

tone from acidified mixtures of cyclohexanone and 2,2-dimethoxypropane, even at reduced pressure and with acid concentrations of the order of 0.001*M*, resulted in the formation of unsaturated ethers and methanol, and thus made it impossible to keep the reaction mixture free of the alcohol. Yields of 20–50% of the ketal were obtained in these cases, depending on the treatment.

The first 100 ml. of distillate from a mixture of 1.0 mole of acetophenone, 1.5 moles of 2,2-dimethoxypropane, 410 ml. of hexane, and 0.2 g. of *p*-toluenesulfonic acid contained 28% (vol.) of isopropenyl methyl ether and 1.0% acetone, while in a second experiment with the same amounts of ketone and ketal but with 2.0 moles of methanol and only 330 ml. of hexane (to make equal dilutions in both cases) the first 100 ml. of distillate contained 20% acetone and less than 1% isopropenyl methyl ether.

*c. Redistribution with acetone dimethyl ketal and cyclohexanone dipropyl ketal.* An equimolecular mixture of acetone dimethyl ketal (52 g., 0.50 mole) and cyclohexanone dipropyl ketal (100 g.) was acidified with 10 mg. of *p*-toluenesulfonic acid and allowed to stand at 24° for 30 min. It was then made basic by the addition of 100 mg. of sodium methoxide in 5 ml. of methanol. Fractional distillation gave first the azeotrope of methanol and acetone dimethyl ketal, then the remainder of the acetone dimethyl ketal, and finally the cyclohexanone dipropyl ketal. Total recoveries of the two ketals were 96% and 99% respectively. No more than traces of the other possible ketals were shown by either the distillation curves or refractive index measurements.

Another equimolecular mixture of these ketals was made as before and 10 g. of methanol and 10 mg. of *p*-toluenesulfonic acid were added. After 30 min. at 24° the solution was made basic in the same manner. Distillation of the solution gave the following fractions (boiling range, mid-range boiling point, and composition of fraction given): I, 36–40.5° (303 mm.), 39° (303 mm.), azeotrope of methanol and 2,2-dimethoxypropane; II, 40.5–65° (303 mm.), 47° (303 mm.), azeotropes of methanol and propyl alcohol with 2,2-dimethoxypropane; III, 65° (303 mm.) to 50° (81 mm.), 45° (81 mm.), azeotrope of propyl alcohol and acetone methyl propyl ketal; IV, 50–71° (81 mm.), 58° (81 mm.), acetone methyl propyl ketal; V, 71–93° (81 mm.), 88.5° (81 mm.), acetone dipropyl ketal; VI, 93° (81 mm.) to 75° (19 mm.), 60.5° (19 mm.), cyclohexanone dimethyl ketal; VII, 75–87.5° (19 mm.), 87.5° (19 mm.), cyclohexanone

methyl propyl ketal; VIII, above 87.5° (19 mm.), —, residue and column holdup (isolated by washing the packed column with ether and evaporating the ether, and identified as a mixture of the methyl propyl and dipropyl ketals of cyclohexanone by infrared spectroscopy). The mid-range boiling points were taken from well defined plateaus on the distillation curve, except for fraction II which gave no plateau. From the known composition of the azeotropes and by means of infrared spectrophotometric analyses the following recoveries were determined (given in gram-moles): methanol 0.24 (including 0.12 added when inactivating the catalyst), propyl alcohol 0.19, and the six ketals in order of increasing molecular weight 0.14, 0.25, 0.09, 0.15, 0.25, 0.10.

*Ketals from ketone, alcohol, and 2,2-dimethoxypropane. Method E. Acetophenone dipropyl ketal.* A solution of acetophenone (120 g., 1.00 mole), propyl alcohol (480 g., 8.00 moles), 2,2-dimethoxypropane (156 g., 1.5 moles), 300 ml. of hexane, and 0.2 g. of *p*-toluenesulfonic acid was distilled through a 1000 × 25 mm. column packed with 1/8-in. glass helices with the reflux ratio being adjusted so that the head temperature remained below 50°. After each 150–200 ml. of distillate was obtained, an equal volume of hexane was added to the boiling solution until 530 ml. of distillate had been collected. The still-head temperature then slowly rose to 64° at which time the total distillate volume was 770 ml. The reaction mixture was made basic by rapidly adding 0.2 g. of sodium methoxide in 10 ml. of methanol. Distillation was resumed and the pressure was reduced as necessary in order to keep the temperature in the flask below 100–110°. After a forerun which included some acetone dipropyl ketal, a residue of 190 ml. ( $n_D^{25}$  1.4820) remained. After two distillations through a 3-in. column packed with Berl saddles, this residue gave 141 g. of acetophenone dipropyl ketal, b.p. 61° (1 mm.),  $n_D^{25}$  1.4750, 63% yield (lit.<sup>13</sup> b.p. 112–115° (10 mm.)).

