THE CLEAVAGE OF CERTAIN UNSYMMETRICAL 1,3-DIKETONES

BY WALTER M. KUTZ AND HOMER ADKINS

A diketone of the type $R'C(O)CR_2C(O)R''$ may undergo alcoholysis to form either the ester $R'COOEt$ or $R''COOEt$, together with the corresponding ketones. Bradley and Robinson[1] found in the case of 18 out of 20 aryl 1,3-diketones that alkaline hydrolysis took place in such a way that the stronger of the two possible acids was produced in the larger amount. It was shown in a previous paper[2] that acetylbenzoylmethane and benzylacetylbenzoylmethane underwent alcoholysis in the presence of hydrogen chloride to give ethyl acetate unmixed with any ethyl benzoate. Having these facts in mind, the alcoholysis and hydrolysis of certain unsymmetrical 1,3-diketones were carried out with the view to ascertain to what extent structural factors and experimental conditions determine the point of cleavage. The ratios of products in the hydrolysis and alcoholysis of the following list of 1,3-diketones have been determined

$CH_3C(O)CH_2C(O)C_4H_9$-n $CH_3C(O)CH_2C(O)C_6H_5$(phenyl)

$CH_3C(O)CH_2C(O)C_5H_{11}$-$n$ $CH_3C(O)CH(CH_2C_6H_5)C(O)C_6H_5$(phenyl)

$CH_3C(O)CH_2C(O)C_5H_{11}$-$iso$ $CH_3C(O)CH_2C(O)C_6H_{11}$(cyclohexyl)

$CH_3C(O)CH_2C(O)C_5H_{11}$-$sec.$ $CH_3C(O)CH_2C(O)C_4H_3O$(furyl)

$CH_3C(O)CH_2C(O)C_5H_{11}$-$tert.$
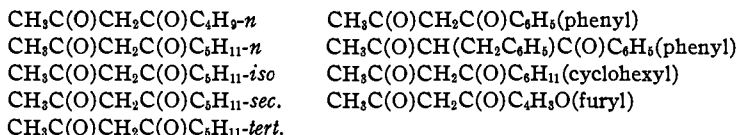
Alcoholysis was carried out by placing the desired amount of diketone, together with a one-half molar ratio of hydrogen chloride in ethanol, in a thermostat at 60° for four days. The volume of the alcoholysis mixture was approximately 25 ml. per 0.01 mole of diketone. Two ml. of phenylhydrazine per 0.01 mole of sample was then added to combine with the hydrogen chloride and ketones. After standing for two hours, the reaction mixture was distilled from an oil-bath at a temperature of 110–120°. At this stage the reaction mixtures from the five aliphatic diketones were treated with four successive portions (15 ml.) of butanol, each portion being distilled out under a pressure of 100 mm. before the addition of the next. This procedure was necessary in order to distil out the esters of the various butyric and valeric acids. The ester in the distillate was saponified with 0.1 N sodium hydroxide and the excess back titrated with sulfuric acid of the same concentration, phenolphthalein being used as an indicator. The mixture was evaporated to dryness and an amount of 0.3 N sulfuric acid, equivalent to the sodium salts of the fatty acids present, added. This solution was diluted with water until 50 ml. contained approximately 7.5 millimoles of acid.

In the case of four of the diketones, one of the esters which could be formed was too high boiling to be conveniently distilled out in the presence of phenylhydrazine. After completion of alcoholysis, the mixture was divided into two equal portions. To one phenylhydrazine was added and the ethyl acetate present distilled out with ethanol. The other half was analyzed for acetone by the sodium sulfite method as previously

[1] Bradley and Robinson, J. Chem. Soc., 129, 2356 (1926).

[2] Adkins, Kutz and Coffman, THIS JOURNAL, 52, 3212 (1930).

described.[3] The alcoholysis sample was distilled, giving a distillate which contained ethyl acetate, ethanol, hydrogen chloride and any acetone; aqueous sodium hydroxide was then added to neutralize the acid and to saponify the ester. This mixture was distilled, any acetone present being thus obtained in an ethanol–water solution.

The method of analysis for the ratio of acids (or esters) produced in the cleavage of the diketones involved the partition of the acids between water and benzene, the titration of each layer with standard alkali and the calculation of the ratios of the acids present from the result of this titration and a knowledge of the partition of the acids involved between water and benzene.

