

a.  $X = H$ .—The hydrazo compound was partially oxidized during evaporation of the ether, leading to a yellow solid. This was dissolved in 600 ml. of absolute ethanol and concentrated in vacuum below room temperature leading to 14.7 g. (0.0425 mole), 77% yield, of crude azo compound, m.p. 107–108° dec., reported 111°.<sup>21</sup> Decom-

methanol, m.p. 108–109°, reported<sup>17</sup> 110°, 3.9 g. (0.0091 mole), 41% yield. The yields of nitrogen from this and the preceding compound, when determined in the kinetic runs were  $100 \pm 3\%$ .

d.  $X = m\text{-CH}_3$ .—The crude hydrazo compound was oxidized as described above, the reaction in this case being vigorous and requiring cooling in ice. The ether was evaporated and the azo compound was crystallized from methanol, m.p. 108–109°, 6.0 g., (0.0165 mole), 64% yield. *Anal.* Calcd. for  $C_{24}H_{22}N_2$ : C, 86.15; H, 6.12. Found: C, 84.88; H, 6.16. The yield of nitrogen from this compound in the kinetic runs was  $100 \pm 2\%$ .

Products of Decomposition.—Phenylazotriphenylmethane, 8.6 g. (0.025 mole), was heated in 100 ml. of acetic acid at 63° for 24 hours under nitrogen. Air was then passed through the solution with no apparent effect. The solution was distilled through a 10" glass spiral column, leading to benzene, b.p. 78–80°, 0.80 g., (0.010 mole), 40% yield; this was converted to *m*-dinitrobenzene, 1.5 g. (0.009 mole), m.p. and mixed m.p. 88–89°. In a blank run distillation of a solution of 1 g. of benzene in 100 ml. of acetic acid through the same apparatus led to recovery of benzene in 70% yield. The remainder of the acetic acid was distilled off and the residue was extracted with 40 ml. of hot water. Concentration of the aqueous extract to dryness led to no succinic acid.

The residue was further extracted with 80 ml. of hot ethanol, leading to an insoluble tar; a suspended solid, 0.025 g., m.p. 270°, apparently tetraphenylmethane, 0.3% yield, reported<sup>21</sup> m.p. 267°; and the alcoholic extract. The latter was cooled, leading to a tar; a solid, 0.5 g., m.p. 120–140°, from which, after recrystallization from alcohol there was obtained a product, 0.030 g., m.p. 146°, possibly hexaphenylethane 0.5% yield, reported<sup>22</sup> m.p. 145–147°; and the alcohol solution. The latter was steam distilled, leading to biphenyl, 0.2 g. (0.0013 mole), 10% yield, m.p. and mixed m.p. 68–69°. Extraction of the tars with hot benzene led to an impure solid, 0.42 g., m.p. 80–92, which was not worked up further.

**Acknowledgment.**—We are pleased to acknowledge generous support of this work by the National Science Foundation.

(22) M. Gomberg and L. H. Cone, *ibid.*, **37**, 2037 (1904).  
WALTHAM, MASSACHUSETTS

TABLE II

REACTION OF TRIPHENYLMETHYL CHLORIDE WITH PHENYL-HYDRAZINE

$m\text{-X-C}_6\text{H}_4\text{NHNH}_2\text{H}_2\text{Cl}$ X	g.	$(\text{C}_6\text{H}_5)_3\text{CCl}$ g.	$\text{C}_6\text{H}_5\text{N}$ ml.
H	8.0	16.0	120
NO <sub>2</sub>	9.7	14.1	130
Br	5.0	6.2	80
CH <sub>3</sub>	4.1	8.0	80

position of a sample at 100° in decalin led to 67% of the theoretical yield of nitrogen. The nitrogen was swept with carbon dioxide and collected over 50% potassium hydroxide. Four additional crystallizations from absolute ethanol led to a product melting at 110–112° which, when decomposed, led to 96% yield of nitrogen.

b.  $X = m\text{-NO}_2$ .—The crude hydrazo product melted at 140–150° and was somewhat difficult to oxidize. It was not affected by treatment in ether solution at room temperature with 35% hydrogen peroxide in the presence and absence of sodium bicarbonate. It was oxidized slowly by hydrogen peroxide in acetone. It was apparently oxidized by nitrogen dioxide in acetic acid, but the results were not consistent. Amyl nitrite led to satisfactory results and was used in subsequent syntheses. The hydrazo compound, 2.32 g., was suspended in anhydrous ether and treated with two molar equivalents of amyl nitrite and a few drops of acetyl chloride, a clear yellow solution resulting. The solution was filtered and evaporated in vacuum and the azo compound was crystallized from methanol, m.p. 111–112°, reported<sup>17</sup> 111–112°.

c.  $X = m\text{-Br}$ .—The crude hydrazo product was suspended in ether and oxidized as described above. The ether was evaporated and the product was washed with

(21) M. Gomberg, *Ber.*, **30**, 2044 (1897).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SIR JOHN CASS COLLEGE]

## The Kinetics of Ring Closure of Alkyl-substituted 3,3-Dimethyl-5-keto-hexanoic Acids by Sulfuric Acid

BY W. E. SILBERMANN AND T. HENSHALL<sup>1</sup>

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Acid-catalyzed ring-closures of 3,3-dimethyl-5-keto-hexanoic acid and of 6-alkyl-substituted homologs have been found to give dimedone and 3,3-dimethyl-6-alkyl-cyclohexanediones-1,5, respectively. The kinetics of the cyclizations of the hexanoic acid and of four alkyl-substituted derivatives have been investigated in aqueous sulfuric acid. The reaction has also been followed in acetic acid-sulfuric acid solution. The kinetic results are consistent with a reaction sequence in which the rate-controlling stage is electrophilic attack by  $C_1^+$  on the double bond of the enolized form of the keto-acid.