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(13) F. Sigmund and R. Uchann, *Monatsh.*, **51**, 251 (1920)

[CONTRIBUTION FROM THE ORGANIC BASIC RESEARCH LABORATORY, THE DOW CHEMICAL COMPANY]

## Ketals of Monohydric Secondary Alcohols<sup>1</sup>

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Alkoxy interchange between secondary alcohols and simple ketals gives ketals containing secondary alkoxy groups in good yields. Such ketals can also be made by the addition of secondary alcohols to  $\alpha,\beta$ -unsaturated ethers and by disproportionation reactions. Ketals with secondary alkoxy groups can be prepared directly from ketones and secondary alcohols by coupling the reaction with the hydrolysis of another ketal. Mixed ketals in which the alkoxy groups may be either both secondary or only one secondary and one primary can also be made by these methods.

The preparation of ketals of primary alcohols by alcohol interchange reactions with dimethyl ketal has been discussed in a previous paper.<sup>2</sup> This reaction has now been extended to include

the preparation of ketals of monohydric secondary alcohols. There are two previous references in the literature to the successful preparation of ketals of this type. Stevens, McLean, and Weinheimer<sup>3</sup> obtained relatively unstable  $\alpha$ -hydroxyketals by

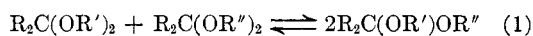
(1) Presented in part at the Gordon Research Conference on Organic Reactions and Processes, July 1958.

(2) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **25**, 521 (1960).

(3) C. L. Stevens, R. L. McLean, and A. J. Weinheimer, *Chem. & Ind. (London)*, 1957, 1321; *J. Am. Chem. Soc.*, **80**, 2276 (1958).

the addition of secondary alcohols to epoxyethers. These authors pointed out that this reaction is an alcohol interchange with an intramolecular ketal, and they ascribed the driving force for the reaction to the opening of the epoxide ring. Reichle has obtained diisopropyl ketals from cyclic ketones and triisopropyl orthoformate.<sup>4</sup> A recent patent<sup>5</sup> states that secondary and tertiary alcohols will react with allene to form the corresponding acetone ketals, but no examples of such compounds are given. Also without examples, an older patent<sup>6</sup> states that ketals can be formed with secondary alcohols. Other attempts to prepare ketals with secondary alkoxy radicals were not successful.<sup>7</sup>

In the interchange reaction with secondary alcohols, ketals of primary alcohols give symmetrical ketals of the secondary alcohols and mixed ketals containing one secondary and one primary alkoxy group. Mixed ketals in which the different alkoxy groups are both secondary can be prepared by alcohol interchange with a symmetrical ketal and a secondary alcohol or by disproportionation between two symmetrical ketals, Reaction 1.



No special driving force for the alcohol interchange reaction is needed other than that provided by the removal of the by-product alcohol by distillation. The equilibrium of Reaction 1 is rapidly attained after the addition of a trace of strong acid.

The addition of alcohols to  $\alpha,\beta$ -unsaturated ethers to give ketals has been demonstrated with secondary alcohols. The product ketal may contain one primary and one secondary alkoxy group, or both alkoxy groups may be secondary, depending on the nature of the alkoxy group in the ether. Symmetrical ketals are obtained along with the mixed ketals because of the simultaneous occurrence of the disproportionation Reaction 1. The yields of ketals by this method have been shown to be nearly quantitative both by isolation of the reaction products and by infrared spectroscopy. An absorption band ( $6.1\mu$ ) due to the carbon-carbon double bond of the ether almost completely disappears, and the spectrum of the ketal appears. The loss of the  $6.1\mu$  absorption band was demonstrated with mixtures of the following ethers and alcohols: 1-cyclohexen-1-yl methyl and ethyl ethers, isopropenyl methyl, ethyl, and propyl ethers, and isopropyl, *sec*-butyl, 2-pentyl, and cyclohexyl alcohols. Disappearance of the  $6.1\mu$  absorption band and appearance of the spectrum of a known ketal occurred with cyclohexyl isopropenyl

ether and cyclohexanol, isopropenyl methyl ether and isopropyl alcohol, and 1-cyclohexen-1-yl methyl ether and isopropyl alcohol. These properties also served to identify 1-cyclohexen-1-yl isopropyl ether (not isolated) as the principal constituent of a distillate fraction obtained in the forerun during the preparation of cyclohexanone diisopropyl ketal by alcohol interchange. The addition reaction did not occur with *t*-butyl alcohol.

The readily available ketals, 2,2-dimethoxypropane<sup>8</sup> and 1,1-dimethoxycyclohexane,<sup>2,9</sup> were usually used as starting materials for the alcohol interchange reactions, and the methanol produced was removed azeotropically with hexane or benzene.<sup>2</sup> In general, equilibrium concentrations of the methanol and product ketals have been lower, thus necessitating more tedious distillations, than in the preparation of ketals of primary alcohols. For this reason somewhat lower than the best attainable yields have been accepted to avoid long reaction times. Decomposition to unsaturated ethers is more serious when the ketals contain secondary alkoxy groups, and conversions to these ethers are greater and lead to greater losses during long distillations from acid solutions. The ethers can often be recovered, however, and used in addition reactions to prepare the same or other ketals. The product ketals were isolated and purified by distillation from alkaline media, or in some cases by crystallization.