Behrens[4] described the determination of a number of acids by the partition between ether and water. The greater insolubility in each other of benzene and water and the greater differences in the partition coefficients of the aliphatic acids for this pair of solvents[5] indicated that benzene was to be preferred to ether as the organic solvent.[6]

The results of the determination of the partition of the various acids (except acetic) at various concentrations between equal volumes of benzene and water is shown in Fig. 1. The concentration of acetic acid in the benzene layer was found to be from 1.9 to 2.2 millimoles per liter when the concentration in the water layer was from 75 to 110 millimoles per liter. In the later calculations the concentration of acetic acid in the benzene layer was taken as 2 millimoles per liter. Since all of the samples to be analyzed contained approximately 1.5×10^{-1} moles of sodium sulfate per liter, that concentration of the salt was always present in the water layer during the determination of the partition of the acids. The titrations were made on 25-ml. samples with 0.1 N sodium hydroxide, using phenolphthalein as an indicator, after partition had taken place over a two-hour period, the samples being shaken frequently while they were held in a thermostat at 25°.

The acid solutions obtained by the alcoholysis and hydrolysis of the various diketones were analyzed for the two acids present. Fifty ml. of the solution prepared as described above was placed in a separatory funnel and shaken with 50 ml. of benzene. After shaking for a few minutes it was placed in a thermostat at 25° and shaken at intervals of fifteen minutes over a period of two hours. The layers were separated and titrated with carbonate-free 0.1 N sodium hydroxide. From the previously determined partition ratios the amount of each acid present and consequently the amount of split was calculated. Using the data which were found in the analysis for the acids formed in the hydrolysis of acetylbutyrylmethane, a calculation of the percentage of acetyl split as compared to the total amount of hydrolysis is shown below. After partition of the aqueous acid solution with benzene, 63.0 ml. of 0.1 N alkali was required to neutralize 50 ml. of the water layer and 18.5 ml. of 0.1 N alkali for the same volume of the benzene layer. Therefore the amount of acid in the water layer was 6.3 millimoles and in the benzene layer 1.85 millimoles. The concentration of acetic acid in the benzene layer under the conditions used here had been determined to be approximately 2.0

[3] Child and Adkins, THIS JOURNAL, 45, 3013 (1923).

[4] Behrens, Z. anal. Chem., 69, 97 (1926).

[5] Brown and Bury, J. Chem. Soc., 123, 2430 (1923); Smith and White, J. Phys. Chem., 33, 1953 (1929).

[6] Cf. Werkman, Ind. Eng. Chem., Anal. Ed., 2, 302 (1930).

millimoles per liter or 0.1 millimole in 50 ml. of solution. The concentration of butyric acid in the benzene layer was accordingly 35 millimoles per liter. From the graph on which the partition data for the various acids had been plotted, the corresponding concentration of the butyric acid in the water layer was shown to be 48 millimoles per liter or 2.4 millimoles in 50 ml. The total amount of acetic acid was equal to the amount of
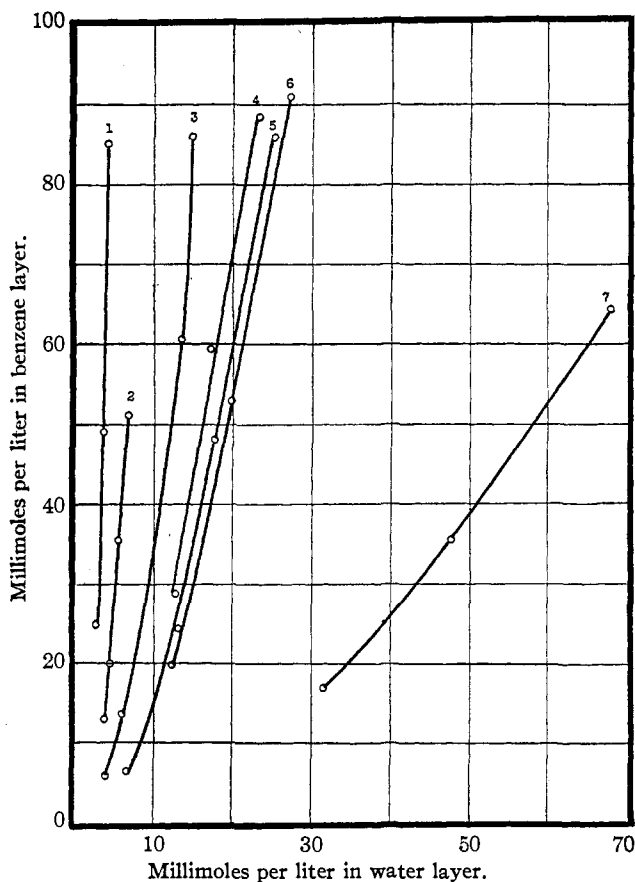

