Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.27; H, 7.34.

Elution of the band of intermediate polarity gave 20.6 mg. A second chromatography removed a small amount of the most polar material and gave 17.5 mg of white product, mp 177–179.5°. The analytical sample was obtained by recrystallization from methyl alcohol: mp 182–183.3°; λ_{max}^{KBr} 5.84, 8.41, and 8.56 μ (IVb or IVc). *Anal.* Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.04; H, 7.15.

Elution of the least polar (minor) zone gave 4.1 mg of a yellow solid. Both the R_f value and an infrared spectrum indicated that this material was identical with the lactone, mp 177.2–178°, obtained from oxidation of IIIa.

Glpc analysis[8] of the sample of ketone IIIb used in the Baeyer–Villiger oxidation (column temperature 220°, helium flow 85 ml/min) indicated the presence of 5.7% of the mp 188° ketone (retention time 7 min).

Baeyer–Villiger Oxidation of IIIc.—A solution of IIIc (720 mg, mp 142.1–142.9°), tetrahydrofuran (5 ml), 30% aqueous hydrogen peroxide (0.6 ml), and 40% aqueous selenic acid (0.04 ml) was heated at reflux for 25 hr. The solvent was removed at the aspirator and the residue was taken up in ether. The ether solution was extracted with 15% aqueous sodium carbonate solution, washed with water, and dried over magnesium sulfate. The ether was filtered and the filtrate was removed at the aspirator to give 672 mg of a pink solid (mp 144.6–149.1°, λ_{max}^{KBr} 8.51 μ) which appeared to be homogeneous. The compound was recrystallized from methyl alcohol to constant melting point (150.5–151.9°) and gave a satisfactory analysis for 2,4-diphenyl-5-hydroxycyclooctanecarboxylic acid lactone (IVd). *Anal.* Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.18, 82.01; H, 7.55, 7.53.

See Table I for ultraviolet data for saturated ketones.

TABLE I
ULTRAVIOLET ABSORPTION DATA FOR THE SATURATED KETONES

$\lambda_{max}^{C_6H_{12}}$, mμ	IIIa	IIIb	IIIc	Lit.[a] for IIIc
252–253	415	414	442	477
258–259	565	535	579	545
265	400	393	433	433

[a] See ref 2.

Registry No.—IIa, 13116-61-5; 2,4-dinitrophenylhydrazone of IIa, 13116-62-6; oxime of IIa, 13116-63-7; IIb, 13116-64-8; IIIa, 13116-65-9; IIIb, 13116-66-0; IIIc, 13116-67-1; IVa, 13116-68-2; IVb, 13116-69-3; IVc, 13116-70-6; IVd, 13116-71-7.

The Stereochemistry of Favorskii Rearrangement of Chloromethyl Ketones[1a]

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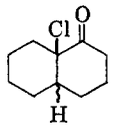
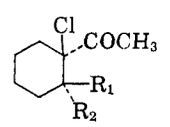
Received January 11, 1967

The *cis* and *trans* isomers of 2-methylcyclohexyl chloromethyl ketone **12** and **13** have been synthesized and allowed to react with sodium methoxide in methanol or in 1,2-dimethoxyethane. In all cases the major volatile products are the two esters **24** and **25** formed in approximately equal amounts by nonstereospecific Favorskii rearrangement. These results indicate that a planar intermediate, presumably an enolate anion, precedes further steps in the Favorskii rearrangement of these compounds.

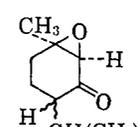
The reactions of α-chloro ketones **1** and **2** and the α,β-epoxy ketone **3** with metal alkoxides[2,3] in aprotic nonpolar solvents such as 1,2-dimethoxyethane (DME)



1a, *trans*-fused rings
b, *cis*-fused rings



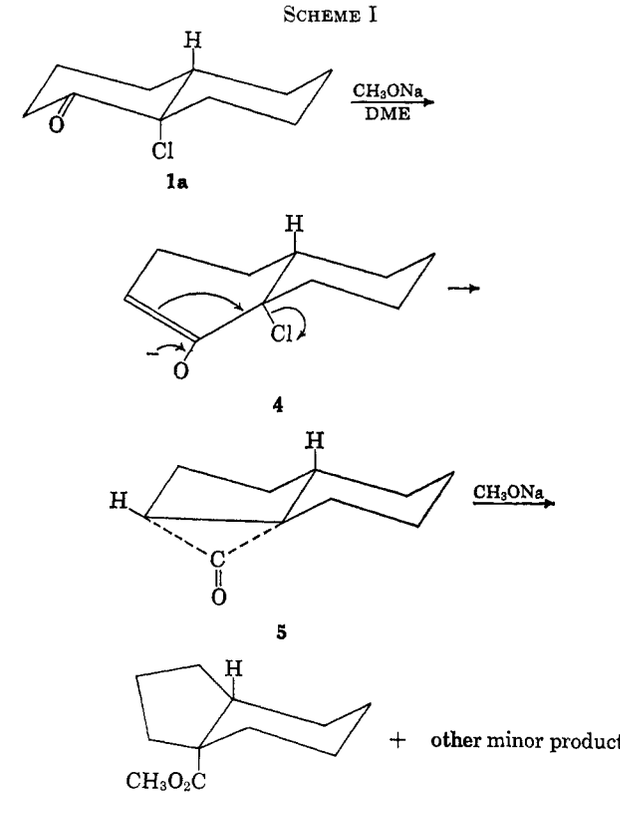
2a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$



3

were each found to yield the Favorskii rearrangement product expected from a stereospecific displacement of the α-halogen atom (or epoxide oxygen atom) as illustrated in structure **4** (Scheme I). When the more polar, protic solvent methanol was employed in the same reactions,[2] both solvolysis products (methoxy derivatives) and products of a nonstereospecific Favorskii rearrangement were obtained from ketones **2** and **3** and only solvolysis products were obtained from the decalones **1**. Since the rates of stereospecific rearrangement of the *trans*-chloro ketone **1a** (axial chlorine atom) and the *cis* isomer (mixture of axial and equatorial chlorine atoms) were approximately equal, the expecta-