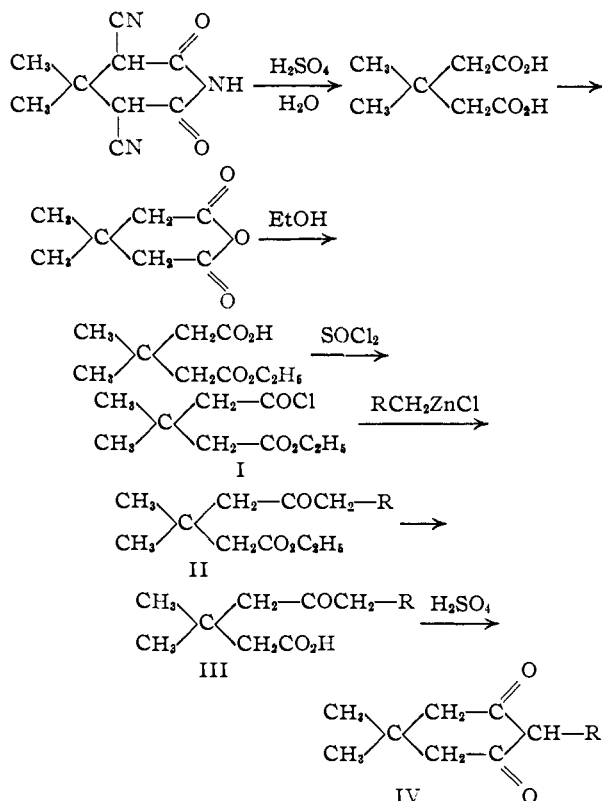
The results of preliminary experiments on the cyclization of 3,3-dimethyl-5-keto-hexanoic acid (III, R = H) to dimedone by aqueous sulfuric acid already have been reported.<sup>2</sup> In further work on this reaction, the range of acid concentrations has been extended, and it has been observed that the activation energy for the process is markedly dependent on the acidity of the solvent, decreasing as the concentration of sulfuric acid increases (Table II). This effect is interpreted in terms of

an acid-base equilibrium involving the keto-acid and the oxonium ions present in the solution and suggests that the reaction proceeds by way of a protonated intermediate. The most reasonable reaction path appears to involve the protonated carboxyl group of the keto-acid and the enolic double bond at  $C_5=C_6$  (see Discussion). Accordingly it was thought that the most profitable approach toward the elucidation of this reaction lay in an investigation of the effects of substituent groups with definite electronic properties on the  $\pi$ -electrons of the enol form. The choice of suitable substituents, is, however, strictly limited both by the ease of unambiguous synthesis and by the stability

(1) Material taken from part of a thesis presented by W.E.S. in support of candidature for the Ph.D. degree of London University.

(2) T. Henshall, W. E. Silbermann and J. G. Webster, *THIS JOURNAL*, **77**, 6656 (1955).

of such groups to the reaction medium. A start has been made with those keto-acids substituted on  $C_3$  by methyl, ethyl, *n*-propyl and isopropyl groups. These were prepared by the route outlined below, in which  $\alpha,\alpha'$ -dicyano- $\beta,\beta$ -dimethylglutarimide, obtained from acetone and cyanoacetic ester by Guareschi's method, is converted successively into  $\beta,\beta$ -dimethylglutaric acid, anhydride, half-ester, ester chloride, keto-ester and keto-



acid. In kinetic measurements on these acids, only the trimethyloctanoic acid (III, R = isopropyl) showed any departure from simple kinetic order, an effect which may arise from the bulky nature of the isopropyl group. The activation energies for ring closure of the substituted acids were found to be significantly lower than for the parent compound, and the same dependence of activation energy on sulfuric acid concentration of the medium was observed also for the heptanoic, octanoic and nonanoic acids. The curves of  $E_a$  against "%  $H_2SO_4$ " are roughly parallel (see figure) corresponding to a differential heat,  $\Delta H$ , of the order of 2 kcal. mole<sup>-1</sup> over the range of investigation.

Additional evidence in support of the proposed mechanism has been obtained from kinetic measurements in acetic acid-sulfuric acid mixtures; in the presence of high concentrations of sulfuric acid the kinetics in this medium are much more complicated than those in aqueous solution, but

(3) The 3,3-dimethyl-5-keto-acids are numbered conventionally: abbreviated names: hexanoic acid, heptanoic acid, octanoic acid, trimethyloctanoic acid and nonanoic acid occasionally used in the subsequent text all refer to keto-acids of type III (R = H,  $CH_3$ ,  $C_2H_5$ , iso- $C_3H_7$ , *n*- $C_3H_7$ , respectively.) In order that each carbon atom shall retain the same number, the cyclic products IV will be named as 3,3-dimethyl-6-alkyl-cyclohexane-1,5-diones.

good first-order rate constants are obtained from measurements in acetic acid containing small proportions of sulfuric acid. Rates similar to those obtained in aqueous solutions were induced by these relatively smaller amounts of the mineral acid, indicating the probability of easier proton transfer from the acetoxonium ion to the basic centers of the keto-acid molecule. The activation energies in acetic acid solution were also much lower than in water. Traces of water added to the acetic acid-sulfuric acid solvent had only slight effects on the total rate but raised the energy of activation and correspondingly reduced the entropy of activation. Small quantities of acetic anhydride apparently inhibited the reaction rate in acetic acid-sulfuric acid solution, and in the presence of sufficient anhydride (up to 5%) the reaction was completely suppressed. Also there was no measurable reaction in pure acetic acid or in "moist" acetic acid free of mineral acid.

A correlation of reaction rate of the substituted acids with the Hammett acidity function  $H_0$  and with stoichiometric acid concentration  $C_{H_2SO_4}$  has been attempted. The results are similar to those for the hexanoic acid, *i.e.*, plots of  $\log k_{100}^4$  against  $H_0$  were slightly curved (except for the heptanoic acid) and the average slopes lie between 0.42 and 0.47, while the linear plots of  $\log k_{100}$  against  $\log C_{H_2SO_4}$  show gradients of 4.0, 4.8 and 5.0 for the heptanoic, octanoic and nonanoic acids, respectively. There is apparently no simplification of these relationships in aqueous perchloric acid solution; for preliminary experiments with the heptanoic acid gave

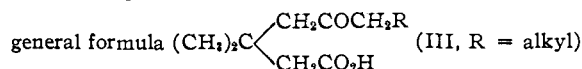
$$\delta(\log k)/\delta(\log C_{HClO_4}) \approx 5 \text{ and } -\delta(\log k)/\delta(H_0) \approx 0.5$$

and the investigations in these solutions were not pursued further.

It is proposed to extend the study of the cyclization reactions and especially to determine the influence of substituents on  $C_2$  and of different groups on  $C_3$  of the keto-acids; the results of such experiments will be communicated.