Fig. 1.—Distribution of (1) cyclohexanoic, (2) benzoic, (3) trimethylacetic, (4) n-valeric, (5) methylethylacetic, (6) iso-valeric, and (7) n-butyric acids at various concentrations between equal volumes of benzene and water containing 0.15 mole of sodium sulfate per liter.

acid in the water layer plus the amount of acetic acid in the benzene layer minus the amount of butyric acid in the water layer, i. e., 6.3 + 0.1 − 2.4 = 4.0 millimoles. The amount of butyric acid was determined by difference, the total acidity of the water and benzene layers less the amount of acetic acid, i. e., 8.15 − 4.0 = 4.15 millimoles. The percentage of "acetyl" cleavage was therefore 49% (4.0/8.15 × 100).

The accuracy of the method of analysis was tested by the analysis of mixtures of known composition of acetic and butyric acids, of acetic and valeric acids, of ethyl ace-

tate and ethyl butyrate, and of ethyl acetate and ethyl valerate. The results were as follows. A solution containing the acids in the ratio 51.5% acetic acid and 49.5% butyric acid was found to contain 50 and 50% acetic acid in two analyses. A solution containing 52.4% acetic and 47.6% valeric acids showed by analysis 53 and 53% acetic acid. A mixture of esters containing 49.8% ethyl acetate and 50.2% ethyl butyrate showed 47 and 46% acetic acid upon analysis. A mixture of ethyl acetate (56.7%) and ethyl valerate (43.3%) showed 55% acetic acid after saponification and partition. Another sample containing 74.9% of ethyl acetate showed by analysis 77%.

The determination of the products formed in hydrolysis was very similar to the method just described. The diketone was placed in a thermostat at 60° with an excess of 0.1 N sodium hydroxide. Twenty-four hours were sufficient to give practically complete hydrolysis, except in the case of acetyltrimethylacetylmethane, which required at least twice that length of time. The hydrolysis sample was back titrated with standard sulfuric acid and then evaporated to dryness. The procedure from this point on was the same as for the alcoholysis samples, $i. e.$, the addition of a calculated quantity of standard sulfuric acid, partition, titration and calculation.

In the hydrolysis of acetylbenzoylmethane, benzylacetylbenzoylmethane, acetylcyclohexoylmethane and acetylfuroylmethane, one of the acids which could be formed is only slightly soluble in water at 25°, so in these cases the whole of an hydrolysis sample was subjected to partition rather than an aliquot portion. The aqueous acid solution was not homogeneous and a representative sample could not be secured.

The amounts of acids, expressed in millimoles, from the esters formed in the alcoholysis of five diketones are given below: from acetylbutyrylmethane, acetic acid 4.15 and 4.30, butyric acid 5.47 and 5.35; from acetylvalerylmethane, acetic acid 6.26 and 5.53, valeric acid 4.06 and 3.37; from acetylisovalerylmethane, acetic acid 4.04 and 5.25, isovaleric acid 2.55 and 2.75; from acetyl-$sec.$-valerylmethane, acetic acid 5.80 and 5.90, $sec.$-valeric acid 1.38 and 1.38; from acetyltrimethylacetylmethane, acetic acid 6.04, 6.14 and 6.44, trimethylacetic acid 0.56, 0.56 and 0.80.

The amounts of ethyl acetate and acetone expressed in millimoles formed in the alcoholysis of four diketones (which might split to give high-boiling esters) are given below: from acetylbenzoylmethane, ethyl acetate 8.66 and 8.66, acetone, none; from acetylcyclohexanoylmethane, ethyl acetate 5.80 and 6.02, acetone 4.3 and 4.0; from benzylacetylbenzoylmethane, ethyl acetate 7.70 and 8.30, ethyl benzoate, none; from acetylfuroylmethane, ethyl acetate 13.1 and 12.4, acetone, none.

The amounts of acids, expressed in millimoles, from the alkaline hydrolysis of nine diketones are given below: from acetylbutyrylmethane, acetic acid 4.00 and 4.04, butyric acid 4.15 and 4.15; from acetylvalerylmethane, acetic acid 4.38 and 4.42, valeric acid 3.58 and 3.66; from acetylisovalerylmethane, acetic acid 5.52 and 5.80, isovaleric acid 2.71 and 2.87; from acetyl-$sec.$-valerylmethane, acetic acid 4.85 and 4.90, $sec.$-valeric acid 2.95 and 2.95; from acetyltrimethylacetylmethane, acetic acid 4.25, 4.35 and 4.93, trimethylacetic acid 3.15, 3.15 and 3.35; from acetylbenzoylmethane, acetic acid 5.09 and 5.67, benzoic acid 0.82 and 0.93. From acetylcyclohexanoylmethane, acetic acid 4.69 and 4.74, cyclohexanoic acid 3.71 and 3.76; from benzylacetylbenzoylmethane, acetic acid 5.25 and 5.90, benzoic acid 2.35 and 2.70; from acetylfuroylmethane, acetic acid 8.62 and 8.78, furoic acid, none.