SCHEME I

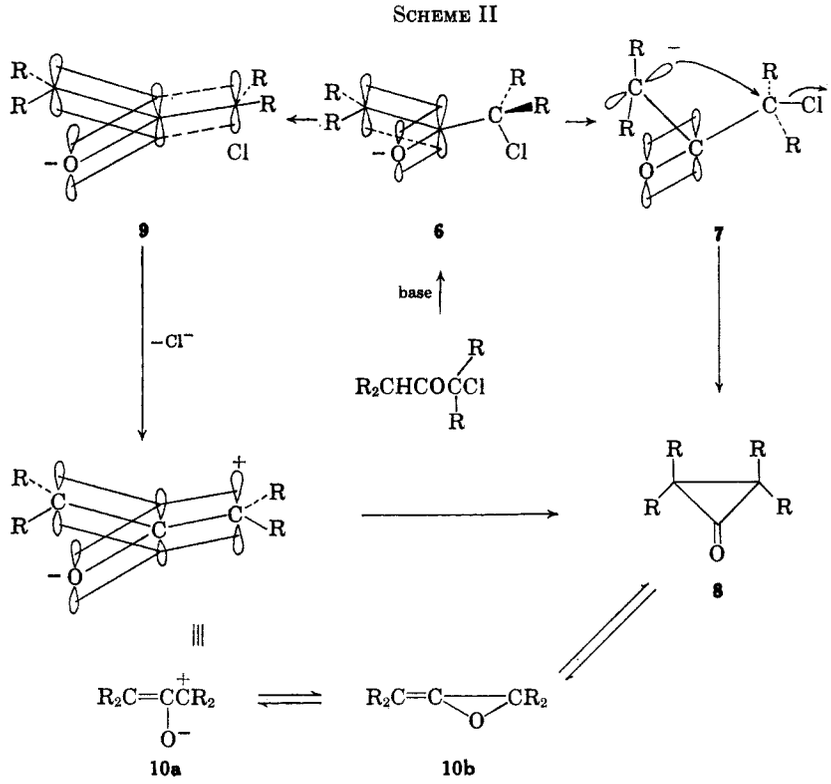


(1) (a) This research has been supported by a grant from the National Institutes of Health (Grant No. GM-08761); (b) National Institutes of Health Predoctoral Fellow, 1964–1966.

(2) (a) H. O. House and W. F. Gilmore, *J. Am. Chem. Soc.*, **83**, 3972, 3980 (1961); (b) H. O. House and H. W. Thompson, *J. Org. Chem.*, **28**, 164 (1963); (c) H. O. House and G. A. Frank, *ibid.*, **30**, 2948 (1965).

(3) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **82**, 4307 (1960).

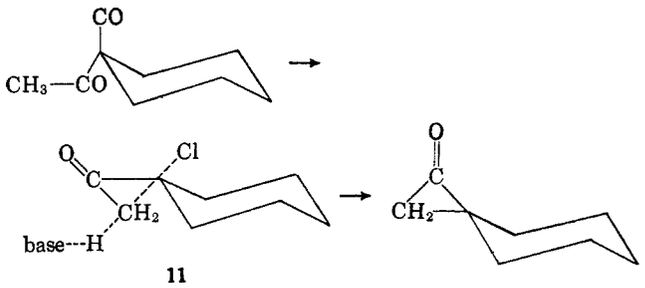
SCHEME II



tion[2b,4] that this displacement process **4** → **5** would be unfavorable when the leaving group was fixed in an axial position received no support.

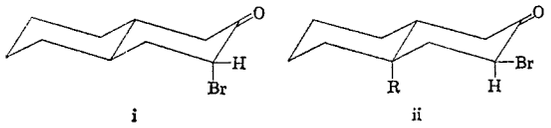
Although the stereochemical results obtained when the above rearrangements were conducted in nonpolar solvents are consistent with an intervening, intramolecular SN2-like displacement reaction, the distortion of the normal enolate anion geometry required to achieve the usual geometrical arrangement (*i.e.*, **6** → **7** → **8**) (Scheme II) for an SN2 displacement appears to pose a formidable energy barrier. It was a consideration of this difficulty which initially led to support[5] of the idea[6] that the halo enolate anion **6** first lost halide ion in the stereoelectronically favorable process (see structure **9**) to form a dipolar intermediate **10** which subsequently closed to a cyclopropanone intermediate. Although the dipolar structure **10a** or an allene epoxide **10b** could be considered as an intermediate leading to nonstereospecific Favorskii rearrangement[2] and to solvolysis products,[2,5] this planar intermediate **10** is clearly not adequate to account for stereospecific Favorskii rearrangements. As a possible means of circumventing the difficulties posed by a transition state of the type **7**, we were led to wonder whether a concerted proton abstraction–halogen displacement step of the sort pictured in structure **11** could have merit.[7,8]

Although such a 1,3-concerted elimination process has deficiencies, it would appear able to account for the



stereochemical results observed in stereospecific rearrangements without the difficulty of localizing the negative charge (as in **7**) present in a preformed enolate anion (*e.g.*, **6**). In appropriately substituted chloro ketones (*e.g.*, **12**; Scheme III), this concerted proton abstraction–displacement process would lead to the stereochemical result indicated in the accompanying equation if inversion of configuration occurs at the

(4) E. E. Smissman, T. L. Lemke, and O. Kristiansen, *J. Am. Chem. Soc.*, **88**, 334 (1966). These authors found that reaction of methyl alkoxides with the axial bromo ketone i gave only solvolysis and displacement products



i ii

while the equatorial bromo ketones ii gave solvolysis and displacement products accompanied by relatively low yields of Favorskii rearrangement products. Although these results were interpreted to indicate that Favorskii reaction was relatively slow with the axial bromide i, they can equally well be interpreted to mean that solvolysis and displacement reactions are faster with the axial bromide i than with the equatorial bromide ii. In any event, it is clear from our study of the *trans*-decalone derivative **1a** that α-halo ketones with an axial halogen atom will undergo Favorskii rearrangement in a stereospecific manner.

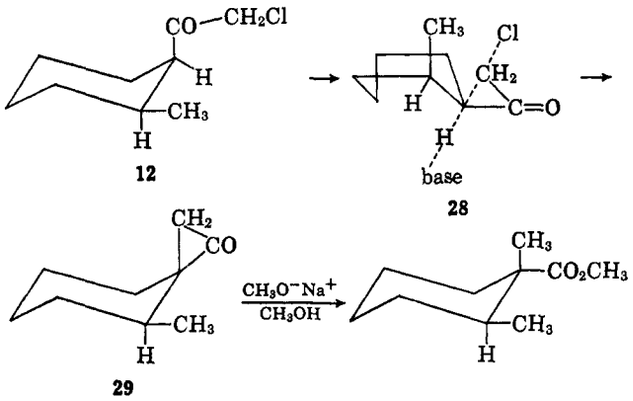
(5) (a) J. G. Burr and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954); (b) A. W. Fort, *J. Am. Chem. Soc.*, **84**, 2620, 2625, 4979 (1962).

