed time neutralized with glacial acetic acid, and shaken with ether and water. The organic phase was washed twice with water, combined, dried, and concentrated under reduced pressure and analyzed by nmr. Integration of the aromatic region (five protons) *vs.* peaks corresponding to the methoxy ketone products (*vide supra*) gave ratios of 2.3–3:1 of cis/trans. Other products included 2-hydroxy-6-phenylcyclohexanone[15] (42%) from reaction of **1** with 1.0 *M* potassium *tert*-butoxide in *tert*-butyl alcohol, and methyl 2-phenylcyclopentanecarboxylate (*ca.* 40%) from 4.8 *M* potassium methoxide in methanol. The ester was identified (nmr) by comparison with a sample prepared from the corresponding acid (see below).

**Rates of Halide Ion of 2-Chloro-6-phenylcyclohexanone, 1, and 2-Bromo-6-phenylcyclohexanone.**—The kinetic procedure followed a previously described method.[7a] Typically, 4.70 ml of 0.1085 *N* sodium methoxide in methanol cooled to 0° was rapidly added to 50.0 ml of 0.00118 *M* **1** kept at 0° under nitrogen in a single-neck pear-shaped flask. A 5-ml-capacity automatic

(11) For example, methoxide ion is $10^1$ to $10^3$ more effective in attacking the carbonyl group in aryl acetates than is piperidine.[12]

(12) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, **90**, 2622 (1968).

(13) Another possible route to **19** would be attack of piperidine on the enolate chloride to give an adduct which forms **19** by loss of hydroxide ion. Deprotonation of **1** would then presumably be rate limiting. It seems doubtful, however, that addition of piperidine to the enolate chloride (or enol chloride) could be fast enough to make deprotonation rate limiting.

(14) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **22**, 190 (1966).

(15) Identified by comparison of the nmr spectrum with that of an authentic sample prepared by the method of W. Treibs, M. Weissenfels, *Ber.*, **93**, 1374 (1960).

pipet (plunger type, Cole Parmer) was inserted and secured with a tightly fitting syringe cap. The flask was shaken and immersed above the pipet chamber in an Aminco Model 4-8600 constant temperature bath held at 0.0 ± 0.003°. Aliquots (4.0 ml) were drawn at various times and delivered into a quenching solution of 2 ml of acetone and 0.5 ml of 1 *M* nitric acid and titrated potentiometrically with 0.00283 *M* silver nitrate solution using a Sargent Model D titrator equipped with a constant rate buret and platinum electrodes. The second-order data were treated in the usual way and analyzed by a least-squares program.[16] Acceptable runs were followed to 3 half-lives, gave $r = 0.991$ or greater and standard deviations of 6% or less of the calculated rate constant. Rates (followed to 3 half-lives) were reproducible to within 15%.

**Reactions of 1 with Secondary Amines.**—Reaction of 1 with 1.0 *M* piperidine in methanol or neat piperidine gave conversion into amide **4** in high yield. Typically, 50 mg (0.00024 *M*) of **1** was added to a chilled mixture of 851 mg of piperidine in 10 ml of methanol. The solution was stirred and maintained at 0° for 3 hr and poured into water, rinsed with ether, and shaken. Excess piperidine was removed by washing several times with water. The organic phases were combined, dried, and concentrated to yield 52 mg (85%) solid, mp 83–85°, whose nmr spectrum showed no peaks corresponding to **2** or **3** or methyl 2-phenylcyclopentanecarboxylate. One crystallization from ether–hexane gave *trans*-2-phenylcyclopentanecarboxpiperidide (**4**): mp 87–88°; nmr δ 1.2–1.7 (m, 6), 1.8–2.3 (m, 6), 3.0–3.7 (m, 6), 7.15 (m, 5, Ph); $\lambda_{max}^{KBr}$ 3.40, 3.50, 6.12, 6.95.

*Anal.* Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9, 01. Found: C, 79.55; H, 9.13.

The amide **4** produced was shown to possess the more stable trans configuration by an exchange–equilibration run similar to one reported for isomers of methyl 2-methyl-2-phenylcyclopentanecarboxylate.[7a] To 4 ml of methanol-*O*-*d* (Diaprep, 99% isotopic purity) was added 230 mg of freshly cut sodium and 100 mg of **4**. The solution was refluxed under nitrogen for 100 hr and then 0.2 ml of deuterium oxide was added. The reaction was treated in the manner described above. The neutral and base fraction, 70 mg (70%), mp 80–82° (crude), possessed an nmr spectrum closely similar to that of the untreated pure amide, except that integration showed the loss of 0.8–1.5 of one proton in the region 3.0–3.7 ppm. No methyl ester was detected. The aqueous rinsings were acidified and reextracted to produce, after treatment, 30 mg of solid, mp 78–80° identified as *trans*-2-phenylcyclopentanecarboxylic acid[5d] (see below) whose nmr spectrum showed 0.8–1.2 of one proton loss in the methine region ($\delta_{TMS}^{CDCl_3}$ 3.0–3.6).

