

Preparation of VIII.—To 10 ml of water was added 0.306 g (0.00114 mole) of *erythro*-1,2-diphenyl-2-chloroethylamine hydrochloride prepared from reaction of *trans*-2,3-diphenylaziridine and hydrogen chloride according to the procedure of Weissberger.¹⁴ A solution of 55.9 mg of sodium hydroxide in 5 ml of water was added and the mixture extracted four times with 40-ml portions of ether. The ether extracts were dried for a few min over anhydrous magnesium sulfate and filtered. The ether filtrate was added to 0.121 g of triethylamine in 10 ml of dry ether. To this solution was added 0.212 g of *p*-nitrobenzoyl chloride dissolved in 10 ml of dry ether. The precipitate was filtered and the ether evaporated. The crude VIII weighed 0.415 g (95.6%) and melted at 159–161°. Several recrystallizations from absolute ethanol gave VIII, mp 166–168°.

Anal. Calcd for C₂₁H₁₇ClN₂O₃: C, 66.22; H, 4.50; N, 7.33. Found: C, 65.99; H, 4.49; N, 7.44.

Conversion of VIII to VI.—The same procedure and the same quantities of reagents were used as for the conversion of IX to VII. The *erythro* isomer VII formed VI in 95% yield and melted at 116–119°. The infrared spectrum of crude VI was identical with an authentic sample.

***erythro*-N-1,2-Diphenyl-2-hydroxyethyl-*p*-nitrobenzamide.**—A solution of 11.13 (0.0599 mole) of *p*-nitrobenzoyl chloride dissolved in 100 ml of benzene was added portionwise to a solution of 12.80 g (0.0600 mole) of *erythro*-1,2-diphenyl-2-hydroxyethylamine and 6.06 g (0.0600 mole) of triethylamine in 250 ml of benzene. The reaction mixture was allowed to stand overnight and then filtered. The solid residue was treated with water and filtered again. The crude product weighed 15.0 g (69%) and

was recrystallized from ethanol. The recrystallized material melted at 212–213°.

Anal. Calcd for C₂₁H₁₈N₂O₄: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.78; H, 5.03; N, 7.73.

***threo*-N-1,2-Diphenyl-2-hydroxyethyl-*p*-nitrobenzamide** was prepared in the same manner as the *erythro* isomer in 68% yield. Recrystallization from absolute ethanol gave material melting at 217.5–219.5°.

Anal. Calcd for C₂₁H₁₈N₂O₄: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.11; H, 5.08; N, 7.68.

Conversion of *threo*-N-1,2-Diphenyl-2-hydroxyethyl-*p*-nitrobenzamide to VI.—To 20 ml of cooled concentrated sulfuric acid was added gradually over 0.5 hr with stirring 4.0 g (0.011 mole) of the *threo* amide. After another 10 min at room temperature the reaction mixture was poured over 300 g of ice; the mixture was stirred vigorously and neutralized with 30% sodium hydroxide solution. The mixture was filtered and the solid residue stirred with water and filtered again. Recrystallization from methanol gave 3.0 g (79%) of VI, mp 122–124°.

Conversion of *erythro*-N-1,2-diphenyl-2-hydroxyethyl-*p*-nitrobenzamide to VI was carried out in the same manner as the acidolysis of the *threo* isomer. The yield of recrystallized VI, mp 122–124°, was 40%.

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Notes

Acetal Formation for Cyclic Ketones¹

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A previous study of neat cyclohexanone-methanol mixtures demonstrated that in acidic media the predominant reaction is acetal formation.³ Recently it has been shown that cyclohexanone and 3- and 4-alkyl substituted cyclohexanones form a small amount of hemiacetal (about 10–12%) along with a large amount of acetal in dilute methanol solutions. Other cyclic and acyclic ketones and some aromatic aldehydes do not form significant amounts of hemiacetals.⁴

During earlier studies on the acetal equilibrium we evaluated the use of short-path quartz cells (down to 0.025 mm) to measure the absorbances of carbonyl compounds in neat mixtures with methanol. This permitted us to study more concentrated solutions than have been previously reported for such systems. Thus we could decide whether hemiacetal or acetal

equilibrium was predominant since in concentrated solutions both equilibria are quite sensitive to concentration changes, while in very dilute solutions the values tend to be constant whether calculated for hemiacetal or acetal. Furthermore, in dilute solutions, errors for acetal formation are magnified in the absence of accurate analyses for water content in the reactants. Although the short-path measurements lacked versatility, we did complete a study of the effect of ring size of ketones upon the extent of formation of methyl acetals and these results are reported.