(6) J. G. Aston and J. D. Newkirk, *ibid.*, **73**, 3900 (1951); A. A. Sacks and J. G. Aston, *ibid.*, **73**, 3902 (1951).

(7) The concerted loss of a proton and chloride anion to form a zwitterion intermediate has been suggested previously.[5b] Although we are aware of no published examples of *concerted* 1,3-dehydrohalogenation reactions leading to the formation of cyclopropane derivatives, the phenomenon of homoenolization can be regarded as an instance in which an unactivated proton is removed to permit the formation of a cyclopropane ring. See A Nickon and J. L. Lambert, *ibid.*, **88**, 1905 (1966); A. Nickon, J. L. Lambert, and J. E. Oliver, *ibid.*, **88**, 2787 (1966); and earlier papers cited.

(8) In the reaction of 1-chlorocyclohexyl methyl ketone with sodium phenoxide, incorporation of deuterium into the starting ketone was more rapid than rearrangement suggesting that under the reaction conditions employed rearrangement of the enolate anion was the rate-limiting step. See M. Charpentier-Morize, M. Mayer, and B. Tchoubar, *Bull. Soc. Chim. France*, 529 (1965).

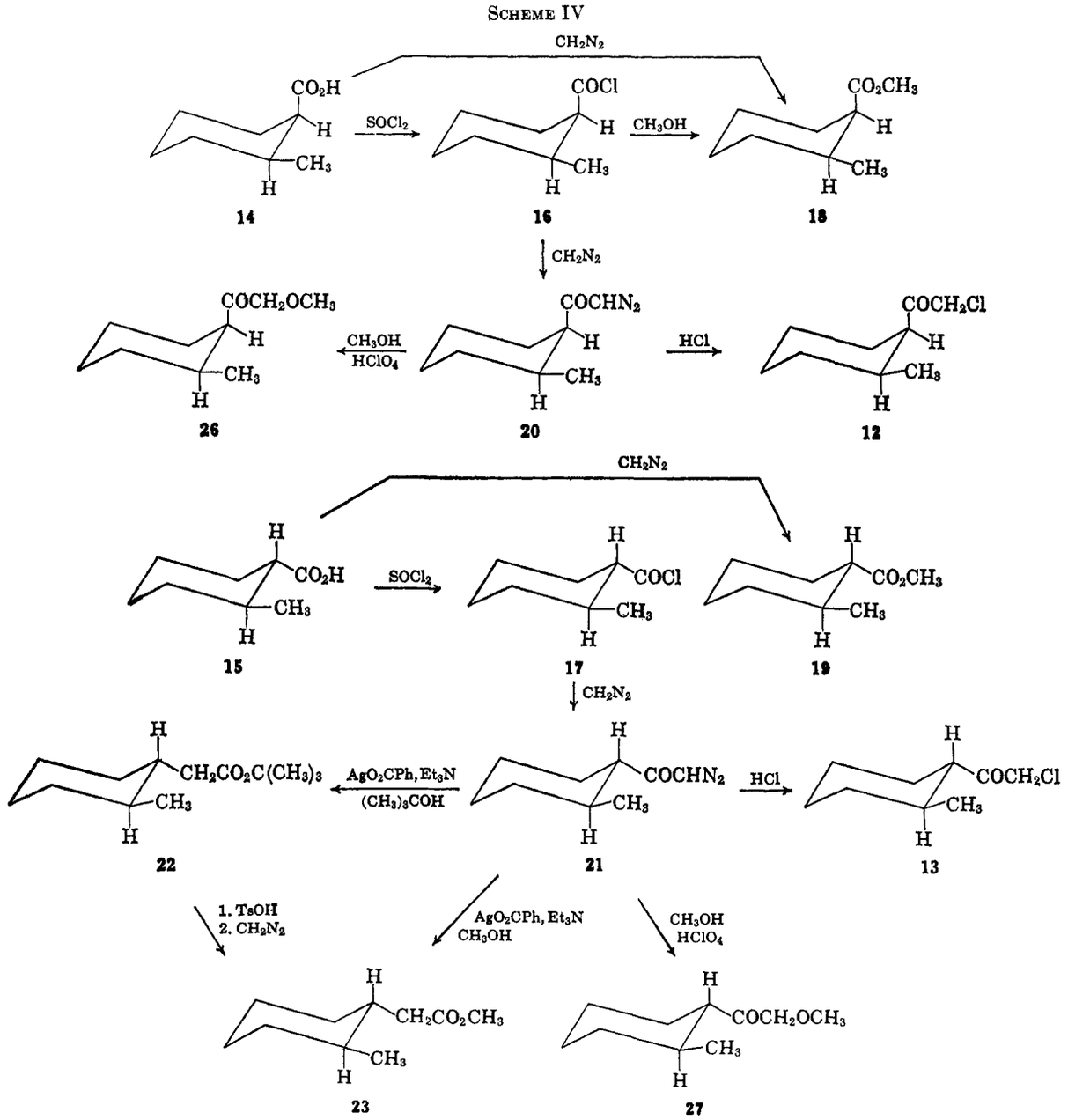
SCHEME III



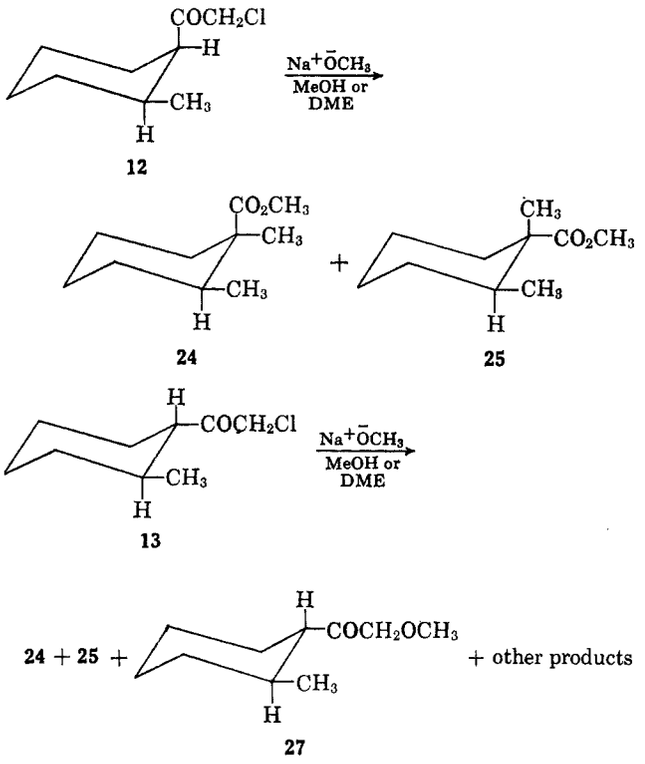
carbon atom from which the proton is removed. If the proton abstraction occurs with retention of configuration, the reaction would be stereospecific with the opposite stereochemical outcome. In either case, it is possible to test this hypothesis by examining the stereochemistry of the Favorskii rearrangement products obtained from each of the chloromethyl ketones **12** and **13**.