There is given in Table I a summary calculated from the above data which indicates the extent to which the linkage on the one side or the other of the "methane" carbon atom was split by alcoholysis or hydrolysis.

There does not appear to be a close agreement between the strength of the acids and the ratio in which they were produced through hydrolysis,

TABLE I

THE RATIO OF PRODUCTS IN THE CLEAVAGE OF CERTAIN 1,3-DIKETONES

Diketone	Alcoholysis		Hydrolysis	
	CH_3—C=O, %	R—C=O, %	CH_3—C=O, %	R—C=O, %
Acetylbutyrylmethane	43.5	56.5	49	51
Acetylvalerylmethane	61	39	55	45
Acetylisovalerylmethane	65.5	34.5	67	33
Acetyl-sec.-valerylmethane	81	19	62	38
Acetyltrimethylacetylmethane	91	9	58	42
Acetylbenzoylmethane	100	0	86	14
Acetylcyclohexanoylmethane	58.5	41.5	56	44
Benzylacetylbenzoylmethane	100	0	69	31
Acetylfuroylmethane	100	0	100	0

although in the case of the hydrolysis of four of the five aliphatic diketones the stronger acid was produced in the larger amount. Furoic acid is forty times as strong as acetic acid, yet none was produced in the hydrolysis of acetylfuroylmethane. Benzoic acid is three to four times stronger than acetic acid yet over five times as much acetic as benzoic acid was produced in the hydrolysis of acetylbenzoylmethane, while when one of the hydrogens on the "methane" carbon atom had been replaced by a benzyl group the ratio of acetic to benzoic acid was slightly more than 2 to 1. Butyric and acetic acids were produced in almost equal amounts by the hydrolysis of acetylbutyrylmethane, while twice as much acetic acid as isovaleric acid was produced in the hydrolysis of acetylisovalerylmethane despite the fact that isovaleric acid is stronger than butyric acid.

In the case of three of the nine diketones (acetylisovalerylmethane, acetyl-cyclohexanoylmethane and acetylfuroylmethane) there was no essential difference between the ratio of the products produced in hydrolysis and alcoholysis. In one case (acetylbutyrylmethane) the cleavage to produce an acetyl compound was slightly less in alcohol than in water, but in this determination (acetic and butyric acids) the experimental error was largest. In the other five cases there was from 10 to 45% greater production of the acetyl compound in acid alcoholysis than in alkaline hydrolysis. In general it would seem that the ratio of products is less modified by changes in structure in the case of alkaline hydrolysis than in acid alcoholysis.

The data for the four diketones which have a butyl group at one end of the diketone molecule show clearly that increased branching in the radical greatly slows up the rate of alcoholysis (both actually and relatively) at that side of the molecule. The diketone having the n-butyl group breaks to give 39% of the five-carbon acid, the diketone having the isobutyl group gives 34.5% of the corresponding acid, the sec.-butyl group gives 19% of the acid while with the tert.-butyl group the production of the five-carbon acid has dropped to 9%. In contrast with this is the fact that the alkaline hydrolysis was but little affected by these changes in structure. In this

connection it should be pointed out that the alcoholysis of the diketones containing the *sec.*-butyl and *tert.*-butyl groups was very slow and did not go more than 20 to 30% to completion in 150 hours, while in the case of all the other diketones (except benzylacetylbenzoylmethane) alcoholysis was 100% in less than 100 hours. These facts might be explained on the basis of steric hindrance were it not for the fact that the unsaturated cyclic radicals phenyl and furyl decreased alcoholysis on that side of the diketone to the vanishing point while the cyclohexyl radical permitted a 41.5% cleavage to form ethyl cyclohexanoate. It appears then that the factors which are operating in these cases to determine the point of cleavage are probably constitutional rather than steric.

It has been pointed out[2] that there is a correlation between the extent of enolization of a diketone and the rate of alcoholysis in the presence of hydrogen chloride. Thus it is possible that the ratio of the products in the acid alcoholysis of an unsymmetrical diketone represents approximately the ratio of the extent of the enolization of the two carbonyl groups.