An authentic sample of *trans*-2-phenylcyclopentanecarboxylic acid was prepared from **4** with 48% aqueous hydrobromic acid refluxing for 10 hr.[5d] A sample of methyl 2-phenylcyclopentanecarboxylate was prepared from 100 mg of the acid, mp 82–84°.

**Rates of Reaction of 2-Chloro-6-phenylcyclohexanone, 1, and 2-Bromo-6-phenylcyclohexanone with Piperidine in Methanol at 0°.**—A 5.00-ml portion of a stock solution of 1.00 *M* piperidine in methanol was placed in a 6-ml conductometric cell and equilibrated 0.5 hr in an ice–water bath. Approximately 5 mg (0.023 mmol) of halo ketone dissolved in 0.200 ml of methanol was then added, and the mixture was shaken. The cell leads were attached to a Y.S.I. Model 31 conductivity bridge and readings were taken to 3 half-lives. Infinity readings were taken after 7 half-lives and the pseudo-first-order data were treated in the usual way. Correlation coefficients and standard deviations were obtained by a least-squares program,[16] and the second-order rate constants were corrected for dilution of base and solvent concentration at 0°.

**Reactions of 1-Chloro-3-phenyl-2-propanone (5), 1-Chloro-3-*p*-tolyl-2-propanone (8), 1-Bromo-1,3-diphenyl-2-propanone (12), and 1-Bromo-1,3,3-triphenyl-2-propanone (13) with Piperidine under Various Conditions.**—The reaction and analytical procedures used for reaction of the halo-2-propanone series was the same as that described for 1 above. For **5** and **13** the weighed yield after acidic work-up (see above) was at least 85% of theory. For **8** and **12** the crude products were obtained by pouring the reaction mixture into distilled water and washing five times. The organic phases were combined, dried, and concentrated as before and then analyzed. Procedures and analytical data for pure products are given below.

(16) Kindly supplied by W. J. Boyle, Jr.

**3-Phenylpropionylpiperidide** (6).—To 41 mg of 1-chloro-3-phenyl-2-propanone[3] was added 4.8 ml of methanol containing 278 mg (0.67 *M*) of piperidine at 0°. The reaction was maintained at 0° for 6 hr, neutralized, and extracted. The crude organic product 34 mg, contained 40% of starting material and 60% of 3-phenylpropionylpiperidide: $\delta_{TMS}^{CHCl_3}$ 1.4–1.7 (m, 6), 3.3–3.8 (m, 4), 2.5–3.1 ($A_2B_2$, 4), 7.2 (m, 5).

**3-*p*-Tolylpropionylpiperidide** (9), **and 1-Piperidino-3-*p*-tolyl-2-propanone** (10).—To 0.8 g of 2-*p*-tolyl-3-chloro-2-propanone[3] was added a solution of 8.5 g of piperidine and 40 ml of methanol. The mixture was kept at 0° for 18 hr, washed with dilute hydrochloric acid, and rinsed with ether. The organic phase was combined, dried, and concentrated to yield 666 mg of pale yellow oil, identified as 3-*p*-tolylpropionylpiperidide: $\delta_{TMS}^{CDCl_3}$ 1.4–1.7 (m, 6), 2.3 (s, 3), 2.5–3.1 ($A_2B_2$, 4), 3.2–3.7 (m, 4), 7.0 (s, 4); $\lambda_{max}^{film}$ 3.40, 3.45, 6.05.

*Anal.* Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15, Found: C, 78.13; H, 9.28.

The amide product was hydrolyzed (water, methanol, and potassium hydroxide) to yield the known[17] 3-*p*-tolylpropionic acid, mp 115–116° (lit.[17] mp 116°). Analysis showed $\delta_{TMS}^{CDCl_3}$ 2.3 (s, 3), 2.5–3.0 ($A_2B_2$, 4), 7.0 (s, 4), 10.0 (s, 1).