The syntheses of the two chloromethyl ketones **12** and **13** are summarized in Scheme IV and the results of reaction of each ketone with sodium methoxide in methanol or in 1,2-dimethoxyethane are summarized in Scheme V. Within the experimental error of our analytical method the same mixture of Favorskii products (50–54% of **24** and 46–50% of **25**) was obtained from each chloromethyl ketone **12** or **13**. Consequently, we conclude that neither ketone is forming a cyclopropanone intermediate (*e.g.*, **29**) by a concerted hydrogen abstraction–displacement reaction of the type illustrated in structure **28**. Instead, each ketone is apparently being converted to a common intermediate, presumably the enolate anion **30**, which serves as a precursor for the rearranged esters **24** and **25**. The possibility that the two chloro ketones **12** and **13** were rapidly equilibrated and then each compound rearranged stereospecifically was excluded by analyzing each reaction mixture as it progressed. The *cis*-chloro ke-

SCHEME IV



SCHEME V

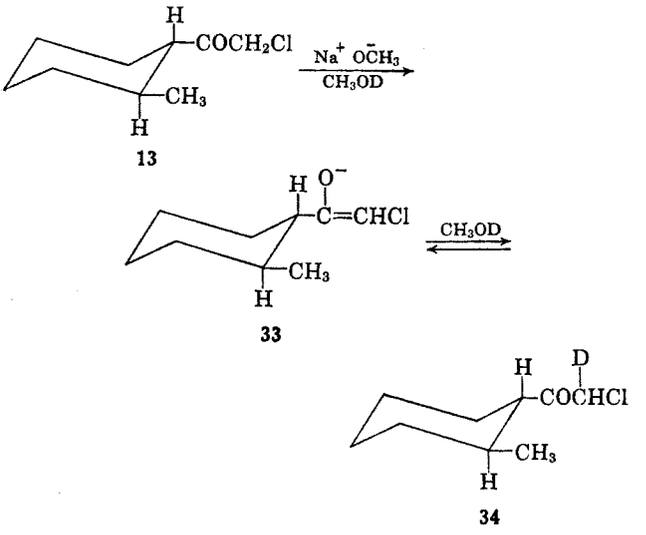


tone **12** reacted approximately 100 times more rapidly than the *trans* isomer **13** and yet no significant amount of the *trans* isomer **13** could be detected in a reaction mixture containing the *cis*-chloro ketone **12**. Consequently, neither of the products **24** and **25** which were obtained from reaction of the *cis* isomer can have been formed by a prior isomerization of this *cis* ketone **12** to the *trans* isomer **13**.

The relative rates of rearrangement of the two chloro ketones (*i.e.*, **12** >> **13**) presumably reflect the relative ease of proton abstraction as illustrated in structures **31** and **32** (Scheme VI).

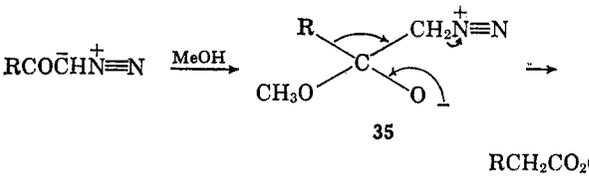
The carbonyl group must lie in a plane perpendicular to the breaking C—H bond if the carbonyl function is to assist in bond breaking by continuous overlap with the developing p orbital. For the *trans* isomer **13** to fulfill this requirement involves either creating a serious nonbonding interaction (heavy arrow in structure **31a**) in the diequatorial conformer or abstracting a proton from the energetically unfavorable diaxial conformer **31b**.[9] However, one of the axial–equatorial conformers **32b** derived from the *cis* ketone **12** is able to fulfill this requirement with relatively little interference from nonbonding interactions. The relatively slow conversion of the *trans*-chloromethyl ketone **13** to the enolate anion resulted in a lower yield of Favorskii products with the concurrent formation of a number of by-products such as the methoxy ketone **27** and others described in the experimental section. Although the protons at the chloromethyl group of the *trans* ketone **13** were apparently removed readily to form the enolate anion **33** which could be recovered as the partially deuterated ketone **34**, we have no evidence from this study which indicates what reaction products might be produced from the

(9) (a) An analogous case of resistance to enolization was reported by H. E. Zimmerman, *J. Am. Chem. Soc.*, **79**, 6554 (1957). (b) This phenomenon has been generalized and given the name $A^{1,3}$ strain by F. Johnson and S. K. Malhotra, *ibid.*, **87**, 5492, 5493 (1965).



chloro enolate anion **33**. Further discussion of this point will be deferred until studies now in progress are completed.

In an ancillary investigation, the silver-catalyzed decomposition of the diazo ketone **21** was examined in both *t*-butyl alcohol and methyl alcohol. This study was prompted by earlier observations[10] that hindered diazo ketones yielded products of the sort to be expected if an intermediate keto carbene had undergone C–H bond insertion in addition to the expected Wolff rearrangement. The suggestion was offered[11] that normal Wolff rearrangements involved decomposition of the diazo ketone hemiketal (*e.g.*, **35**) and that hindrance at the carbonyl function would favor the formation



of an intermediate keto carbene which could undergo other reactions as well as rearrangement. Although the diazo ketone **21** is relatively hindered and would not be expected to yield any significant portion of a *t*-butoxy hemiketal, we found no evidence for the presence of abnormal products in either *t*-butyl alcohol or methanol. In particular, neither of the Favorskii esters **24** or **25** could be detected in the crude methyl ester products derived from either of the diazo ketone rearrangements.