In the preparation of mixed ketals yields of mixed and symmetrical ketals usually were in approximate accord with the requirements of the redistribution reaction of Calingaert and Beatty,<sup>10</sup> when the alkoxy radicals were both secondary (isopropyl and cyclohexyl). When they were not of the same order (methyl and isopropyl) the disproportionation equilibria favored the mixed ketal. This is further evidence of the relatively greater difficulty of formation of ketal groupings with secondary alcohols and the greater stability of primary alkoxy groups in ketal linkage.

Interchange of ketone groups, similar to alcohol interchange, probably does not occur directly at an appreciable rate although an apparent transketonation can be accomplished if alcohol is present. When equimolar amounts of acetone diisopropyl ketal, cyclohexanone, and isopropyl alcohol were acidified and kept for thirty minutes at room temperature, infrared analysis showed the appearance of cyclohexanone diisopropyl ketal and acetone in considerable amounts. However, when equimolar amounts of acetone diisopropyl acetal and cyclohexanone, without alcohol, were treated in the same manner, no cyclohexanone diisopropyl ketal

(4) W. T. Reichle, *Dissertation Abstr.*, 19, 3134 (1959); private communication.

(5) E. U. Elam and R. H. Hasek, Eastman Kodak Co., U. S. Patent 2,875,252, February 24, 1959.

(6) W. H. Carothers and H. B. Dykstra, E. I. du Pont de Nemours and Co., U. S. Patent 2,124,686, July 26, 1938.

(7) C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, 20, 1695 (1955).

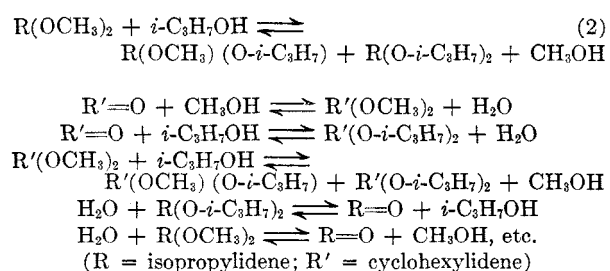
(8) 2,2-Dimethoxypropane is available from The Dow Chemical Co., Midland, Mich.

(9) R. E. McCoy, A. W. Baker, and R. S. Gohlke, *J. Org. Chem.*, 22, 1175 (1957).

(10) G. Calingaert and H. A. Beatty, *Organic Chemistry, an Advanced Treatise*, Vol. II, 2nd ed., H. Gilman, Ed., John Wiley & Sons, New York, 1947, Chap. 24.

was detectable in the spectrum after thirty minutes. Absorptions due to small amounts of isopropenyl isopropyl ether and isopropyl alcohol were present, however, and the intensity of absorptions due to acetone diisopropyl ketal had decreased. After 130 minutes absorption shoulders due to cyclohexanone diisopropyl ketal had begun to appear and they were stronger after 190 minutes. At least part of the observed slow formation of the cyclohexanone ketal can be accounted for by the presence of isopropyl alcohol from the decomposition of the acetone ketal indicated by the spectrum after thirty minutes, since it has been shown that the cyclohexanone ketal is formed rapidly when an equimolar amount of isopropyl alcohol is present; and this also indicates that its rate of formation depends on the alcohol concentration. Evidently the cyclohexanone ketal is formed only slowly if at all by direct interchange. From measurements of the ultraviolet absorption spectra of acidified mixtures of several ketones and isopropyl alcohol, Wheeler concluded that no reaction occurred.<sup>11</sup> The apparent transketonation just described indicates that ketones and secondary alcohols do react to form ketal and water to a small extent, and that coupling of this reaction with the hydrolysis of another ketal to remove water will provide enough driving force to shift the equilibrium of ketal formation considerably in the direction of ketal. We believe that this is the first evidence of the existence of the reaction of formation of a ketal directly from a ketone and a monohydric secondary alcohol.