The solutions of ketones in neutral methanol were found to follow Beer's law for fairly wide concentration ranges. Generally we used from 0.3 to 1.5 *M* ketone in methanol. From the known weight of reactants, from the measured concentration of the ketone by ultraviolet analysis, and from the stoichiometry for acetal formation, the mole fraction equilibrium constants were calculated. The results are summarized in Table I. We have also calculated mole-fraction equilibrium constants for hemiacetal formation which are shown in the last column of Table I.

The calculated K_x values for acetal formation are sensibly constant for all of the ketones studied while K_x for hemiacetal change significantly, and we conclude that the predominant reaction is acetal formation. There have been reports that ketones form only hemiacetals^{5–7} and other reports that ketones form

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TABLE I
EQUILIBRIUM CONSTANTS (K_x) FOR ACETAL FORMATION FOR KETONES AND METHANOL

Ketone	Moles of ketones ^a $\times 10^2$	Mole ratio, methanol/ 1-ketone	Absorbance, λ (m μ) ^b			$K_x \times 10^4$ ^c		Hemi-acetal, K_x , ^e 25°
			Neutral soln	10°	25°	10° (av)	25° (av) ^d	
Acetone	6.58	7.55	1.040 (280)	0.797	0.854	14.3	8.1	0.28
	3.61	15.3	0.585	0.375	0.416	14.9 (15.3)	8.6 (8.6)	0.43
	1.99	29.0	0.322	0.168	0.198	16.7	9.1	0.66
Cyclobutanone	3.92	13.8	0.865 (282)	0.192	0.222	268 (277)	199 (199)	3.0
	0.896	66.5	0.199	0.010	0.014	236	199	13.6
Cyclopentanone	3.33	16.2	0.738 (288)	0.499	0.540	10.8	6.8	0.39
	2.22	25.4	0.495	0.296	0.329	11.4 (11.7)	7.1 (7.3)	0.48
	0.91	65.5	0.201	0.084	0.100	12.9	8.0	1.02
Cyclohexanone	7.55	5.57	1.532 (288)	0.564	0.708	347	189	1.43
	6.63	6.74	1.332	0.447	0.582	321	172	1.54
	4.12	12.2	0.838	0.169	0.497	342 (341)	172 (175)	2.50
	2.52	21.7	0.499	0.063	0.204	340	170	4.15
	1.44	39.4	0.278	0.020	0.071	358	173	7.22
Cycloheptanone	1.51	37.6	0.366 (288)	0.301	0.306	1.12	0.88 (0.98)	0.20
	0.93	63.2	0.227	0.168	0.178	1.41	0.91	0.27
Cyclooctanone	2.36	22.8	0.470 (288)	...	0.452	...	0.067 (0.069)	0.040
	1.57	35.8	0.312	...	0.297	...	0.071	0.052
Cyclopentadecanone	1.37	38.8	0.564 (281)	0.468	0.495	0.93	0.45 (0.43)	0.12
	0.492	118.3	0.202	...	0.162	...	0.41	0.25

^a The total volume of reaction mixture was 25 ml in each case. ^b All measurements were made with a cell of approximately 0.3-mm path length. ^c $K_x = X_{\text{acetal}}X_{\text{water}}/X_{\text{ketone}}X_{\text{methanol}}$, where X = mole fraction of the component. ^d The average deviation for K_x for acetal formation for the 25° data was 3.2% over-all. ^e The over-all average deviation was 35.7% for the 25° data for hemiacetal formation.

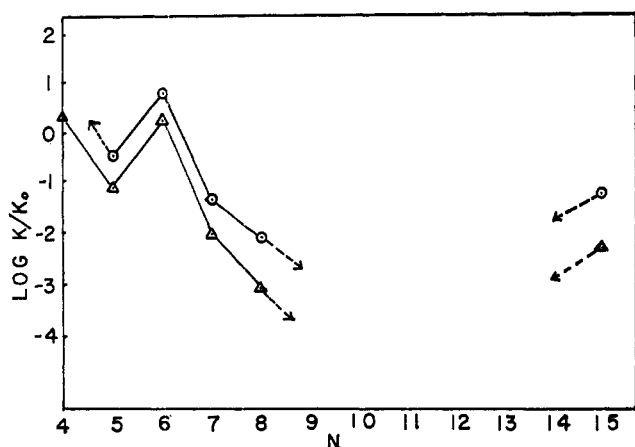


Figure 1.—Log K/K_0 for acetal formation and cyanohydrin formation as a function of ring size of ketone (n). K_0 is the value for acetone. Points marked with \odot are those for cyanohydrin; points marked with \triangle are for acetal formation.