### Experimental

**Preparation and Purification of Materials.** 3,3-Dimethyl-5-keto-hexanoic acid was prepared and purified as described previously.<sup>2</sup>  $\delta$ -Keto-acids of



Ethyl hydrogen  $\beta,\beta$ -dimethylglutarate was obtained by heating  $\beta,\beta$ -dimethylglutaric anhydride<sup>6</sup> (0.84 mole) on the steam-bath for 29 hr. with 300 ml. of absolute ethanol. The excess of alcohol was removed and the residue fractionally distilled, the main fraction (b.p. 148–150° (2.5 mm.)) being collected very slowly. The distillate failed to crystallize at  $-12^\circ$ ; it was freed of about 9 g. of the acid anhydride. The colorless oily half-ester was obtained in 82% yield (equivalent weight found 186.2, calcd. for  $C_{17}H_{30}O_4$ , 188.2).

**Acid Chloride I, Keto-esters II and Keto-acids III.**—The acid chloride I was prepared as required by treating 20- to 30-g. portions of the half-ester with twice the theoretical quantity of thionyl chloride (b.p. 76–78°) for 1.5 to 1.8 hr. at room temperature and then for 0.5 hr. at 40°. The excess of thionyl chloride was removed and the residual liquid immediately distilled. The acid chloride was col-

(4)  $k_{100}$  is the first-order rate constant at 100.0° on the scale of the Anschütz standard thermometer.

(5) A. I. Vogel, *J. Chem. Soc.*, 1761 (1934).

lected (70–85% yield) between 115° (13 mm.) and 121° (16 mm.).

Ethyl esters II of the required keto-acids were prepared by reaction of the ester acid chloride I with alkyl zinc chlorides,  $RCH_2ZnCl$ . The latter reagents were prepared in the usual way<sup>7</sup> from the Grignard reagent,  $RCH_2MgBr$ , and freshly fused and ground anhydrous zinc chloride in dry ether. Most of the ether was replaced by dry benzene before the acid chloride, dissolved in dry benzene, was gradually added to the alkyl zinc chloride reagent. The well-stirred reaction mixture was heated under gentle reflux (temp. in liquid, 62°) for about 3 hr. after all the acid chloride had been added, then cooled in ice-water and decomposed by cold water containing some hydrochloric acid. The organic liquid layer was separated, combined with a benzene washing of the aqueous layer, dried ( $MgSO_4$ ) and the solvent removed. The residual liquid was fractionally distilled. Yields of the colorless oily keto-esters were between 67 and 85% based on the acid chloride.

Ethyl ester	B.p., °C.	Mm.
3,3-Dimethyl-5-keto-heptanoate	95	2
3,3-Dimethyl-5-keto-octanoate	104–105	3
3,3-Dimethyl-5-keto-nonanoate	129.5–131	1
3,3,7-Trimethyl-5-keto-octanoate	123–125	3.5

Hydrolysis of the esters with concentrated aqueous alcoholic potassium hydroxide gave the corresponding  $\delta$ -keto-acids III, which were collected by means of ether and purified by distillation. (It is noteworthy that hydrolysis of ethyl 3,3-dimethyl-5-keto-heptanoate by aqueous alcoholic potash gave also about 15% of the cyclized product, 3,3,6-trimethylcyclohexanedione-1,5.) The colorless or faintly yellow oily acids did not crystallize at  $-12^\circ$ ; they were freed of any traces of solid and stored in the desiccator.

The  $\delta$ -keto-acids III had the following properties:

R =  $CH_2$ : b.p. 129.5° (0.7 mm.); equiv. wt. found 176.3, calcd. for  $C_9H_{16}O_2$  172.2;  $n^{20}_D$  1.4490<sup>8a</sup>; ultraviolet spectrum of Na salt:  $\lambda_{max}$  294  $\mu$ ,  $\epsilon$  560; semicarbazone, m.p. 137.5–138°.<sup>8b</sup>

R =  $C_2H_5$ : b.p. 146–147° (2 mm.); equiv. wt. found 189.3, calcd. for  $C_{10}H_{18}O_2$  186.3;  $n^{20}_D$  1.4463; ultraviolet spectrum of Na salt:  $\lambda_{max}$  294  $\mu$ ,  $\epsilon$  163; semicarbazone, m.p. 132° dec. Found: C, 54.4, 54.75; H, 8.6, 8.7; N, 17.4. Calcd. for  $C_{11}H_{20}O_2N_2$ : C, 54.3; H, 8.7; N, 17.3.

R = iso- $C_3H_7$ : b.p. 142.5–143° (1.3 mm.); equiv. wt. found 199.0 and 198.5,  $C_{11}H_{20}O_2$  requires 200.3;  $n^{20}_D$  1.4444; ultraviolet spectrum of Na salt:  $\lambda_{max}$  288  $\mu$ ,  $\epsilon$  54; semicarbazone, m.p. 156.5–157.5° dec. Found: C, 55.9, 55.9; H, 9.2, 9.0; N, 16.5.  $C_{12}H_{22}O_2N_2$  requires: C, 56.0; H, 9.0; N, 16.3.

R = *n*- $C_3H_7$ : b.p. 170–171° (0.9 mm.). The distilled acid was dissolved in 150 ml. of 5 *N* (pure) sodium hydroxide solution, and after 50 hr. at room temperature the solution was cooled in ice-water and carefully acidified to congo red by hydrochloric acid. The oily keto-acid was collected by means of pure ether, and the ether was completely removed under low pressure (with agitation of the liquid by dry air), any last traces of solvent being removed by heating *in vacuo* for 10 min. at 100°; equiv. wt. 193.2,  $n^{20}_D$  1.4476; ultraviolet spectrum of Na salt:  $\lambda_{max}$  294  $\mu$ ,  $\epsilon$  173; semicarbazone, m.p. 132° dec. Found: C, 56.2; H, 8.9; N, 16.8.

Sulfuric acid solutions for the kinetic runs were prepared by weighing colorless, concentrated sulfuric acid (May & Baker, 99%), and the acid content was checked by alkali titration.

Acetic acid for use as solvent in the kinetic runs was purified by distilling AnalaR glacial acetic acid through a 50 × 1.5 cm. Fenske column. The purified acid melted at 16.52–16.55° (three-quarters melted)—16.60° (last crystals); this indicated a purity of 99.95%.<sup>9</sup>

(6) A. J. Birch and R. Robinson, *J. Chem. Soc.*, 488 (1942). give 110° (10 mm.).