The authors wish to emphasize that in their opinion the ratios of products formed in the solvolysis of the 1,3-diketones as reported in this paper are simply a measure of the relative rates of two competitive reactions and are in no sense measures of the strength or thermodynamic stability of the linkages involved. As noted in another paper they have so far failed in all attempts to determine the latter values for any 1,3-diketones. Such values are as much a characteristic of a given structure as its absorption spectra, while the ratio of the rates of two alternative modes of reaction are modifiable almost without limit. It is interesting to note that the experimental work reported in this paper shows that increased branching in the butyl radical decreases the *rate* of cleavage of the acyl radical containing it from the remainder of the molecule to which it is attached, while Conant, Small and Sloan[7] have shown that increased branching in the butyl group increases the extent of dissociation of hexasubstituted ethanes. This latter determination is, of course, a measurement of the thermodynamic stability of the carbon to carbon linkage.

Preparation and Purity of Reagents.—Acetylbutyrylmethane, acetylvaleryl-methane, acetylisovalerylmethane, acetyl-*sec.*-valerylmethane, acetyltrimethylacetyl-methane, acetylbenzoylmethane and acetylcyclohexanolmethane were prepared by the method previously described,[3] *i. e.*, by condensing ethyl acetate with the proper methyl ketone in the presence of metallic sodium. Acetylfuroylmethane was prepared by condensing ethyl furoate with acetone in the presence of sodium ethoxide, the method being the same as for diacetylmethane, except that toluene was substituted for the excess ester used as a solvent in that preparation. The preparation of benzylacetylbenzoyl-methane was described in the previous paper. There is given below a summary showing the physical constants, yields and analyses where necessary of the various reagents used in this investigation. Acetylbutyrylmethane: yield 48%, b. p. 173–175°, d_{25}^{25} 0.9375

[7] Conant, Small and Sloan, THIS JOURNAL, **47**, 3068 (1925); **48**, 1743 (1926).

[Morgan and Drew, *J. Chem. Soc.*, **125**, 737 (1924)]; acetylvalerylmethane: yield 58%, b. p. 64–66° (5 mm.), d_{25}^{25} 0.9218 [Morgan and Holmes, *ibid.*, 760 (1924)]; acetyl-*sec.*-valerylmethane: yield 52%, b. p. 62–65° (5 mm.), d_{25}^{25} 0.9160 [*Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.55%; H, 9.93%. Found: C, 67.32, 67.26%; H, 9.77, 9.62%]; acetyl-trimethylacetylmethane: yield 51%, b. p. 164–167°, d_{25}^{25} 0.9155 [Couturier, *Compt. rend.*, **150**, 928 (1910)]; acetylbenzoylmethane: m. p. 57–58° (see earlier paper); benzylacetylbenzoylmethane: m. p. 55–56° (see earlier paper); acetylcyclohexanoyl-methane: yield 55%, b. p. 104–107° (10 mm.), d_{25}^{25} 1.0080 [Godchot, *Compt. rend.*, **151**, 1131 (1910)]; acetylfuroylmethane: yield 20%, m. p. (from ethanol and water), 30–31° [*Anal.* Calcd. for $C_8H_8O_3$: C, 63.13%; H, 5.30%. Found: C, 62.98, 62.80%; H, 5.41, 5.38%]; acetic acid: b. p. 116–117° (after crystallization); butyric acid: b. p. 161–161.5°; valeric acid: b. p. 180–182°; isovaleric acid: b. p. 172–174°; methyl-ethylacetic acid: b. p. 172–174°; trimethylacetic acid: m. p. 34–35°; benzoic acid: m. p. 120–121°; cyclohexanoic acid: m. p. 28–30°.

Summary

The ratio of esters and of salts of acids produced in the acid alcoholysis and the alkaline hydrolysis, respectively, of nine unsymmetrical 1,3-diketones has been determined and the results summarized in tabular form. There was not found to be a close correlation between the amounts and the strength of the acids produced in hydrolysis such as had previously been observed in the case of certain diaryl 1,3-diketones. The ratio of products was less modified by changes in structure in the case of alkaline hydrolysis than in acid alcoholysis. Increased branching in the radical at one end of the diketone molecule decreased the cleavage on that side but this does not appear to be due entirely to steric effects, for the cyclohexyl group was much less effective in this regard than the phenyl or furyl radical. It has been suggested that the ratio of products is a measure of the relative extent of enolization of the two carbonyl groups in these unsymmetrical diketones.

The preparation of acetyl-*sec.*-valerylmethane and acetylfuroylmethane is reported for the first time.

MADISON, WISCONSIN