Experimental Section[12]

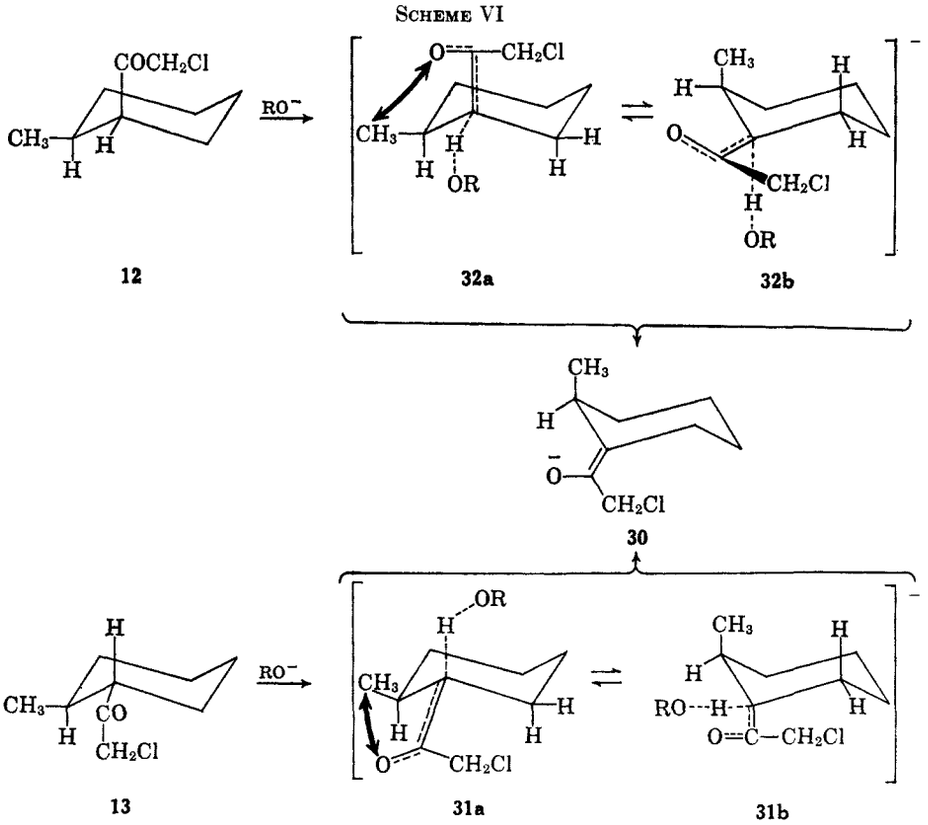
Preparation of the 2-Methylcyclohexanecarboxylic Acids 14 and 15.—Hydrogenation of an acetic acid solution of *o*-toluic acid

(10) (a) A. L. Wilds, J. V. D. Berghe, C. H. Winestock, R. L. von Trebra and N. F. Woolsey, *ibid.*, **84**, 1503 (1962); (b) H. O. House, S. G. Boots, and V. K. Jones, *J. Org. Chem.*, **30**, 2519 (1965).

(11) A. L. Wilds, N. F. Woolsey, J. V. D. Berghe, and C. H. Winestock, *Tetrahedron Letters*, 4841 (1965).

(12) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nuclear magnetic resonance (nmr) spectra were determined at 60 Mc with a Varian, Model A-60, nmr spectrometer. The chemical shift values are expressed either in cycles per second or δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained with a CEC, Model 21-130 mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates.

SCHEME VI



over the catalyst from platinum oxide at room temperature and 50-psi hydrogen pressure followed by fractional distillation of the product afforded 89.5% of the crude *cis* acid **14**, bp 77–78° (0.25 mm), mp 19–21°, n^{24}D 1.4631 (lit.[13] n^{20}D 1.4644). Reaction of this crude product with piperazine in acetone solution afforded a piperazine salt which was recrystallized from acetone to separate the **piperazine salt of the *cis* acid 14** as white prisms, mp 94–96° (lit.[13] mp 97°), recovery 80%. The liquid acid **14** recovered from this piperazine salt was distilled in a short-path still and then esterified with excess ethereal diazomethane. The resulting neutral product contained[14] approximately 5% of the *trans* ester **19** (eluted first) and 95% of the *cis* ester **18** (eluted second). Collection from the gas chromatograph[15] separated a pure sample of the *cis* ester **18**:[16] infrared spectrum[17] 1740 cm^{-1} (ester C=O); mass spectrum, molecular ion peak at *m/e* 156, abundant fragment peaks at *m/e* 124, 87, 55, and 41.

Reaction of butadiene with *trans*-crotonic acid yielded a product which was repeatedly recrystallized from pentane to separate ***trans*-2-methylcyclohex-4-ene-1-carboxylic acid** as white prisms, mp 60–64° (lit.[18] mp 64–65°). A solution of 828 mg (5.9 mmoles) of this unsaturated acid in 2.0 ml of ethanol was hydrogenated at room temperature and atmospheric pressure over the catalyst from 144 mg of platinum oxide. After 1 hr the hydrogen uptake (159 ml or 1.1 equiv) was complete and the reaction mixture was filtered and concentrated to leave 833 mg of the crude *trans* acid **15**, mp 48–53°. A mixture of this crude acid with 172 mg (3.0 mmoles) of piperazine was dissolved in a minimum volume of boiling acetone and allowed to cool. The **piperazine salt of the *trans* acid 15** separated as 733 mg (67%) of white needles, mp 133.5–136° (lit.[13] mp 135–136°).

A more satisfactory preparative route for *trans* acid **15** involved the base-catalyzed isomerization of the crude *cis* acid **14**.[19] The crude product obtained from hydrogenation of 20 g (0.15 mole) of *o*-toluic acid over a platinum catalyst as previously described was dissolved in 200 ml of ethylene glycol containing 121 g of potassium hydroxide. After the resulting solution had been refluxed for 6 hr, it was cooled, diluted with water, acidified with hydrochloric acid, and extracted with three portions of methylene chloride. The combined organic layers were extracted with aqueous sodium bicarbonate and this bicarbonate extract was acidified and extracted with methylene chloride. This final organic extract was concentrated under reduced pressure to leave 18.8 g of the crude *trans* acid, mp 40–53°, which was converted to its piperazine salt. Recrystallization of this salt from acetone separated 17.51 g (63%) of the **piperazine salt of the *trans* acid 15**, mp 132–135° (lit.[13] mp 135–136°). A 500-mg (1.35 mmole) portion of this piperazine salt was converted to the *trans* acid **15**, mp 52–53° (lit.[13] mp 51–52°), yield 342 mg (89%). Sublimation (25° and 0.005 mm) of this acid **15** did not alter its melting point. The samples of the *trans* acid **15** obtained by hydrogenation of the cyclohexene derivative and by base-catalyzed isomerization were shown to be identical by comparison of their infrared spectra. Reaction of the *trans* acid **15** with excess ethereal diazomethane afforded the pure[14] *trans* ester **19**: infrared spectrum,[17] 1740 cm^{-1} (ester C=O); mass spectrum, molecular ion peak at *m/e* 156, abundant fragment peaks at *m/e* 124, 97, 87, 55, and 41.