As with ketals of primary alcohols,<sup>2</sup> ketals of secondary alcohols can be prepared by the simultaneous reaction of a ketone, a secondary alcohol, and another ketal such as 2,2-dimethoxypropane or 1,1-dimethoxycyclohexane. A mixture of cyclohexanone, isopropyl alcohol, and 2,2-dimethoxypropane gave yields of 57% of cyclohexanone isopropyl methyl ketal and 17% of cyclohexanone diisopropyl ketal. A number of concurrent and interrelated reactions (2) undoubtedly occur in



this mixture and ultimately lead to the isopropyl ketals of cyclohexanone. The water produced is consumed by the hydrolysis of the acetone ketals, and the equilibria are shifted in the direction of the cyclohexanone isopropyl ketals by the removal of acetone and methanol by distillation. This is a

(11) O. H. Wheeler, *J. Am. Chem. Soc.*, **79**, 4191 (1957).

convenient preparative method which utilizes readily available starting materials.<sup>8,9</sup>

All of the ketals of secondary alcohols so far prepared undergo the same endothermic hydrolysis that is characteristic of the ketals of primary alcohols. Examination of the hydrolyzates from the hydrolytic degradation of two of these ketals showed only the ketone and alcohol, thus providing additional evidence for the acetal structure. The hydrolysis was essentially quantitative with the stoichiometric amount of water at room temperature, indicating a large hydrolysis constant and thus a very small constant for the reverse reaction of ketal formation. This observation corroborates Wheeler's failure to detect the reverse reaction with isopropyl alcohol and ketones<sup>11</sup> and suggests that the reason was lack of sensitivity of his method.

Suitable combinations of these preparative reactions and those of our previous paper<sup>2</sup> afford methods for the convenient preparation of many ketals of secondary alcohols from readily available starting materials. Table I gives the properties of some of these ketals which have already been obtained.

#### EXPERIMENTAL

*Materials.* Acetone dimethyl acetal (2,2-dimethoxypropane) supplied by The Dow Chemical Co. was used as received. Cyclohexanone dimethyl acetal was prepared from methanol and cyclohexanone directly<sup>9</sup> or with added 2,2-dimethoxypropane.<sup>2</sup> The *p*-toluenesulfonic acid was used as the monohydrate (Eastman Kodak Co.) except where noted. The other materials were commercial products and were used without drying. The isopropyl alcohol used contained 0.2% water.

*Alcohol interchange. Method A. a. Acetone isopropyl methyl and acetone diisopropyl ketal.* A solution composed of 832 g. (8.00 moles) of 2,2-dimethoxypropane, 1349 g. (23.2 moles) of isopropyl alcohol, 3500 ml. (2403 g.) of hexane, and 0.05 g. of *p*-toluenesulfonic acid was set for distillation through a glass Oldershaw fractionating column approximately 1 meter long and having 30 trays. The column was fitted with a magnetically controlled liquid-dividing take-off head actuated by an electric timer. The timer was powered by a Wheelco "Capacitrol" arranged to respond to the temperature in the still head. The Capacitrol was set to operate the timer and thus remove distillate at head temperatures below 50°, in order to collect the azeotrope of methanol and hexane, b.p. 48°. At first a reflux ratio of 10 was satisfactory but it soon had to be increased to 20 and then to 50. Finally, with the timer set at 2% take-off, distillate was collected intermittently whenever the temperature in the still head fell below 50° and actuated the timer through the Capacitrol. The distillation required 13 days and 1866 g. of distillate was collected before the rate of distillation was deemed impracticably slow and the process stopped. The solution was cooled and 0.4 g. of sodium dissolved in 24 g. of isopropyl alcohol was added.

The mixture was then distilled through a 1200 × 19 mm. column packed with 1/8-in. glass helices and fitted with a vapor-dividing head with similar automatic controls. The azeotrope of hexane and isopropyl alcohol was first obtained (boiling range 57–65°), and during the distillation an additional 2 l. of hexane was added to accomplish the removal of the remaining alcohol. The distillation was finished at reduced pressure, finally giving the three fractions: (a) 31 g. boiling from 53° (350 mm.) to 47.5° (164 mm.), (b) 91 g. boiling from 47.5° (164 mm.) to 63° (52 mm.), (c) 798 g.

TABLE I  
PROPERTIES OF KETALS R<sub>2</sub>C(OR')OR''

Ketone	Ketal R'	R''	Method	Yield, %	B.P. °C.	mm.	n <sub>D</sub> (T)	Density g./ml. (T)	Analyses			
									Calcd.	Found <sup>a</sup>		
								C	H	C	H	
Acetone	CH <sub>3</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub> <sup>b</sup>	C	42	47	68	1.3882 (25)	0.833 (25)	63.6	12.2	63.6	12.2
Acetone	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub> <sup>c</sup>	A	65	62	50	1.3987 (23)	0.827 (25)	67.5	12.6	67.4	12.4
Acetone	CH <sub>3</sub>	<i>sec</i> -C <sub>4</sub> H <sub>9</sub> <sup>d</sup>	A	38	61	50	1.3986 (25)	0.836 (25)	65.7	12.5	65.8	12.6
Acetone	<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	A	10	67	12	1.4123 (25)	0.833 (25)	70.2	12.9	70.2	12.9
Acetone	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<i>cis</i> -Hex <sup>e</sup>	B	39	116-118	41	1.4383 (24)	0.896 (25)	71.9	12.1	72.0	12.1
Acetone	<i>cis</i> -Hex	<i>cis</i> -Hex <sup>f</sup>	A	49	110-115	3	1.4673 (24)	0.950 (25)	75.0	11.7	75.1	11.9
Cyclohexanone	CH <sub>3</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	A <sup>g</sup>	57	68	8	1.4390 (24)	0.918 (24)	69.7	11.7	69.8	11.8
Cyclohexanone	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	A <sup>g</sup>	33	85	8	1.4410 (24)	0.905 (24)	72.0	12.1	72.2	12.0
Cyclohexanone	<i>cis</i> -Hex	<i>cis</i> -Hex <sup>h</sup>	A	29	150-160	3	1.4903 (26)	—	77.1	11.5	77.1	11.6

