[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Enolization as Directed by Acid and Basic Catalysts. III. The Acid-Catalyzed Enolization of Some Secondary Butyl Ketones

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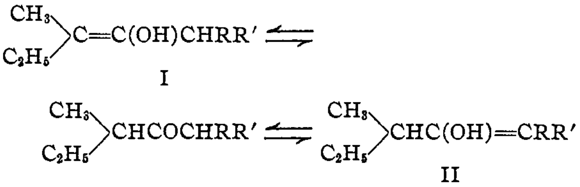
Qualitative facts in the literature indicate that the activity of hydrogen in the alpha position to a carbonyl group varies in a manner that is not understood according as the alpha carbon atom is primary, secondary or tertiary. For example, the product of monochlorination of methyl ethyl ketone in a slightly acid medium, either at room temperature or at 70°, contains about 80% of 3-chloro-2-butanone and only 20% of 1-chloro-2-butanone;[1] the chlorination and bromination of menthone and carvomenthone have led to tertiary halogen compounds[2] as the only identified products. Such facts convey an impression that hydrogen in the alpha position to a carbonyl group is most active toward substitution when tertiary and least active when primary. Results from a study of the base-catalyzed Michael condensation,[3] which also depends upon the activity of hydrogen, lead to the opposite view. In the condensation of methyl ethyl ketone with benzaldehyde, it is reported[4] that the use of an acid catalyst leads to condensation at the methylene group, while a basic catalyst brings about condensation at the methyl group.

It is not surprising that no simple parallelism among these results should appear. In a two-step reaction, the yield alone affords no clue as to the equilibria and rates of the two steps involved, and the dependence of the rates on different catalysts. In the halogenation of an unsymmetrical ketone, the yields of the two products may well be affected, not only by the relative rates of formation of the two possible intermediate enols,[5] but by the possibility of establishment of an equilibrium between the products, altering the original ratio in which they were formed.[6] If, as is commonly postulated, enols and enolates are involved in the aldol, Claisen, Claisen–Schmidt, Michael and Perkin condensations, then the yields in these reactions may be functions of the rate and equilibrium of enolization, and also the rate and equilibrium of the further reaction of the enol. No one of these variables can be singled out and alone correlated with the final yield.

The reactions dependent upon active hydrogen are of wide enough importance to render a quantitative study of the first of these factors—the competitive rates of enolization—of interest, even though it is but a partial attack upon the problem of "reactivity" of such hydrogen atoms. We have applied the method of the first paper of this series[5] to the determination of the relative rates of formation of the enols I and II in a series of optically active secondary butyl ketones.



$$\underset{\text{I}}{\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>C{=}C(OH)CHRR'} \rightleftarrows \begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>CHCOCHRR' \rightleftarrows \underset{\text{II}}{\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>CHC(OH){=}CRR'}$$

Conditions of acid catalysis similar to those of the first paper were used; glacial acetic acid was the solvent, and nitric acid (1.19 *N*) served the double purpose of a catalyst for enolization and an oxidizing agent to ensure irreversible iodination. The rate of racemization divided by the rate of iodination, measured under identical conditions, is then a measure of the relative rates of formation of the enols I and II.

These experiments were carried out with phenyl secondary butyl ketone as a check upon the method, for this ketone has only one hydrogen available for enolization and the rates of iodination and of racemization should be identical. This question was tested by Ingold and Wilson[7] for the racemization and bromination of 2-*o*-carboxybenzylindanone-1; in our case, as in theirs, the rates are identical within the experimental error. At 36.75°, the velocity constant for iodination of phenyl *s*-butyl ketone is 0.0298, that for racemization, 0.0296.

The rates of iodination and racemization for $RCOCH(CH_3)C_2H_5$, where R is methyl, ethyl,

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[1] Kling, *Bull. soc. chim.*, [3] **33**, 325 (1905).

[2] Kötz and Steinhorst, *Ann.*, **379**, 13 (1911).

[3] Andrews and Connor, THIS JOURNAL, **57**, 895 (1935).

[4] Harries and Müller, *Ber.*, **35**, 966 (1902).

[5] Part I of this series, THIS JOURNAL, **55**, 4992 (1933); other references there.

[6] For an example of this, see L. I. Smith, *ibid.*, **44**, 216 (1922).

[7] Ingold and Wilson, *J. Chem. Soc.*, 773 (1934).

and benzyl, were measured at different temperatures from 15 to 40°, with the intention of resolving the rates into action and activation constants. The low optical rotations of the ketones prevented sufficiently accurate racemization runs for this purpose. As far as can be judged from the data, the relative rates of the two modes of enolization of a ketone do not vary with temperature.