Preparation of the *cis*-Chloromethyl Ketone 12.—A solution of 2.70 g (19.3 mmoles) of the acid **14** and 1.8 ml (2.9 g or 24 mmoles) of thionyl chloride in 10 ml of benzene was allowed to stand overnight at room temperature and then distilled to separate 1.986 g (63%) of the *cis* acid chloride **16**, bp 40–41° (1.0 mm). A portion of this product was added to excess methanol; the neutral product recovered from this solution contained[14] the *cis* ester **18** contaminated with not more than 5% of the *trans* isomer **19**. A sample of the acid chloride **16** was redistilled: n^{25}D 1.4700; infrared spectrum,[17] 1800 cm^{-1} (acid chloride C=O); nuclear magnetic resonance (nmr) spectrum,[17] δ 2.92 (1 H multiplet, CHCOCl), 1.02 (3 H doublet with J = 7 cps, CH_3C), and 1.2–2.7 (9 H multiplet, aliphatic CH); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 81, 67, 55, 41, and 39.

A solution of 2.568 g (16.0 mmoles) of the *cis* acid chloride **16** and 43.5 mmoles of diazomethane in 700 ml of ether was allowed to stand at 0° for 33 hr and then concentrated to leave the crude

(13) A. K. Macbeth, J. A. Mills, and D. H. Simmonds, *J. Chem. Soc.*, 1011 (1949).

(14) A gas chromatography column packed with LAC-728 (diethylene glycol succinate) suspended on Chromosorb P was employed for this analysis.

(15) A gas chromatography column packed with Apiezon M suspended on Chromosorb G was employed for this analysis.

(16) (a) J. S. Meek and J. W. Ragsdale [*J. Am. Chem. Soc.*, **70**, 2502 (1948)] reported bp 181–183° (623 mm), n^{20}D 1.432 for the *cis* ester **18**; (b) A. Skita [*Ann.*, **431**, 1 (1923)] reported bp 191.5–192°, n^{20}D 1.4476, for the *cis* ester **18** and bp 190–190.5°, n^{20}D 1.4440, for the *trans* ester **19**.

(17) Determined as a solution in carbon tetrachloride.

(18) N. Green and M. Beroza, *J. Org. Chem.*, **24**, 761 (1959).

(19) Use of this procedure for the isomerization of the 4-*t*-butylcyclohexanecarboxylic acids has been described previously: M. Tichy, J. Jonas, and J. Sicher, *Collection Czech. Chem. Comm.*, **24**, 3434 (1959).

product (2.704 g of yellow liquid): infrared spectrum,[20] 2100 (strong, diazo grouping), 1790 (weak, acid chloride C=O), and 1730 cm^{-1} (weak, chloromethyl ketone C=O). A solution of the crude product in pentane was repeatedly recrystallized at Dry-Ice temperature to separate 2.20 g (83%) of the ***cis*-diazo ketone 20** as a yellow liquid which solidified at *ca.* −10°; infrared spectrum,[20] 2095 and 1640 cm^{-1} (diazo ketone bands); ultraviolet maximum,[21] 250 mμ (ε 9600) and 272 mμ (ε 6900) (sh); nmr spectrum,[17] δ 5.26 (1 H singlet, $COCHN_2$), 0.90 (3 H doublet with J = 6.5 cps, CH_3C), and 1.1–2.6 (10 H multiplet, aliphatic CH); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 94, 81, 68, 55, and 41.

A solution of 1.047 g (6.55 mmoles) of the *cis*-diazo ketone **20** in 25 ml of pentane was cooled in an ice bath and hydrogen chloride gas was passed through the solution until the yellow color of the diazo ketone was discharged. The solution was concentrated under reduced pressure and the residual light orange oil (1.119 g) was distilled in a short-path still (bath temperature 80–90° and 0.2-mm pressure). This distillate, 0.763 g (65.5%) of colorless liquid, contained[22] *ca.* 95% of the *cis*-chloro ketone **12** (eluted second) accompanied by *ca.* 5% of the *trans*-chloro ketone **13** (eluted first). A sample of the *cis* isomer **12** was collected:[15] infrared spectrum,[17] 1730 and 1715 cm^{-1} (C=O of two conformations of an α-chloro ketone); ultraviolet maximum,[21] 288 mμ (ε 76); nmr spectrum,[17] δ 3.92 (2 H singlet, $COCH_2Cl$), 2.85 (1 H multiplet, >CHCO), 0.80 (3 H doublet with J = 7 cps, CH_3C), and 1.0–2.5 (9 H multiplet, aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 174 (^{35}Cl isotope), abundant fragment peaks at *m/e* 125, 97, 55, 41, and 39.

Anal. Calcd for $C_9H_{15}ClO$: C, 61.88; H, 8.66; Cl, 20.30. Found: C, 61.83; H, 8.60; Cl, 20.45.

Preparation of the *trans*-Chloromethyl Ketone 13.—After a solution of 3.393 g (23.9 mmoles) of the *trans* acid **15** and 3.52 ml (48 mmoles) of thionyl chloride in 5 ml of methylene chloride had been allowed to stand at room temperature for 20 hr, the mixture was concentrated and distilled to separate 3.391 g (88.5%) of the *trans* acid chloride **17**: bp 41–42° (1.2 mm); $n^{25}D$ 1.4635; infrared spectrum,[20] 1790 cm^{-1} (acid chloride C=O); nmr spectrum,[17] δ 1.00 (3 H doublet, J = 6 cps, CH_3C) and 0.9–2.6 (10 H multiplet, aliphatic CH); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 124, 97, 81, 67, 55, 41, and 39.