(7) R. Adams, Ed., "Organic Reactions," Vol. VIII, John Wiley & Sons, Inc., New York, 1954, Ch. 2.

(8) R. D. Desai, *J. Chem. Soc.*, 1079 (1932), gives: (a) 1.4492; (b) 138°; (c) describes preparation of this acid ambiguously and gives  $n^{20}_D$  1.4491, semicarbazone m.p. 137°.

(9) G. L. Foster, *ibid.*, 2788 (1954).

Cyclization of the  $\delta$ -Keto-acids to 3,3-Dimethyl-6-alkylcyclohexanediones-1,5.—A sample of each of the keto-acids was heated in aqueous sulfuric acid solution (10 ml.), and the reaction mixture was cooled and poured into water. After cooling in ice-water the solid product was filtered off and dried *in vacuo* over concentrated sulfuric acid.

The 3,3-dimethyl-5-keto-heptanoic acid (0.9 g.) (72%  $H_2SO_4$ , 132°, 1 hr.) gave 0.8 g. of crude white 3,3,6-trimethylcyclohexanedione-1,5 (m. range 152–162°); the dione was recrystallized from aqueous alcohol and dried *in vacuo* and finally had m.p. 163–165.5°<sup>10</sup> (flat white needles),<sup>11a</sup> equiv. wt. found 153.5, calcd. for  $C_9H_{14}O_2$  154.1.

The 3,3-dimethyl-5-keto-octanoic acid (0.9 g.) (72%  $H_2SO_4$ , 130°, 1.3 hr.) gave 0.7 g. of crude 3,3-dimethyl-6-ethylcyclohexanedione-1,5, (m. range 154–158°); the recrystallized product had m.p. 156–157.5° (colorless crystals)<sup>11b</sup>; equiv. wt. found 167.5, calcd. for  $C_{10}H_{16}O_2$  168.1.

The 3,3,7-trimethyl-5-keto-octanoic acid (1.1 g.) (79%  $H_2SO_4$ , 100°, 3.3 hr.) gave 0.55 g. of 3,3-dimethyl-6-isopropylcyclohexanedione-1,5; m.p. of recrystallized dione, 167° (softening from 155°).<sup>11c</sup> Found: C, 72.9; H, 10.05; equiv. wt., 178, 180.5. Calcd. for  $C_{11}H_{18}O_2$ : C, 72.5; H, 9.96; equiv. wt., 182.2.

The 3,3-dimethyl-5-keto-nonanoic acid (0.75 g.) (63%  $H_2SO_4$ , 130°, 1.5 hr.) gave 0.62 g. of 3,3-dimethyl-6-*n*-propylcyclohexanedione-1,5, m.p. (recrystallized) 161.5–163° (colorless lustrous plates and needles).<sup>11d</sup> Found: C, 72.3; H, 9.7; equiv. wt., 180.5.

Kinetic Studies. (a) The Analytical Method.—The cyclic reaction products were estimated by means of the ultraviolet absorption spectra of their sodium enolates, as previously indicated for dimedone. Samples of the hot reaction mixtures were taken with a calibrated 1-ml. pipet, and each sample was mixed with 500 ml. of 0.1 *N* NaOH solution. The optical density of each alkaline solution was measured, at the wave length for maximum absorption, by comparison with a standard blank solution containing identical amounts of NaOH and sulfuric acid.

Ultraviolet spectra of the diones were recorded on freshly prepared and purified samples in 0.1 *N* aqueous NaOH. Measurements on two series of standard alkaline solutions of each dione showed that Beer's law was accurately obeyed in every case. Measurements were made in 10.0 mm. quartz cells, using a Unicam SP500 spectrophotometer.

	$\lambda_{max}$ (enol ion) m $\mu$	
3,3,6-Trimethylcyclohexanedione-1,5 <sup>12</sup>	294.5	24300
3,3-Dimethyl-6-ethylcyclohexanedione-1,5	295	24050
3,3-Dimethyl-6-isopropylcyclohexanedione-1,5	295	23450
3,3-Dimethyl-6- <i>n</i> -propylcyclohexanedione-1,5	295.5	23250

(b) Rate Measurements.—A vapor-bath thermostat, with pure liquids boiling under atmospheric pressure, was again used; temperature constancy to within  $\pm 0.1$ – $0.15^\circ$  generally was obtained without difficulty. All runs were started by adding a weighed sample of the keto-acid in a small glass thimble to the solvent after the temperature had become quite steady and then shaking rapidly.

(c) The Reaction in Aqueous Solution. (i) Order of Reaction with Respect to the Keto-acids.—Ring-closures of the heptanoic, octanoic and nonanoic acids followed simple first-order kinetics over all ranges of reaction; very satisfactory reproducibility of the rate constants was observed. The cyclization of the trimethylcyclohexanedione-1,5 did not quite conform to the simple first-order law, the value of  $2.303 \log (C_0/C_t) + t$  declining by about 10–15% from time  $t = 0$  to later stages of the reaction, but no evidence was found for any marked reversibility of this ring closure. Rate

(10) The m.p.'s of the diones appear to depend somewhat on the conditions of heating; values recorded here are for samples immersed in a Thiele tube at about 20° below the m.p. and then heated at a normally slow rate.

(11) R. D. Desai, ref. 8, gives m.p.'s: (a) 163°, (b) 153°, (c) 156°, (d) 162°.

(12) E. G. Meek, J. H. Turnbull and W. Wilson, *J. Chem. Soc.*, 2891 (1953), report  $\lambda_{max}$  295  $\mu$ ,  $\epsilon$  24200 in aqueous ethanolic NaOH.

constants for the latter acid were derived from careful estimates of the initial rate.

(ii) **Activation Energy.**—First-order rate constants were measured at three or more temperatures in each of a number of sulfuric acid solutions. Activation energies were obtained from the linear plots of  $5 + \log k$  against  $1/T$ . Reaction temperatures were indicated by a sensitive mercury thermometer kept liquid-immersed next to the reaction tube. When two thermometers were both used in the measurement of an activation energy, these were compared directly and appropriate correction was made to the reading of one.