acetals^{3,4,8} as the major product in acidic methanol mixtures. The evidence in favor of acetal formation being predominant over hemiacetal formation in acidic methanol for most ketones and aromatic aldehydes is substantial.^{3,4,9,10} When the ketone or aromatic aldehyde contains strongly electronegative substituents, the extent of hemiacetal formation may be substantial but acetal formation is not precluded. For example, *p*-nitrobenzaldehyde has been shown to exist predominantly as the hemiacetal in neutral or basic methanol solutions, but it forms the dimethyl-acetal in acidic methanol.⁴ Substantial dimethyl-acetal formation for *p*-nitrobenzaldehyde is to be expected since there is a well-established procedure for

the equilibrium formation in methanol of the dimethyl acetal of *m*-nitrobenzaldehyde in 79% yield.¹¹

There is a simple and effective analytical method to distinguish between hemiacetal formation and acetal formation. If the absorbance of the carbonyl compound is measured as a function of time in neutral methanol, and if the hemiacetal forms, the absorbance will decrease. The absorbance measurements should be started as soon as possible after dissolution because the half-life for hemiacetal formation may be as low as 2 min or less.⁴ Addition of a trace of base, such as sodium acetate to the neutral mixtures, will effect a rapid decrease in the absorbance to the equilibrium value. If no hemiacetal forms, the absorbance will not change in neutral or basic methanol, but for these systems, if acetal formation is possible, the absorbance will decrease in acidic methanol. Finally it should be noted that the acetal equilibrium (acidic conditions) is extremely sensitive to dilute water concentrations whereas the hemiacetal equilibrium is not. It is imperative that the concentration of water (Karl Fischer) in the reactants be known since the equilibrium conversions often are quite small for the type ketones used in this study. Failure to determine the effect of water concentration on the acidic equilibrium may lead to the erroneous conclusion that the absorbance changes are due to hemiacetal formation.^{3,5-7}

The results shown in Table I represent a further example of the effect of ring size on carbonyl addition reactions. Relief of I strain is probably responsible for the more favorable equilibria for the 4 and 6-carbon rings while an increase of I strain has an adverse effect on the equilibrium for the 5- to 8-carbon cyclic ketones.¹² Figure 1 compares our data with the equilibrium formation of the cyanohydrins for

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these same ketones.¹³ The results are seen to be essentially parallel for the two reactions.

While our results for cyclic ketones show the same trends as Wheeler's,⁵ it is probably not meaningful to compare our numbers. His equilibrium constants are calculated for the hemiacetal reaction but our results demonstrate that they should be calculated for acetal formation. One cannot recalculate the data for his systems for the acetal equilibrium since the water concentrations for these systems are not known and thus his numbers are of only qualitative value.³ One should note that whether the reaction involved only hemiacetal or only acetal formation one should expect the results to be parallel for the effects of ring size on equilibria because both involve a change from sp^2 to sp^3 geometries. We would also note a serious calculation error in Wheeler's results in that he used the molecular weights of methanol and of ethanol as the molarity of the alcohol.

Experimental Section

Materials.—Methanol was purified by the method of Lund and Bjerrum.¹⁴ Each portion was distilled (on a column of 30 theoretical plates) until the transmittance was 97% or better when measured against distilled water at 250 $m\mu$ before collecting good material. In all cases the water content (Karl Fischer) was less than 0.010% and was usually 0.005% or less.

The ketones used in this study were purified just before use. The sources of the ketones, the purification method, and the observed physical properties have been previously reported⁴ except for cyclobutanone, cycloheptanone, and cyclooctanone (these were obtained from Aldrich Chemical Co.). Cyclobutanone was distilled at atmospheric pressure, collecting only a middle cut [bp 96–97° (740 mm); n_D^{25} 1.4162; λ_{max}^{OH} 282 $m\mu$ (ϵ 18.4)]. Cycloheptanone was extracted with dilute sodium bicarbonate solution, dried, and distilled under reduced pressure [n_D^{25} 1.4592; λ_{max}^{MeOH} 288 $m\mu$ (ϵ 20.3)]. Cyclooctanone was extracted with dilute sodium bicarbonate and distilled under reduced pressure [bp 70° (10 mm); n_D^{25} 1.4658; λ_{max}^{MeOH} 288 $m\mu$ (ϵ 16.5)].