Table I shows the results of the reaction rate measurements, together with an estimate of their precision, obtained by taking the mean deviation of the results of individual runs from the weighted mean, at each temperature. In Fig. 1 the logarithm of the rate constant is plotted against the reciprocal of the absolute temperature, to show the similar slopes of all lines and the agreement of the data for the methyl and ethyl ketones with the Arrhenius equation.

TABLE I

RATES OF IODINATION AND RACEMIZATION OF RCOCH-$(CH_3)C_2H_5$

R	Temp., °C.	$k_{\text{Iod.}}$	No. of runs	% deviation	$k_{\text{Rac.}}$	No. of runs	% deviation
CH_3	15	0.578	2	7.8			
	25	1.41	2	3	0.248	4	29
	38.75	4.54	2	6			
	38.95	4.61	2	5.4			
	38.7				1.3	1	3.5
C_2H_5	15	0.33	2	9			
	25	.852	3	4.2	0.103	4	10
	38.75	2.74	2	3	.339	2	21
$C_6H_5CH_2$	24.45	.309	4	10			
	25				.0118	1	14
	38.75	1.325	1	3			
	44.6				.0708	1	28
Cyclohexyl	25	.026	1	50	.0183	2	20

For the purpose of interpreting the results, the standard temperature of 25° was taken, since the competitive enolizability of different active hydrogens seems but little affected by temperature. To get an expression of the mobility of a single hydrogen atom in the position in question, a statistical correction needs to be made by dividing the fractional velocity by the number of equivalently situated hydrogen atoms, as has been done in Table II.

TABLE II

COMPETITIVE ENOLIZATION VELOCITY OF HYDROGEN IN SECONDARY BUTYL KETONES, $RCOCH(CH_3)C_2H_5$, 25°

R	$k_{\text{Iod.}}$	$k_{\text{Rac.}}$	v_R	v_H
CH_3	1.41	0.248	4.68	1.56
C_2H_5	0.852	.103	7.27	3.63
Benzyl	.324	.0118	26.4	13.2
Cyclohexyl	.026	.0183	0.42	0.42

In this table v_R is the enolization velocity of all the active hydrogen in the group R, relative to that of the secondary butyl hydrogen taken as unity; v_H is the enolization velocity of a single active hydrogen atom in the group R, relative to that of the secondary butyl hydrogen as unity.

The competitive velocities per hydrogen in the four ketones measured vary over a 31-fold range. It is not surprising that benzyl hydrogen should be the most active competitively; but the result is unexpected that under these acid catalytic conditions the tertiary hydrogen atoms are less active, as regards rate of enolization, than either primary or secondary hydrogen. This is directly contrary to the indications of Part I of this series, wherein it was found that, using our present notation, v_H for one of the secondary hydrogen atoms of position 2 of menthone is only 0.13 relative to the tertiary hydrogen of position 4.

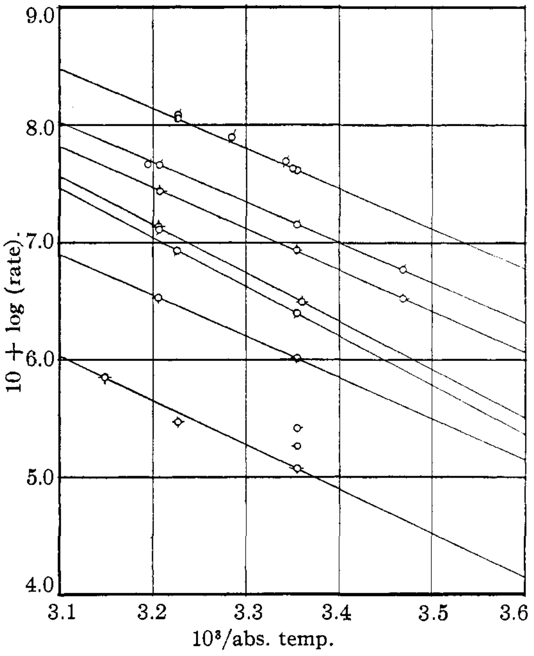

Fig. 1.—The common logarithms of the rate constant plotted against the reciprocal of the absolute temperature: ϕ iodination of *l*-menthone; O racemization of *l*-menthone; ó iodination of methyl *s*-butyl ketone; ϙ racemization of methyl *s*-butyl ketone; ó- iodination of ethyl *s*-butyl ketone; -ϙ racemization of ethyl *s*-butyl ketone; -ó- iodination of benzyl *s*-butyl ketone; -ϙ- racemization of benzyl *s*-butyl ketone; O- iodination of cyclohexyl *s*-butyl ketone; -O racemization of cyclohexyl *s*-butyl ketone; -ϕ- iodination and racemization of phenyl *s*-butyl ketone.