<sup>a</sup> Average of duplicates. <sup>b</sup> Heat of vaporization,  $\Delta H_v$ , 9.6 kcal./g. mole. <sup>c</sup>  $\Delta H_v$ , 11.1 kcal./g. mole. <sup>d</sup>  $\Delta H_v$ , 10.4 kcal./g. mole. <sup>e</sup> Mol. wt.: calcd. 200, found 198 (cryo.). <sup>f</sup> M.p. 25°; density and refractive index values are for supercooled liquid; mol. wt.: calcd. 240, found 236 (cryo.). <sup>g</sup> For yields by method D, see text. <sup>h</sup> M.p. 43-43.5°; refractive index value for supercooled liquid; isolated by crystallization.

boiling at 63-64.5° (52 mm.),  $n_D^{25}$  1.3987, and 27 g. of residue. Fractions a and b and the residue were combined, 100 ml. of hexane and 50 ml. of *cis*-decalin were added, and the mixture was washed with water and dried. Distillation of this solution gave two fractions (d) 35 g. boiling from 41-50° (51 mm.),  $n_D^{25}$  1.3909, and (e) 21 g. boiling from 50-67° (51 mm.),  $n_D^{25}$  1.3988.

Fractions c and e were identified as acetone diisopropyl ketal, yield 819 g. (5.12 moles) or 65% based on 7.85 moles of 2,2-dimethoxypropane (8.00 moles less 0.15 mole for the amount of water introduced with the isopropyl alcohol). Fraction d was acetone isopropyl methyl ketal, 0.27 mole, 3.4%. In other runs in which the distillation of the hexane-methanol azeotrope was carried on for only 3-4 days, yields of the two ketals were each about 30%. Benzene is not so satisfactory as hexane as the azeotroping agent in this process because it leads to increased losses of isopropenyl isopropyl ether whose boiling point is near that of the benzene-methanol azeotrope.

All of the distillate fractions were collected and worked up. Of 6194 g. of material taken, 5624 g. was recovered and 570 g. lost. Alcohols were washed from the hexane distillates with water and recovered by distillation, yielding 10.3 moles of methanol and 11.4 moles of isopropyl alcohol. By difference, unrecovered isopropyl alcohol was 11.4 moles. Isopropenyl methyl ether, 1.40 moles (17.8% on the same basis as for the ketals), was recovered from the hexane-methanol distillate. No 2,2-dimethoxypropane was recovered.

*b. Acetone cyclohexyl isopropyl ketal and cyclohexyl isopropenyl ether.* One mole each of acetone diisopropyl ketal (160 g.) and cyclohexanol (100 g.) were added to 500 ml. of hexane and acidified with 0.05 g. of *p*-toluenesulfonic acid. The solution was fractionally distilled at atmospheric pressure, giving 362 g. of distillate of boiling range 57-61°. (Sixty g. of isopropyl alcohol was obtained as its azeotrope with water<sup>12</sup> by washing this distillate with water and distilling the aqueous phase.) The reaction solution was then cooled and made basic by the instantaneous addition of 0.1 g. of sodium methoxide in 10 ml. of methanol. Distillation was resumed and the remaining hexane was removed, first at atmospheric and finally at reduced pressure to keep the flask temperature below 100°. Two forerun fractions consisted of 16 g. of acetone diisopropyl ketal, b.p. 47-56° (25 mm.),  $n_D^{25}$  1.4013, and 37 g. of a mixture, b.p. 56° (25 mm.),  $n_D^{25}$  1.4507, which was mainly cyclohexyl isopropenyl ether with a small amount of cyclohexanol (determined by infrared spectroscopy). The next fraction boiling at 87.5° (13 mm.),  $n_D^{25}$  1.4398, was 30.5 g. of acetone cyclohexyl isopropyl ketal. The distillation was stopped overnight but the system remained under vacuum.

When the distillation was resumed 34 g. of material distilled at 50° (11 mm.),  $n_D^{25}$  1.4519,  $d_{25}^{25}$  0.893 g./ml., and was identified as cyclohexyl isopropenyl ether. Another 4 g., b.p. 50-55° (11 mm.),  $n_D^{25}$  1.4542, distilled leaving a dry flask. A residue of 41 g. was obtained as column holdup. Evidently a pyrolysis had occurred. A similar unpredictable pyrolysis was observed in other runs, usually occurring spontaneously during the distillation of the ketal and making it impossible to continue the distillation.