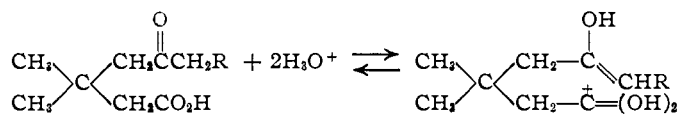
TABLE I

RATE CONSTANTS,  $k$ , IN SEC.<sup>-1</sup>Percentages H<sub>2</sub>SO<sub>4</sub> are by weight; temperature,  $T$ , in °C. abs.

R = H, 61.0% H <sub>2</sub> SO <sub>4</sub>				
$T^a$	390.4	390.2	383.4	372.8
$10^3k$	11.53	11.18	6.32	2.56
R = CH <sub>3</sub>				
44.8% H <sub>2</sub> SO <sub>4</sub> $T^a$	50.7% H <sub>2</sub> SO <sub>4</sub> $T^a$	61.0% H <sub>2</sub> SO <sub>4</sub> $T^b$		
383.1	37.8	383.0	66.50	372.7
378.6	25.55	373.3	31.45	372.3
373.7	18.64	361.1	11.95	360.1
361.0	6.30			359.6
				353.7
				351.7
R = C <sub>2</sub> H <sub>5</sub>				
42.8% H <sub>2</sub> SO <sub>4</sub> $T^a$	50.7% H <sub>2</sub> SO <sub>4</sub> $T^a$	61.0% H <sub>2</sub> SO <sub>4</sub> $T^b$		
382.5	8.31	389.8	37.0	372.9
372.8	3.88	383.2	22.75	359.9
360.6	1.33	373.7	10.98	353.2
		360.4	3.60	
65.4% H <sub>2</sub> SO <sub>4</sub> $T^b$	72.5% H <sub>2</sub> SO <sub>4</sub> $T^b$	79.5% H <sub>2</sub> SO <sub>4</sub> $T^b$		
372.5	67.15	372.0	142.3	359.0
359.2	24.60	359.5	56.0	353.1
353.9	14.90	353.7	35.0	337.1
352.4	13.47			
R = <i>n</i> -C <sub>4</sub> H <sub>7</sub>				
50.7% H <sub>2</sub> SO <sub>4</sub> $T^c$	65.4% H <sub>2</sub> SO <sub>4</sub> $T^c$	72.1% H <sub>2</sub> SO <sub>4</sub> $T^c$		
382.5	26.50	373.1	80.90	370.0
372.7	12.68	360.1	30.77	359.6
359.6	4.43	353.3	18.10	352.8
R = iso-C <sub>3</sub> H <sub>7</sub> , 61.0% H <sub>2</sub> SO <sub>4</sub>				
$T$	390.3	382.9		373.2
$10^3k$	7.5	5.05		2.7

<sup>a</sup> Anschütz standard thermometer. <sup>b</sup> E-MIL standard thermometer with total immersion scale. <sup>c</sup> Gallenkamp standard thermometer (10-mm. immersion scale) for all temperatures in this and the following sections.

Table II summarizes the experimental activation energies for ring closure of the keto-acids III in aqueous sulfuric acid.



(d) **The Reaction in Acetic Acid Solution.**—(i) Samples of 3,3-dimethyl-5-keto-hexanoic acid and of 3,3-dimethyl-5-keto-heptanoic acid were heated in 19% w/w. H<sub>2</sub>SO<sub>4</sub>/acetic acid solution, the reaction products were isolated and identified as the expected dimedone and 3,3,6-trimethyl-cyclohexanedione-1,5, respectively.

TABLE II					
H <sub>2</sub> SO <sub>4</sub> %	R = H $E_a$ , cal. mole <sup>-1</sup>	H <sub>2</sub> SO <sub>4</sub> %	R = CH <sub>3</sub> $E_a$ , cal. mole <sup>-1</sup>	H <sub>2</sub> SO <sub>4</sub> %	R = C <sub>2</sub> H <sub>5</sub> $E_a$ , cal. mole <sup>-1</sup>
72.3	23400	61.0	20050	79.5	20150
61.0	24600	50.7	21650	72.5	19900
50.6 <sup>a</sup>	25400	44.8	22200	65.4	20900
				61.0	20700
H <sub>2</sub> SO <sub>4</sub> %	R = <i>n</i> -C <sub>4</sub> H <sub>7</sub> $E_a$ , cal. mole <sup>-1</sup>	H <sub>2</sub> SO <sub>4</sub> %	R = iso-C <sub>3</sub> H <sub>7</sub> $E_a$ , cal. mole <sup>-1</sup>		
72.1	19800	61.0	17300		
65.4	19800				
50.7	21400				

<sup>a</sup> This corrects a computation error in the earlier communication.<sup>2</sup>

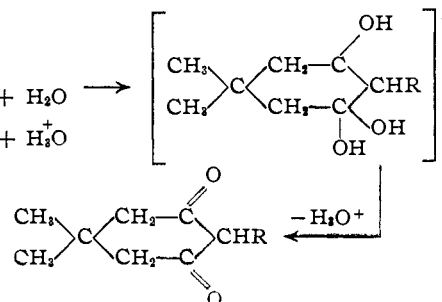
(ii) The ring-closures were found to be of simple first order with respect to the keto-acid in acetic acid solutions containing not too large amounts of sulfuric acid. The solvent mixtures were prepared by direct weighing of the pure acetic acid and of 100% sulfuric acid, prepared by mixing 99% H<sub>2</sub>SO<sub>4</sub> and oleum (20% SO<sub>3</sub>) (repeated gravimetric and volumetric analyses gave results all between 100.0 and 100.7% H<sub>2</sub>SO<sub>4</sub>), and were kept for at least 12 hr. before being used for kinetic experiments. The kinetic and analytical procedures were essentially as for the experiments in aqueous solutions. First-order rate constants for the ring-closures in acetic acid solution are given in Table III.