This striking contrast between acyclic and cyclic ketones led us to repeat the earlier work on menthone, with a resulting revision of the figures, which, however, widens the difference between menthone and the secondary butyl ketones. For the iodination of menthone at 25° we now get a unimolecular rate constant of 4.08, and for the racemization we get 4.27. Allowing for experimental uncertainties we may say that v_H for the methylene hydrogen is not greater than 0.04 relative to the tertiary hydrogen. We cannot account for the difference between this result and the earlier one; the only known differences of conditions in the present experiments were the use of 1.19 *N* instead of 0.955 *N* nitric acid, closer temperature control on both kinds of run, and the use of a spectrophotometer instead of a colorimeter, which resulted in these new iodination runs being very intensely illuminated with white light. The runs did not show the departure from first order kinetics observed in Part I,[5] (p. 4994, 4995) which bears out the suggestion there made that the iodination of the enol may be photochemically promoted. The necessity of revising the figures for menthone is also a warning that these results may have only qualitative significance.

Discussion.—The isolated cases of the acid-catalyzed enolization of menthone and the base-catalyzed enolization of chloracetone[8] supported a mechanism undertaking to account for the direction of enolization in terms of the nature of the catalyst and the alpha-substituted groups and two electronic mechanisms of enolization. The results of the present work show that such a formulation is entirely too simple and is incapable of affording reliable predictions concerning rates of reaction or energies of activation in the enolization process. The ethyl and isopropyl groups are both feebly electron-repelling, relative to hydrogen. One of these, introduced into a cyclohexanone, strongly enhances the competitive enolization rate of the neighboring hydrogen atom; the other, introduced in the alpha position into diethyl ketone, markedly *diminishes* the competitive enolization rate of the neighboring hydrogen atom. In both cases the conditions of study are so strongly acid that there can scarcely be any question of the basic mechanism of enolization coming into play. This work affords a possible further example of the unique character of cyclohexanones, which it might be profitable to investigate in connection with the other abnormalities of these ring compounds.

It is noteworthy also, as Table II shows, that the rates of enolization of the *s*-butyl ketones do not in any sense run parallel to the competitive enolization rates of the groups introduced. Although the benzyl group, for instance, has a v_R five times as great as that of the methyl group, benzyl *s*-butyl ketone enolizes only one-fourth as fast as methyl *s*-butyl ketone.

Experimental

The acetic acid used as solvent was prepared by fractional distillation of acid obtained from the Baker and Adamson Co. The nitric acid was purified by distillation from an equal volume of concentrated sulfuric acid, followed by removal of oxides of nitrogen by passage of dried air through the distilled acid. The iodine used had been resublimed.

Methylethylacetic acid was prepared by the method of "Organic Syntheses,"[9] with the time-saving modification that the *s*-butylmagnesium chloride was carbonated by dropping onto excess solid carbon dioxide. This reduced the yields from 86 to 72%, but was very much more rapid.

Methylethylacetic acid was resolved with brucine as described by Schütz and Marckwald.[10] No attempt was made to carry the resolution to a maximum, acid of a specific rotation as high as +7.2° being obtainable from the mother liquors from which several fractions of the brucine salt had been crystallized. The maximum rotation at 20° for the D line of sodium is reported as −16.67° by Schütz and Marckwald.

The ketones were prepared by the same procedure as was followed by Conant and Carlson[11] in preparing a series of optically active ketones. The active acid was converted into the acid chloride by refluxing with thionyl chloride, this reagent having been purified by distillation first from quinoline, and then from linseed oil.[12] The acid chloride boiled at 118° at 760 mm. pressure. Grignard reagents prepared respectively from methyl iodide, ethyl bromide, benzyl chloride, cyclohexyl chloride and bromobenzene, were treated with equivalent amounts of freshly fused zinc chloride dissolved in dry ether. Magnesium chloride was precipitated and the resulting solutions of organozinc compounds were treated, with warming, with the methylethylacetyl chloride, the solution hydrolyzed after a few minutes with dilute sulfuric acid, the ether layer washed with sodium carbonate solution and water, and dried with sodium sulfate. There was evidently always some racemization in the formation of the ketones, for successive samples of the same ketone showed varying ratios between their optical rotations and the rotations of the acid from which they were prepared. Hydrolyzing the product of the coupling reaction with ammonium chloride instead of dilute sulfuric acid did not eliminate this racemization. In spite of care in removing acids and bases from the ketones, all except menthone were

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[8] Bartlett, THIS JOURNAL, **56**, 967 (1934).