The yield of acetone cyclohexyl isopropyl ketal was 15% by this procedure, or 30% of the amount predicted by the redistribution reaction. In a similar experiment with half-mole quantities of the reactants, the residue after the removal of the hexane was separated into two crude fractions by rapid distillation at room temperature, first at 25 mm. and finally at 1 mm., with a final short heating to 50°. Analysis of these fractions and the residue by infrared spectroscopy showed the presence of 0.22 mole of acetone cyclohexyl isopropyl ketal and 0.10 mole of acetone di-

(12) L. H. Horsley and co-workers, *Azeotropic Data*, American Chemical Society, Washington, D. C., 1952, p. 7.

cyclohexyl ketal. The redistribution reaction predicts 0.25 and 0.125 mole, respectively. Fractional distillation of the residue, which contained the cyclohexyl ketals, gave 25 g. of the mixed ketal before pyrolysis interfered, making the isolated yield 25%.

*Identification of cyclohexyl isopropenyl ether.* The following data identify the material of the preceding experiment, b.p. 50° (11 mm.), as cyclohexyl isopropenyl ether.

*Anal.* Calcd. for  $C_9H_{16}O$ : C, 77.09; H, 11.50; mol. wt., 140. Found: C, 76.93, 77.25; H, 11.54, 11.80; mol. wt., 143 (cryo.).

Calculated as the ether, 0.005 mole (0.70 g.) of the unknown was added to 0.005 mole (0.50 g.) of cyclohexanol and the solution was acidified with a trace of *p*-toluenesulfonic acid. An exothermic reaction occurred, and the product solidified when placed in the refrigerator, remelting over a range ending at about 22° (melting point of acetone dicyclohexyl ketal, 25°). The infrared spectrum of the product mixture was essentially the same as that of acetone dicyclohexyl ketal, band for band, except that trace absorptions corresponding to the strongest bands of cyclohexanol indicated about 1–2% of this impurity. Absence of absorptions at 6.06, 7.8, and 12.6  $\mu$ , all characteristic of the ether, showed that conversion of the ether was practically quantitative.

*Mixed ketals by disproportionation of symmetrical ketals.*

*Method B. a. Acetone cyclohexyl isopropyl acetal.* Half-mole quantities of acetone diisopropyl ketal (80 g.) and acetone dicyclohexyl ketal (120 g.) were combined and acidified with 0.05 g. of *p*-toluenesulfonic acid dissolved in 10 ml. of isopropyl alcohol. The mixture soon became quite pink and then faded to a yellowish color during about 20 min. at room temperature (*cf.* MacKenzie and Stocker<sup>7</sup>). The acid catalyst was then neutralized by the rapid addition of a solution of 0.1 g. of sodium methoxide in 10 ml. of methanol. Fractional distillation of the mixture gave 35 g. of acetone diisopropyl ketal, b.p. 44–64° (36 mm.),  $n_D^{24}$  1.3978; 24 g. of unidentified material, b.p. 64–114° (36 mm.),  $n_D^{24}$  1.4471; 77.5 g. of acetone cyclohexyl isopropyl ketal, b.p. 116–118° (41 mm.),  $n_D^{24}$  1.4383; and a residue of 48 g. of acetone dicyclohexyl ketal,  $n_D^{25}$  1.4650 (estimated nearly pure by infrared spectroscopy). The ketals were isolated in approximately the mole ratio required by the redistribution reaction, 1.1:2.0:1.0, but the recoveries were only about 80%.

*b. Disproportionations involving both primary and secondary alkyl groups.* Acetone isopropyl methyl ketal (142 g., 1.07 moles) was acidified with 0.01 g. of solid *p*-toluenesulfonic acid. Discoloration occurred in the vicinity of the crystals as they dissolved, but there was little further darkening of the solution. The refractive index was the same (1.3882) before, directly after, and 5 days after the addition of the acid. After 5 days at room temperature (about 24°) 0.05 g. of solid sodium methoxide was added and the mixture was distilled. The following fractions were obtained: (a) acetone dimethyl ketal, 21 g., b.p. 41–48° (205 mm.),  $n_D^{24}$  1.3767; (b) transition, 13 g., b.p. 48–73° (205 mm.),  $n_D^{24}$  1.3844; (c) acetone isopropyl methyl ketal, 61 g., b.p. 73–74° (205 mm.),  $n_D^{24}$  1.3890; transition, 7 g., b.p. 40–59° (40 mm.),  $n_D^{24}$  1.3954; (d) acetone diisopropyl ketal, 6 g., b.p. 59° (40 mm.),  $n_D^{24}$  1.3981; and (e) residue. The residue was distilled without fractionation and gave an additional 20 g. of acetone diisopropyl ketal, b.p. 61.5° (42 mm.),  $n_D^{24}$  1.3984. The cold trap contained 11 g. of material identified as a mixture of isopropenyl methyl ether and isopropyl alcohol. Estimating the compositions of the transition fractions by linear interpolation of refractive indices and summing gives a mole ratio of the ketals of 1.0:2.2:0.65 which deviates somewhat from the 1:2:1 required by the redistribution reaction and, considering also the material in the cold trap, favors the mixed ketal.