After a solution of 3.486 g (21.7 mmoles) of the *trans* acid chloride **17** and 80 mmoles of diazomethane in 500 ml of ether had been allowed to stand at 0° for 69 hr, the solution was concentrated to leave 3.952 g of crude diazo ketone, mp 45–47°. Recrystallization of this material from pentane at Dry Ice temperatures separated 2.568 g (71.5%) of the ***trans*-diazo ketone 21** as yellow plates, mp 47.5–48.5°. An additional 0.384 g (total yield 82%) of less pure product, mp 42–44°, was recovered from the mother liquors. Sublimation (27° and 0.05-mm pressure) of a portion of the diazo ketone raised the melting point to 48–49°; infrared spectrum,[17] 2110 and 1650 cm^{-1} (diazo ketone); ultraviolet maximum,[21] 250 mμ (ε 10,600) and 271 mμ (ε 8100) (sh); nmr spectrum,[17] δ 5.33 (1 H singlet, $COCHN_2$), 0.87 (3 H doublet with J = 5.5 cps, CH_3C), and 0.9–2.1 (10 H multiplet, aliphatic CH); mass spectrum, no molecular ion peak, abundant fragment peaks at *m/e* 94, 81, 68, 55, 41, and 39.

Hydrogen chloride gas was passed through a cold (0°) solution of 175 mg (1.05 mmole) of the *trans*-diazo ketone **21** in 10 ml of pentane until the yellow color of the diazo ketone was discharged. After the resulting solution had been concentrated, distillation of the residual oil (191 mg) in a short-path still separated 148 mg (80.5%) of the *trans*-chloro ketone **13**, $n^{24}D$ 1.4759. This material, which melted at approximately 10° and exhibited only one gas chromatographic peak[22] indicating the absence of the more slowly eluted *cis* isomer **12** as a contaminant, has the following spectral properties: infrared spectrum,[20] 1735 and 1720 (shoulder) cm^{-1} (C=O of two conformations of an α-chloro ketone); ultraviolet maximum,[21] 286 mμ (ε 41); nmr spectrum,[17] δ 4.01 (2 H singlet, $COCH_2Cl$), 0.84 (3 H doublet with J = 6 cps, CH_3C), and 1.0–2.6 (10 H multiplet, aliphatic CH); mass spectrum, weak molecular ion peak at *m/e* 174 (^{35}Cl isotope), abundant fragment peaks at *m/e* 125, 97, 55, 41, and 39.

Anal. Calcd for $C_9H_{15}ClO$: C, 61.88; H, 8.66; Cl, 20.30. Found: C, 62.15; H, 8.63; Cl, 20.42.

Other Reactions of the Diazo Ketones 20 and 21.—To a solution of 409 mg (2.46 mmoles) of the *trans*-diazo ketone **21** in 4.0 ml of methanol was added dropwise and with stirring, a silver catalyst prepared by solution of 50 mg of silver benzoate in 0.5 ml of triethylamine.[23] Addition of catalyst solution was stopped when no further gas evolution was apparent and the resulting mixture was partitioned between ether and aqueous ammonium chloride. Short-path distillation (85° and 0.01 mm) of the material obtained from the ether extract afforded 372 mg (89%) of colorless liquid which contained[15] the ester **23** accompanied by several minor components. The pure ester was collected:[15] infrared spectrum,[17] 1740 cm^{-1} (ester C=O); nmr spectrum,[17] δ 3.54 (3 H singlet, OCH_3) and 0.8–2.7 (15 H multiplet, aliphatic CH).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; mol wt, 170. Found: C, 70.79; H, 10.67; mol wt, 170 (mass spectrum).

The same procedure was repeated with a solution of 504 mg (3.04 mmoles) of the *trans*-diazo ketone **21** in 5 ml of *t*-butyl alcohol. A solution of the crude neutral product (600 mg, presumably the *t*-butyl ester **22**) in 5 ml of benzene containing 10 mg of *p*-toluenesulfonic acid was refluxed for 17.5 hr and then the crude acidic product was separated and esterified with excess ethereal diazomethane. The resulting neutral product contained[15] primarily the ester **23** accompanied by minor higher boiling products. However, neither of the esters **24** or **25** (eluted[15] more rapidly than **23**) could be detected. A collected[15] sample of the major product was identified as ester **23** by comparison of infrared spectra and gas chromatographic retention times.

A solution of 200 mg (1.20 mmole) of the *trans*-diazo ketone **21** in 4.5 ml of methanol was treated with 1 drop of aqueous 70% perchloric acid and then stirred for 10 min. After the reaction mixture had been partitioned between water and ether, the ethereal phase was dried and concentrated to leave an oil which contained[24] the *trans*-methoxy ketone **27** (eluted first) accompanied by several per cent of the *cis*-methoxy ketone **26** (eluted second). The *trans* isomer **27** was collected:[24] infrared spectrum,[17] 1715 and 1730 cm^{-1} (two conformations of an α-methoxy ketone); nmr spectrum,[17] δ 3.82 (2 H singlet, $COCH_2O$), 3.36 (3 H singlet, OCH_3), 0.78 (3 H doublet with J = 6 cps, CH_3C), and 0.8–2.5 (10 H multiplet, aliphatic CH).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; mol wt, 170. Found: C, 70.27; H, 10.70; mol wt, 170 (mass spectrum).

The same procedure applied to 100 mg (0.60 mmole) of the *cis*-diazo ketone **20** afforded 128 mg of a crude liquid product which contained[24] the *cis*-methoxy ketone **26** accompanied by several per cent of the *trans* isomer **27**. A sample of the *cis* isomer **26** was collected:[24] infrared spectrum,[17] 1710 and 1725 (sh) cm^{-1} (two conformations of an α-methoxy ketone), nmr spectrum,[17] δ 3.80 (2 H singlet, $COCH_2O$), 3.33 (3 H singlet, OCH_3), 0.83 (2 H doublet with J = 6.5 cps, CH_3C), and 1.1–3.0 (10 H multiplet, aliphatic CH).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; mol wt, 170. Found: C, 70.44; H, 10.72; mol wt, 170 (mass spectrum).

General Procedure for Favorskii Rearrangements.—The reaction solvents were either a methanolic sodium methoxide solution which was 0.985 *M* in sodium methoxide or 1,2-dimethoxyethane which contained finely divided sodium methoxide (from sodium hydride and methanol) at an average concentration of 1.25 mmoles/ml. Two milliliters (1.97–2.5 mmoles of NaOMe) of one of these two mixtures was added to a mixture of a weighed amount of pentamethylbenzene (20–100 mg as an internal standard) and one of the chloro ketones **12** or **13** (0.1–0.3 mmole). The resulting mixtures were stirred for the times specified in Table I and then aliquots were removed and partitioned between water and methylene chloride. The organic layers were separated, dried, concentrated, and analyzed, employing a gas chromatographic apparatus[15] which had been previously calibrated with known mixtures of the internal standard, the chloromethyl ketones **12** and **13**, the Favorskii esters **24** and **25**, and the methoxy ketone **27**. The calculated yields of products for various runs are summarized in Table I.