[9] "Organic Syntheses," Collective Volume I, John Wiley and Sons, Inc., New York City, pp. 353–355.

[10] Schütz and Marckwald, *Ber.*, **29**, 52 (1896).

[11] Conant and Carlson, THIS JOURNAL, **54**, 4056 (1932).

[12] Fieser, "Laboratory Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1935, p. 339.

found to undergo racemization in ordinary glass-stoppered bottles over a period of several days. The following are the rotations of the samples of ketone actually used for the racemization measurements, immediately before use.

TABLE III

SPECIFIC ROTATIONS OF SECONDARY BUTYL KETONES, C_4H_9COR

R	$[\alpha]^{25}_D$ of acid	$[\alpha]^{25}_D$ of ketone
CH_3-	+5.4°	+8.15°
C_2H_5-	+5.0	+8.5
C_6H_5-	+5.7	+9.27
$C_6H_5CH_2$-	+4.5	+4.3
Cyclohexyl	+7.2	+4.4

Measurements of racemization were made in all-glass polarimeter tubes. For the slow racemizations the tubes were simply kept in a thermostat between readings; for the rapid ones water from the thermostat was circulated through the tube jackets. Iodination measurements were carried out with a Keuffel and Esser color analyzer, using a wave length of 620 mμ. The same concentrations of ketone and nitric acid were used in the racemizations as in the iodinations; the amount of iodine used in the latter never exceeded 3% of the total amount of ketone, nor 2% of the total nitric acid present. The period of observation for the racemizations extended until the rotations were too small to measure, and included from five to ten readings; readings were made on the iodination runs up to total disappearance of the iodine, and numbered between ten and twenty to a run.

The velocity constants were determined graphically as the slope of the straight line drawn through the points when the logarithm of the molal concentration of ketone (or of the optical rotation) was plotted against time. The constants were corrected to the basis of natural logarithms, and are expressed in minutes as the time unit. In averaging the results of different check runs, the runs were weighted since they varied among themselves in precision. Most of the runs necessarily consist of determinations made at about equal time intervals, and there is no way of pairing the points for calculation of deviations of the constants calculated from different pairs without unduly weighting those which are close together. We therefore adopted a purely graphical method of assigning weights to the different runs: the lines of maximum and minimum slope were taken which could be reasonably drawn through the points, and the runs were given weights inversely proportional to the individual differences between the maximum and minimum slopes. Figure 2 illustrates this procedure.

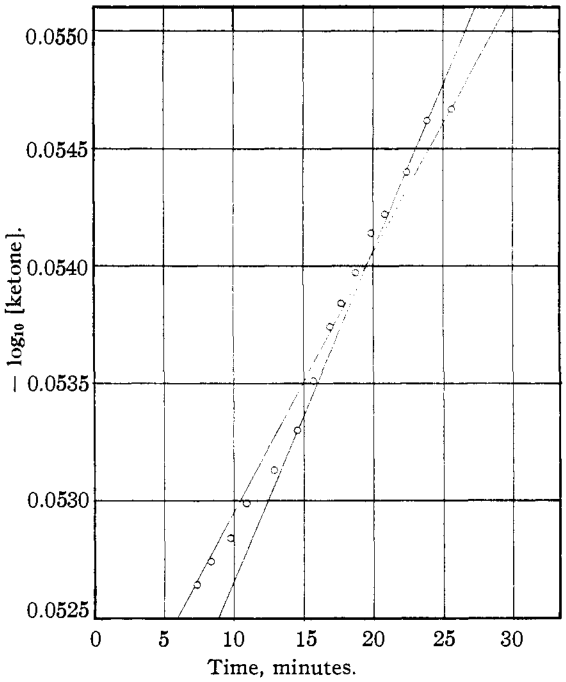

Fig. 2.—An iodination of the benzyl *s*-butyl ketone on which the estimated uncertainty is 20%, showing the two lines of greatest and least slope which might reasonably be drawn through the experimental points.

Summary

1. The competitive rates of enolization in the two possible manners have been measured for the ketones *d*-$C_2H_5(CH_3)CHCOR$, where R is methyl, ethyl, cyclohexyl and benzyl, in glacial acetic acid solution with nitric acid as catalyst.

2. The method has been checked with the observation that under these same conditions the rates of iodination and racemization of *d*-methylethylacetophenone are identical.

3. The relationship between alkyl substitution and competitive enolization rate of an active hydrogen does not bear out any simple hypothesis of enolization mechanism previously advanced.

4. The relationship between alkyl substitution and competitive enolization rate is opposite in menthone to what it is in the acyclic secondary butyl ketones.

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