TABLE III

R = H					
$T$	8.94% H <sub>2</sub> SO <sub>4</sub> $10^3k$	10.05% H <sub>2</sub> SO <sub>4</sub> $w$	$\frac{1}{T}$	w. % water $10^3k$	
373.3	2.303	0	372.8	2.47	
373.3	2.338	0.72	373.1	2.71	
383.5	4.62	.22	373.0	2.96	
360.4	0.986	.22	383.1	5.82	
		.22	360.4	1.22	
R = CH <sub>3</sub>					
$T$	5.47% H <sub>2</sub> SO <sub>4</sub> $10^3k$	4.92% H <sub>2</sub> SO <sub>4</sub> $w$	$\frac{1}{T}$	w. % water $10^3k$	
373.4	12.72	0	373.2	9.0	
373.3	12.95	0.81	373.1	14.20	
373.6	13.10	.40	373.4	15.90	
360.8	7.91	.13	373.3	14.95	
353.8	5.50	.13	360.4	7.33	
		.13	353.7	4.96	

## Discussion

The reaction which is the subject of the present study has been followed in solvents of considerable complexity and possessing thermodynamic and electrical properties which are not quantitatively well known. It is therefore unlikely that any suggested reaction scheme will be susceptible to rigorous analysis, but a possible sequence is

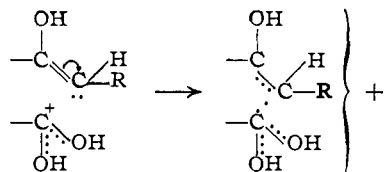


Enolization of keto-methylene groups in acid solutions is well known, and there is good evidence for the protonation of carboxylic acid groups in the presence of sulfuric acid.<sup>13,14</sup> For each keto-acid there is approximately the same change of activation energy corresponding to a given variation of solvent composition (see Fig. 1); this suggests that at least two terms contribute to the experimental activation energy, one a true activation energy for the rate-determining stage involving the transition state and the other a heat change depending on the solvent. In nearly anhydrous solvents proton transfers may be rate-controlling,<sup>15</sup> but in aqueous solution proton transfer to a basic oxygen atom is invariably rapid and leads to an equilibrium concentration of the conjugate acid. Ionization of a molecule of the keto-acid may then be represented by



If the trend of the curves of  $E_a \sim \% H_2SO_4$  is continued to very high sulfuric acid concentrations (at which accurate kinetic measurements cannot be made), a lower limiting value of the activation energy tends to be approached (see especially results for the octanoic acid); this should be the true activation energy for the rate-determining stage. Under those conditions the equilibrium 1 is presumably displaced much more completely to the right, and so the energy change involved ceases to contribute significantly to the measured activation energy. Heat changes occurring on proton transfer to basic oxygen atoms under the conditions of these experiments have not been independently determined, but increments of  $E_a$  from the lower limiting values to values measured in the less acid solvents are consistent with rapid attainment of the pre-equilibrium 1.

Both ketones and carboxylic acids are completely protonated in anhydrous sulfuric acid, but in the aqueous acid solution the base strength of ketones apparently is greater than that of structurally similar carboxylic acids.<sup>14</sup> Since rather high concentrations of sulfuric acid are required for measurable rates of cyclization and since enolization of keto-methylene groups is known to be a reasonably facile process in much less strongly acid solution, the addition of another proton to the carboxylic acid group would appear to be a necessary prerequisite for ring-closure. The carbon atom of the  $-CO_2H$  group can approach close to the terminal methylene group, and when the former bears a partial positive charge while  $C_6$  is attached by an enolic double bond, the situation is favorable to cyclization



(13) R. J. Gillespie and J. A. Leisten, *Quart. Revs.*, **8**, 40 (1954).

(14) L. A. Flexser, L. P. Hammett and A. Dingwall, *This Journal*, **57**, 2103 (1935).

(15) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 284.

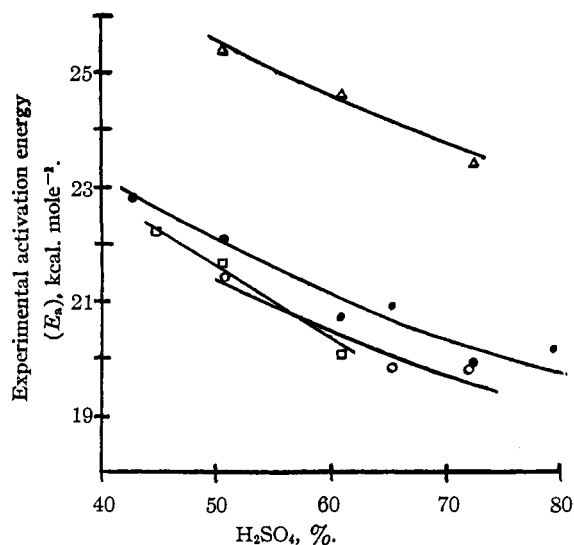


Fig. 1.—Δ, 3,3-dimethyl-5-keto-hexanoic acid; □, heptanoic acid; ●, -octanoic acid; ○, -nonanoic acid.

The rapid and reversible proton transfers may be simultaneous with each other and with any other fast stages preceding the rate-controlling process. The reaction rate may then be determined by rate of conversion to enol or, more probably, by the rate of (unimolecular) ring-closure of the enolized intermediate  $^+AH$ ; in each case the rate equation would be of first order in keto-acid.

If the rate of enolization were rate-determining, the over-all reaction rate would be that for the process<sup>16</sup>



Data recorded for aliphatic ketones show that an alkyl substituent on the  $\alpha$ -carbon tends to accelerate acid-catalyzed enolization because of hyperconjugative electron release,<sup>17</sup> but this effect appears to be very much smaller than the increase in the rate of ring closure which has been found to result from substitution on  $C_6$  of the 5-keto-acid by alkyl groups.

TABLE IV

$C_6$ -Substituent	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	iso-C <sub>3</sub> H <sub>7</sub>
Relative rate <sup>a</sup>	1.00 (ref.)	38	14.5	18.7	1

<sup>a</sup> From rate constants at 100.0° in 61% H<sub>2</sub>SO<sub>4</sub>. The probable reason for the slow reaction of the iso-C<sub>3</sub>H<sub>7</sub> compound will be discussed.

Further, from the large amount of kinetic data available, especially that of Zucker and Hammett,<sup>18</sup> it is clear that rates of enolization of (aromatic) ketones become very great in highly acid solutions, and rates for the aliphatic ketones appear generally to be even greater.<sup>19</sup> Also, activation energies for acid-catalyzed enolization of (aromatic) ketones have normally large values,<sup>20</sup> and so it may be rea-

(16) R. P. Bell, "Acid-Base Catalysis," Clarendon Press, Oxford, 1941, pp. 135-138.