In another experiment equimolar amounts of cyclohexanone dimethyl ketal (1.44 g.) and cyclohexanone diisopropyl ketal (2.00 g.) were mixed and acidified with a few crystals of *p*-toluenesulfonic acid. After 3 hr. at room temperature

the infrared spectrum of the mixture was determined and compared with the spectra of mixtures of known concentrations of the three possible ketals, made up from the pure materials and adjusted to be equimolar in the symmetrical ketals. The spectrum of the acidified mixture closely matched that of the known sample in which the mole ratio of cyclohexanone dimethyl, isopropyl methyl, and diisopropyl ketals was 1.0:4.7:1.0, showing considerable deviation from the 1:2:1 requirement of the redistribution reaction. Acidification of a sample of cyclohexanone isopropyl methyl ketal gave the same spectrum after 30 min. at room temperature, demonstrating attainment of the equilibrium from the other direction. The spectra of the acidified mixtures differed from that of the known mixture in having absorption bands due to small amounts of hydroxyl, carbonyl, and unsaturation (6.06  $\mu$ ).

*Addition of secondary alcohols to unsaturated ethers. Method C. a. Acetone isopropyl methyl ketal.* Isopropenyl methyl ether (60 g., 0.83 mole) was added dropwise to isopropyl alcohol (120 g., 2.0 moles) acidified with 0.035 g. of *p*-toluenesulfonic acid. External cooling was used to keep the temperature below 20° and the addition required about 30 min. The mixture was then made basic by the instantaneous addition of a solution of 0.05 g. of sodium methoxide in 5 ml. of methanol. The reaction product was washed with 600 ml. of water in three portions, and separation gave 82.5 g. of organic phase. The aqueous solution was extracted with 100 ml. of 45–60° petroleum ether which was separated and combined with the first organic phase. After being dried with potassium carbonate, the ether solution was distilled, giving 18.5 g. of acetone dimethyl ketal, 46.5 g. (42%) of acetone isopropyl methyl ketal, b.p. 45°/59 mm.,  $n_D^{25}$  1.3876, and 31 g. of residue identified by refractive index,  $n_D^{25}$  1.3977, as acetone diisopropyl ketal.

*b.* The preparation of acetone dicyclohexyl ketal by this method has been given in connection with the identification of cyclohexyl isopropenyl ether. It can be isolated by crystallization from acetone or methanol at low temperature, m.p. 25°.

*Simultaneous reaction of ketone, secondary alcohol, and a ketal. Method D. a. Evidence for the coupling of the reaction of formation of one ketal and the hydrolysis of another.* Equimolar amounts of cyclohexanone (2.0 g.), isopropyl alcohol (1.2 g.), and acetone diisopropyl ketal (3.2 g.) were mixed and the solution was divided into two parts. One part was used as a control sample, and the other was acidified with a small amount of *p*-toluenesulfonic acid and its infrared spectrum was determined after 30 min. Comparison of this spectrum and that of the control with those of authentic samples showed the following compositions by volume: found in the control sample, 23% cyclohexanone, 48% acetone diisopropyl ketal (calcd. from the amounts taken, 28.6% and 50.6% respectively), no acetone, no ketal of cyclohexanone; found in the acidified sample, 29% cyclohexanone diisopropyl ketal and 16% acetone diisopropyl ketal. Acetone and cyclohexanone were both present in the acidified sample, but they were not determined for want of unobstructed absorption bands in the spectrum.

To determine whether acetone diisopropyl ketal and cyclohexanone react at an appreciable rate by a direct interchange, an equimolar mixture of cyclohexanone (4.0 g.) and acetone diisopropyl ketal (6.5 g.) was made up and divided as before. One part was acidified with a similar amount of *p*-toluenesulfonic acid which had been dissolved in boiling toluene, further boiled, recrystallized by cooling, and stored under petroleum ether. Infrared spectra were determined on samples of this solution after 30, 130, and 190 min. The spectrum of the control indicated 38% (vol.) cyclohexanone (13.4  $\mu$ ) and 62% acetone ketal (11.4  $\mu$ ). The acidified sample after 30 min. still contained 38% cyclohexanone, but the acetone ketal had decreased to 48% and new bands at 6.06 and 7.8  $\mu$  and at 10.5  $\mu$  indicated 9% isopropenyl isopropyl ether and 6% isopropyl alcohol. Strong bands at 8.05, 8.7, and 9.3  $\mu$  characteristic

of cyclohexanone diisopropyl ketal were absent. In the spectrum after 130 min. weak absorption bands due to the cyclohexanone ketal had appeared and the absorption bands of cyclohexanone and the acetone ketal had become weaker. These trends continued in the same direction in the spectrum of the 190-min. sample, in which the concentration of cyclohexanone diisopropyl ketal was estimated at about 10%.