From reactions of the *cis*-chloromethyl ketone **12** only the esters **24** and **25** and the chloro ketones **12** and **13** were detected. Re-

(20) Determined on a thin film of pure liquid.

(21) Determined as a solution in 95% ethanol.

(22) A gas chromatography column packed with silicone gum, SE-30 suspended on Chromosorb P was employed for this analysis.

(23) The procedure of M. S. Newman and P. F. Beal, *J. Am. Chem. Soc.*, **72**, 5163 (1950).

(24) A gas chromatography column packed with Carbowax, 20 M, suspended on Chromosorb P was employed for this analysis.

TABLE I

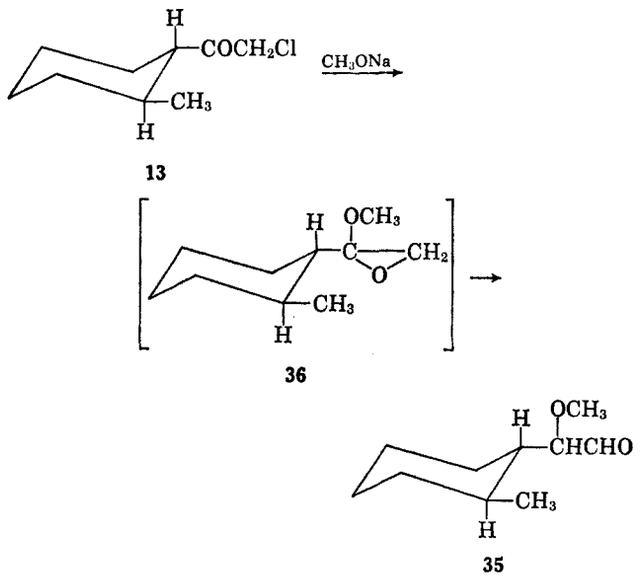
REACTIONS OF THE CHLOROMETHYL KETONES 12 AND 13 WITH SODIUM METHOXIDE

Ketone	Solvent	Reaction time, min	Products, % yield 19	24	25	35	27	13	12
12[a]	DME	0.3	...	5	4	..	..	...	57
		1.0	...	11	11	..	..	...	37
		2.0	...	13	11	..	..	...	27
		5.0	...	20	18	..	..	...	2.5
		30	...	21	18	..	..	...	...
12[b]	DME	5	...	38	34	..	..	...	...
12[a]	MeOH	0.3	...	10	12	..	..	8	54
		1.0	...	31	30	..	..	12	26
		2.0	...	42	41	..	..	13	4
		6.0	...	47	43	..	..	10	...
12[b]	MeOH	3.0	...	46	42	..	..	...	...
13[a]	DME	30	...	3	3	..	..	59	...
		60	<2	5	5	3	3	32	...
		120	<2	7	7	4	10	16	...
		240	<2	8	8	4	13	2	...
		480	<2	8	8	5	4	...	...
13[b]	DME	310	2	19	19	2	6	...	...
13[a]	MeOH	0.3	...	..	..	..	..	100	...
		1.0	...	1	1	..	..	97	...
		6.0	<2	11	12	..	..	65	...
		30	<2	29	27	2	2	19	...
		210	<2	40	37	4	5	...	...
13[b]	MeOH	55	...	28	27	3	1	...	...

[a] In these runs aliquots were removed from the reaction mixture and analyzed at the times indicated. [b] In these runs the entire reaction mixture was subjected to the isolation and analysis procedure after the reaction times specified.

action mixtures from the *trans*-chloro ketone **13** contained, in addition to the esters **24** (eluted second) and **25** (eluted third), low yields (2–5%) of the ester **19** (eluted first), a product believed to be the methoxy aldehyde **35** (eluted fourth), a very minor unknown component eluted fifth, the *trans*-methoxy ketone **27** (eluted sixth), and the unchanged chloro ketone **13** (eluted seventh). Collected[15] samples of the esters **19**, **24**, and **25** and the methoxy ketone **27** were identified with previously described[2a] authentic samples by comparison of retention times, infrared spectra, and mass spectra. We were unable to obtain a sufficient quantity of the component thought to be the methoxy aldehyde **35** (Scheme VII) derived from the intermediate epoxy ether **36** by rearrangement for complete characterization. However, the following data obtained on collected[15] samples support our tentative structural assignment: infrared spectrum,[17] 2690 (aldehyde CH) and 1730 cm^{-1} (C=O); nmr spectrum,[20] δ 9.66 (1 H doublet with J = 1.5 cps, CHO), 3.51 (3 H singlet, OCH_3), 3.4–3.8 (1 H, multiplet, >CH–O), and 0.8–2.2 (13 H, multiplet, aliphatic CH); mass spectrum, no molecular ion peak, abundant fragment peaks at m/e 141 (M − CHO), 109, 67, 55, 45, 41, and 39. Examination of the aqueous extracts from several reactions indicated that no significant amounts of acidic products were being formed. The remaining material not accounted for by the analyses in Table I was mainly present as colored, nonvolatile by-products present in the neutral fraction.

SCHEME VII



A sodium methoxide solution prepared from 85 mg (3.7 mg-atoms) of sodium and 4.1 ml of methanol-d_1 was added to 105 mg (0.602 mmole) of the *trans*-chloromethyl ketone **13**. The resulting solution was stirred for 2 min and then partitioned between methylene chloride and an aqueous solution buffered to pH 4 with an acetate buffer. The organic phase was separated, dried, concentrated, and distilled in a short-path still (60° at 0.05 mm) to separate a colorless liquid which contained[15] 95% of the starting ketone **13** and 5% of a mixture of esters **24** and **25**. The nmr spectrum of this product had a signal at δ 3.96 ($COCH_2Cl$) which corresponded in area to 47% of two protons. We therefore conclude that exchange of deuterium for hydrogen was approximately one-half complete under these conditions.

Registry No.—**12**, 13064-84-1; **13**, 13064-88-5; **14**, 7076-91-7; **15**, 13064-90-9; **16**, 13064-91-0; **17**, 13064-92-1; **18**, 7605-55-2; **19**, 13064-94-3; **20**, 13064-95-4; **21**, 13064-96-5; **23**, 13094-90-1; **26**, 13085-20-6; **27**, 13064-97-6; **35**, 13064-98-7.