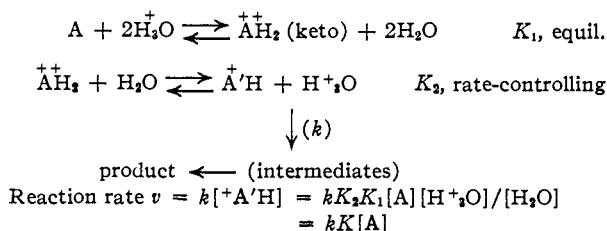
(17) H. M. E. Cardwell and A. E. Kilner, *J. Chem. Soc.*, 2430 (1951); (b) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell & Sons, London, 1953, pp. 558-559.

(18) L. Zucker and L. P. Hammett, *This Journal*, **61**, 2791 (1939).

(19) (a) H. M. Dawson and R. Wheatley, *J. Chem. Soc.*, **97**, 2048 (1910); (b) W. S. Nathan and H. B. Watson, *ibid.*, 217 (1933).

(20) D. P. Evans, *ibid.*, 785 (1938); D. P. Evans, V. G. Morgan and H. B. Watson *ibid.*, 1167 (1935).

sonably supposed that at the higher temperatures, as well as high acidities, required for the ring closure, the enolization must be a very fast process which cannot be rate-determining. Therefore the kinetics of the cyclization are best represented by an initial reversible addition of two protons to the keto-acid molecule, with enolization of the keto-methylene group being followed by ring closure of the unstable intermediate  ${}^+A'H$ .



( $K = K_1K_2[H_3O^+]/[H_2O]$ ;  $[H_3O^+]$  and  $[H_2O]$  in large excess and constant in any one solvent)

The observed rate constant will be  $k_{obs} = kK$ , where  $k$  is the specific rate of the slow stage and the value of  $K$  varies with the solvent composition. It follows that  $E_a = E_{a(\text{true})} + \Delta H$ ;  $E_{a(\text{true})}$  is the true activation energy for the rate-determining stage and  $\Delta H$  is a heat change term depending on the value of  $K$ , *i.e.*, on the nature of the solvent. This conforms to the suggestion already made to account for the change of  $E_a$  with acidity. Some part of the variation of rate with acidity might possibly be due to changes in the dielectric constant of the medium, but this possibility cannot be tested at present.

For this reaction sequence the rate equation is ( $f_T$  = the activity coefficient of the transition

$$v = k[{}^+A'H]f_{A'H}/f_T$$

state) and on insertion of the equilibrium constants in terms of activities thus gives

$$\text{specific rate } k_0 = kK_2K_1[H_3O^+] \times \frac{1}{a_{H_2O}} \times \frac{f_A f_{H_3O^+}}{f_T} \quad (2)$$

This expression would reduce to the form

$$\text{specific rate} = (\text{constant}) [H_3O^+] \times \frac{1}{a_{H_2O}} \times \frac{f_A f_{H_3O^+}}{f_T} = ca_{H^+} \frac{f_A}{f_T}$$

only provided that  $K_2$  and  $K_1$  are constant.

It may be justifiable to assume the ratio of activity coefficients constant in equation 2 because of the constitutional similarity of the transition state and the intermediate  ${}^+A'H$ , which is a keto-acid molecule plus a proton; but the value of  $K_1$  probably increases with the acidity of the solvent. For aqueous sulfuric acid at 25° between 50 and 79% w./w.  $H_2SO_4$ , the data<sup>21</sup> show that  $(a_{H_2O})^{-1}$  is not a simple function of  $[H_3O^+]$ , but on applying the simple relationship  $(a_{H_2O})^{-1} = \alpha[H_3O^+]^n$  to the upper and lower ends of the range, values of  $n$  between 2.5 and 13 are indicated. If  $[H_3O^+]$  is measured by the stoichiometric acid concentration,  $C_{H_2SO_4}$ , it appears from equation 2 that the dependence of rate of ring closure on acidity should be of much higher order than the first. Linear plots of  $\log k_{100}$  against  $\log C_{H_2SO_4}$  show that in

(21) N. C. Deno and R. W. Taft, Jr., *THIS JOURNAL*, **76**, 244 (1954); S. Shankman and A. R. Gordon, *ibid.*, **61**, 2370 (1939).

fact: specific rate = const.  $(C_{H_2SO_4})^m$ , the values of  $m$  being 4.6, 4.0, 4.8 and 5.0 for the hexanoic, heptanoic, octanoic and nonanoic acid, respectively.

The effect of varying acidity on rates of ring-closure is almost wholly through its influence on the activation energy. Results summarized in Table V show that entropies of activation vary little and in no significantly regular manner with the sulfuric acid content of the solution. Therefore the effect on rate of the mineral acid strength apparently is connected principally with the variable pre-equilibrium.

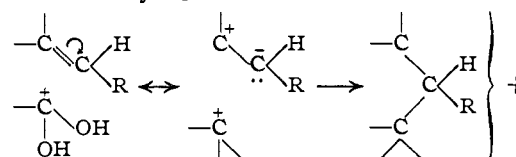
TABLE V

Keto-acid (III) R =	STANDARD ENTROPIES OF ACTIVATION, $\Delta S^\circ$ , AT 100.0° <sup>22</sup>				
	$H_2SO_4$ , %				
	42.8	44.8	50.7	61.0	72.3-72.5
H			-15.5	-16.6	-15.7
CH <sub>3</sub>		-18.6	-19.4	-20.6	
C <sub>2</sub> H <sub>5</sub>	-19.8		-20.3	-20.6	-20.5
<i>n</i> -C <sub>2</sub> H <sub>7</sub>			-21.5	-21.7	-20.9
<i>i</i> -C <sub>2</sub> H <sub>7</sub>				-35.5	

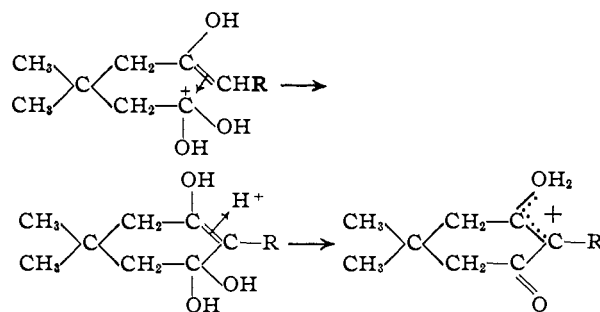
( $\Delta S^\circ = 2.303 \times 1.987 (\log PZ - \log kT/h) - 1.987$ ;  $\log PZ = \log k + E_a/2.303RT$ , where  $E_a$  is the "smoothed" value of  $E_a$  read from the graph. An error of 0.3 kcal. in  $E_a$  would change  $\Delta S^\circ$  by 0.8 e.u.)