Short-Cell-Path Measurements.—To permit the measurement of the ketone absorbances in concentrated methanol solutions, 1-cm quartz cells with matched quartz inserts were obtained from the Pyrocel Manufacturing Co., New York, N. Y. The inserts were made with two dimensions so that the path lengths could be varied as follows: 0.025, 0.045, 0.075, 0.095, 0.200, and 0.300 mm. The matching of the inserts was excellent and checked within 1% transmittance against each other at 288 $m\mu$. The absolute values of the path lengths listed are not accurate because when the various inserts were used, the extinction coefficients for solutions of cyclohexanone in methanol (the ketone molarity varied from 0.05 to 5.2) varied by more than 20%, whereas for a given insert the variation in ϵ was less than 2%. For this reason we used the same insert (0.3 mm for all data reported) for a Beer's law check and for the equilibrium mixtures for any given ketone in methanol.

Portions of the ketone and of methanol were weighed into a glass-stoppered flask and the solutions were thoroughly mixed and maintained at $25 \pm 0.01^\circ$ in a constant-temperature bath. For each ketone studied, two to five mixtures were made. Samples of each solution were placed in the short-path cells and the absorbances determined to check Beer's law. One to two microdrops (drawn capillary) of 0.1 *M* hydrogen chloride in methanol were added to the solutions in the flasks which then remained in the constant-temperature bath until the absorbance readings were constant. All absorbances were measured with a Beckman DU spectrophotometer equipped with thermospacers by means of which the temperature could be maintained at $25 \pm 0.02^\circ$. From 1 to 5 g of ketone with 12–19 g of methanol were used so that the weight of methanol added in the catalyst solution is insignificant. After the equilibrium absorption values were measured at 25° , the temperature of the bath was adjusted to

$10 \pm 0.02^\circ$ and the mixtures were allowed to remain for several hours. Portions of each mixture were removed and poured onto solid sodium bicarbonate in a small flask and the mixtures were shaken to neutralize the acid; all operations were conducted as rapidly as possible to ensure that the equilibrium did not change from the values at 10° . After the bicarbonate had settled, a small sample of the solution was used for absorbance readings with the temperature regulated in the DU cell compartment at $25 \pm 0.02^\circ$. This technique was effective in freezing the equilibrium and no significant drifting of the absorbances were observed over a period of 1 hr or longer. From the measured absorbances, from the weights of the reactants, and from the stoichiometry for acetal formation the mole-fraction equilibrium constants were calculated.

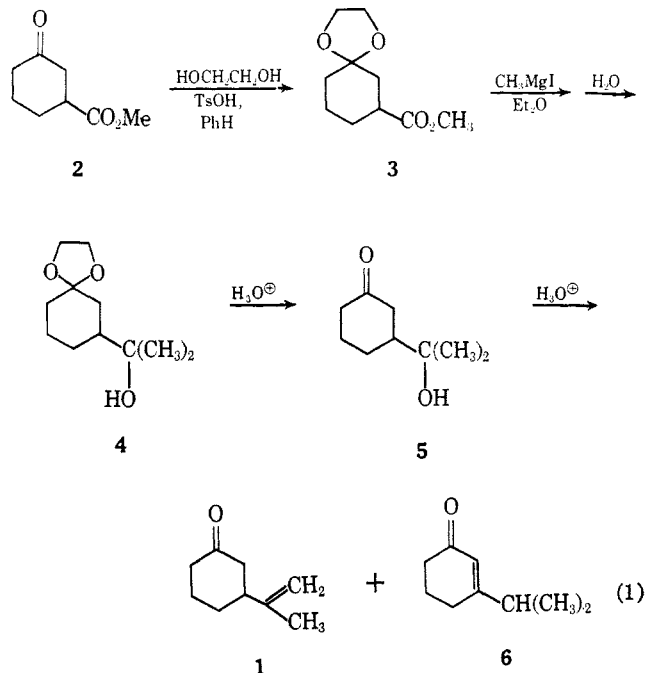
Preparation of 3-Isopropenylcyclohexanone^{1a}

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As a model for other synthetic work, we were interested in preparative routes to the isopropenyl ketone **1**. Our initial route illustrated in eq 1 was relatively unsatisfactory both because of the multistep procedure required and because the final acid-catalyzed dehydration step yielded a mixture of the desired ketone **1** and the more stable conjugated ketone **6** which had to be separated. None of the various dehydration methods



tried with the hydroxy ketal **4** or the keto alcohol **5** avoided this latter problem. Consequently, we were prompted to explore a different route (eq 2), the copper(I) iodide catalyzed addition of isopropenylmagnesium bromide to cyclohexanone (**7**). This route proved to be much more satisfactory, providing the pure un-

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