The combined aqueous washings were neutralized with 10% aqueous potassium carbonate and reextracted, and the ether phase was washed five times with water. The organic layers were combined, dried, and concentrated to yield 300 mg of yellow oil identified as 1-piperidino-3-*p*-tolyl-2-propanone, **10**: $\delta_{TMS}^{CDCl_3}$ 1.3–1.7 (m, 6), 2.1–2.5 (m, 4), 2.3 (s, 3), 3.1 (s, 2), 3.7 (s, 2), 7.1 (s, 4); $\lambda_{max}^{film}$ 3.40, 5.80. An analytical sample was obtained from chromatography on silica gel (16% ether in hexane).

*Anal.* Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15. Found: C, 77.85; H, 9.36.

**1-Piperidino-1,3-diphenyl-2-propanone and 2,3-Diphenylpropionylpiperidide.**—To 0.4 g of 1-chloro-1,3-diphenyl-2-propanone[18] was added 1 ml of piperidine. The solution was kept for 15 min at 25° and then evaporated under reduced pressure. The residue was shaken with dilute hydrochloric acid and ether; the organic phase was washed five times with water, combined, dried, and concentrated to give 217 mg of a solid which was crystallized twice from ether–hexane. The crystalline product, mp 88–89°, was identified as 2,3-diphenylpropionylpiperidide: $\delta_{TMS}^{CDCl_3}$ 1.3–1.6 (m, 6), 2.8–4.2 (m, 7), 7.05 (s, 5), 7.10 (s, 5); $\lambda_{max}^{KBr}$ 3.40, 3.50, 6.15.

*Anal.* Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90. Found: C, 81.72; H, 8.12.

The basic product obtained in the manner described above was 300 mg of pale yellow oil, identified as 1-piperidino-1,3-diphenyl-2-propanone: $\delta_{TMS}^{CDCl_3}$ 1.4–1.8 (m, 6), 2.2–2.5 (m, 4), 3.8 (AB, 2, $J$ = 14 Hz), 4.0 (s, 1), 7.0–7.4 (m, 5), 7.3 (m, 5). An analytical sample was obtained by chromatography on silica gel (8% ether–hexane).

*Anal.* Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90. Found: C, 81.69; H, 8.09.

**2,3,3-Triphenylpropionylpiperidide.**—Freshly distilled piperidine (20 ml) was saturated with nitrogen for 20 min after which 600 mg of 1-bromo-1,3,3-triphenyl-2-propanone[1] was added. The solution was maintained under nitrogen for 30 min at 25° and then poured into excess aqueous hydrochloric acid and shaken with ether. The organic phase was washed twice with water, dried, and concentrated to give 635 mg of a red-brown solid which was crystallized from ether–chloroform. The crystalline product (mp 213–214°) was identified as 2,3,3-triphenylpropionylpiperidide: $\delta_{TMS}^{CDCl_3}$ 1.0–1.4 (m, 6), 3.2–3.6 (m, 4), 4.8 (AB, 2, $J$ = 12 Hz), 7.0–7.4 (m, 15); $\lambda_{max}^{KBr}$ 3.40, 6.15.

*Anal.* Calcd for $C_{26}H_{27}NO$: C, 84.51; H, 7.37. Found: C, 84.41; H, 7.35.

**Registry No.**—**1**, 6824-92-6; 1 bromo analog, 36702-36-0; **2**, 37108-06-8; **3**, 37108-07-9; **4** ($NR_2$ = piperidino), 37108-08-0; **5**, 937-38-2; **6** ($NR_2$ = piperidino), 21924-11-8; **8**, 24253-14-3; **9**, 37112-01-9; **10**, 37112-02-0; **12**, 29417-77-4; **13**, 33609-27-7; piperidine,

(17) K. Kindler and T. Li, *Chem. Ber.*, **74**, 321 (1941).

(18) A. W. Fort, *J. Amer. Chem. Soc.*, **84**, 2620 (1962). The bromo ketone which was used in the product studies was prepared by Dr. A. C. Knipe according to the method of Smith and Wilson: *J. Chem. Soc.*, 1342 (1955).

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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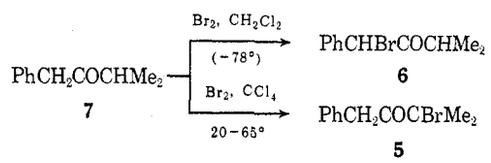
Tertiary bromide (or chloride) $C_6H_5CH_2COCMe_2X$ (**5**) reacted with 0.05 *M* NaOMe to give principally $C_6H_5CH_2COCMe_2OMe$ (**8**) plus a small yield of $C_6H_5CH_2CMe_2CO_2Me$ (**9**). With 1 *M* NaOMe the per cent of Favorskii ester (**9**) increased at the expense of α-methoxy ketone (**8**). 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.

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

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