*b. Cyclohexanone isopropyl methyl ketal and cyclohexanone diisopropyl ketal.* A solution of cyclohexanone (98 g., 1.0 mole), isopropyl alcohol (264 g., 4.40 moles), 2,2-dimethoxypropane (125 g., 1.20 mole), benzene (250 ml.), and *p*-toluenesulfonic acid (0.05 g.) was distilled on a good fractionating column at a pressure of 270 mm. with automatic controls set to remove distillate when the temperature in the still head was below 34°. After about 24 hr. this temperature could not be maintained with a 50:1 reflux ratio, so the distillation was stopped. The volume of the distillate was 226 ml. and contained 109 ml. of water-soluble material. The reaction solution was made basic by adding a solution of 0.1 g. of sodium in 20 ml. of isopropyl alcohol. Infrared analysis showed that less than 2% of the cyclohexanone remained unchanged. Distillation was resumed and after 412 ml. of forerun had distilled, 99 g. (57.5%) of cyclohexanone isopropyl methyl ketal was obtained in the boiling range

47–70° (8 mm.),  $n_D^{25}$  1.4388. The residue was identified by infrared spectroscopy as practically pure cyclohexanone diisopropyl ketal, yield 34 g. (17%). Similar yields were obtained using hexane as solvent instead of benzene.

*Hydrolytic degradation.* Equimolar amounts of acetone di-*sec*-butyl ketal (11.5 g.) and water (1.10 g.) were mixed and acidified with a tiny crystal of *p*-toluenesulfonic acid introduced on the bulb of a thermometer. The temperature began to decrease and the mixture suddenly became homogeneous. The infrared spectrum of the solution, determined after 30 min., indicated the presence of 29% (vol.) acetone and 70% *sec*-butyl alcohol (calcd., 29% and 71%). None of the absorption bands of the ketal was present.

Cyclohexanone dicyclohexyl ketal was hydrolyzed in an equal weight of purified dioxane with a 10% excess of water, and the infrared spectrum of the solution was determined. Absorption bands characteristic of cyclohexanol and cyclohexanone were present, but the bands of the ketal were absent.

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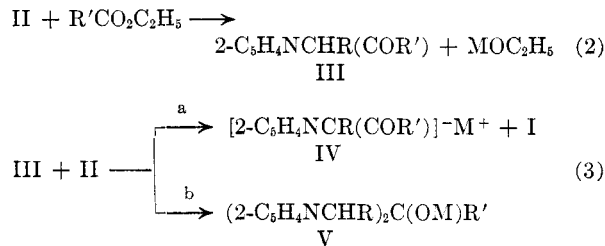
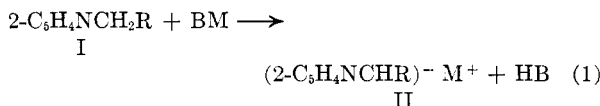
## The Synthesis of Nitrogen-Containing Ketones. X. The Mechanism of the Acylation of Pyridine Derivatives<sup>1,2</sup>

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A new mechanism is proposed for the course of the acylation of pyridine derivatives. Evidence in its support is presented.

As a result of previous work from this laboratory,<sup>4–7</sup> the following series of reactions was proposed, using a 2-alkylpyridine as an example, to rationalize the results which were obtained when 2-picoline and certain related 2-alkylated tar bases were acylated with esters in the presence of the basic condensing agent, BM.



An acid-base reaction occurs between I and the basic condensing agent, BM, to give the metalated pyridine derivative, II (equation 1). Then it is assumed (Equation 2) that the free ketone, III, is formed by the reaction of II with the ester. Finally, III may react with II in two ways: (1) III and II may undergo an acid-base reaction to give the anion of the ketone, IV, and I (Equation 3a) and (2) a carbinol may be formed as its metallic salt, V, by the addition of II across the carbonyl group of III (Equation 3b). Thus, when the lithium derivatives of 2-picoline,<sup>4,5</sup> quinaldine,<sup>5</sup> 2,6-lutidine,<sup>5</sup> 2-ethylpyridine,<sup>7</sup> and 2-isobutylpyridine<sup>7</sup> were acylated with esters only ketones of type III (where R' is aromatic or heterocyclic) or mixtures of ketones and carbinols of type V (where M = H and R' is aliphatic) were obtained. When

(1) For paper IX in this series, see S. Raynolds and R. Levine, *J. Am. Soc.*, in press.

(2) This paper is based on part of the thesis presented by S. R. to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

(3) Monsanto Chemical Co. Research Fellow for the academic year 1958–59.

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