The largely negative values of  $\Delta S^\circ$  are consistent with the rate-determining process being the formation of a cyclic transition state from a non-cyclic intermediate (*cf.* later discussion of solvent effects.)

Formation of the transition state in the ring-closure may be classically represented as electrophilic attack by  $C_1^+$  on the enolic double bond



A better description of this step would seem to be the creation of a molecular bond<sup>23</sup> by donation of the  $\pi$ -electrons of the double bond to the vacant bonding orbital of  $C_1^+$ , according to the scheme



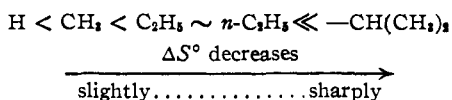
Further, a notable feature of the reaction is the lowering of activation energy by alkyl substituents on  $C_2$  and the concomitant reduction in the frequency factor (expressed logarithmically by the entropy of activation). The electron-releasing

(22) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941.

(23) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, 1949, p. 17.

alkyl groups must tend to reduce the electron affinity of the double bond which they flank, *i.e.*, they lower the ionization potential of the  $\pi$ -electrons. Consequently the energy needed to make these electrons available for donation to the vacant orbital of the acceptor atom  $C_1^+$  is diminished. This is consistent with the activation energy for electrophilic attack by  $C_1^+$  on the double bond of the enol form, as the postulated rate-determining stage, being reduced by alkyl substitution on  $C_6$  of the keto-acid. The effect would be expected to increase with higher tendency for electron release by the substituent, *i.e.*, primary alkyl  $<$   $-\text{CH}(\text{CH}_3)_2$  if inductive electron release only is considered. Some contribution by first-order hyperconjugation may account for the methyl group being a little more effective than the ethyl.

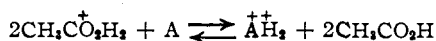
Inspection of models indicates that whereas in the keto-acid molecule there is likely to be little restriction on the positions of any of the alkyl substituents, in a cyclic transition state the isopropyl substituent at  $C_6$  can be accommodated only in a narrowly defined range of configurations, whilst the positions of the ethyl and *n*-propyl groups appear to be less severely limited and that of the methyl group hardly at all. Thus the relative restriction in numbers of favorable configurations as between transition state and keto-acid molecule would be predicted to increase in the order shown, and entropies of activation are found to fall in this order.



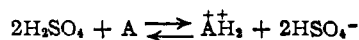
(The change of  $\Delta S^\circ$  on substitution with methyl, ethyl and *n*-propyl might perhaps be explicable on general statistical grounds,<sup>24</sup> the primary effect of structural modification being on the activation energy. The bulky isopropyl group, however, exerts a direct spatial effect.)

The *gem*-dimethyl groups on  $C_3$  of the keto-acid must greatly facilitate ring-closure by constraining the molecule to adopt a configuration in which the potential reaction centers are fairly close together; in the absence of these groups or of one of them it seems likely that the molecule would exist preferentially in an extended form. It has in fact been observed that 3-phenyl-5-keto-hexanoic acid and 5-keto-hexanoic acid do not cyclize measurably under conditions like those used for the 3,3-dimethyl compounds. This point is being investigated.

**The Ring-closure in Non-aqueous Solution.**—Proton transfer to a keto-acid molecule in anhydrous sulfuric acid-acetic acid solvent must be represented by



or



Since acetic acid is a much weaker base than water, the first equilibrium should lie much more com-

pletely to the right than that for the corresponding proton transfer between oxonium ion and keto-acid, while the second reaction is not subject to competition from possible proton transfers to a base other than keto-acid A. Thus the acid-catalyzed ring-closure would here be expected to be very much faster than that in aqueous solution, or for corresponding rates a much smaller amount of sulfuric acid should be necessary. In fact, stoichiometric quantities of sulfuric acid about one-fifth as large as those required in aqueous solution gave conveniently measurable rates of cyclization in acetic acid. The reaction in acetic acid has not been studied in presence of large amounts of sulfuric acid; good first-order kinetics apparently cease to be followed if certain though fairly small mineral acid concentrations are exceeded. Under conditions leading to reaction rates similar to those observed in the aqueous solutions, the reactions in acetic acid show much smaller activation energies and also lower entropies of activation.

TABLE VI

Acid	Catalyst	$E_a$ , cal. mole <sup>-1</sup>	$\Delta S^\circ$	$\Delta G^\circ$ , cal. mole <sup>-1a</sup>
3,3-Dimethyl-5-keto-hexanoic	8.94% w./w. $\text{H}_2\text{SO}_4$ (anhydrous)	18300	-33.1	29900
	10.05% w./w. $\text{H}_2\text{SO}_4$ + 0.2% water	18900	-30.9	29750
3,3-Dimethyl-5-keto-heptanoic	5.47% w./w. $\text{H}_2\text{SO}_4$ (anhydrous)	11450	-48.0	28600
	4.92% w./w. $\text{H}_2\text{SO}_4$ + 0.13% water	14900	-38.5	28450

<sup>a</sup>  $\Delta G^\circ$  = free energy of activation.

Because of the very low dielectric constant of acetic acid,<sup>25</sup> electrostatic orientation effects are probably very much less important in this solvent than in aqueous solution. Formation of the cyclic transition state from the intermediate  $^+\text{A}'\text{H}$  involves a decrease in polarity, and it might thus be expected that solvation of the reactant is more effective (relative to that of the transition complex) in the solvent of high dielectric constant (water). Since greater solvation of the reactant may lead to increased activation energies due to the inclusion of a "heat of solvation" term,<sup>26</sup> the observed lowering of activation energy when acetic acid is substituted for water as reaction solvent is consistent with the assumptions made about the polar nature of the reactant species and of the transition complex. Also, if solvent orientation tends to diminish when the transition state is formed, the entropy of activation should be least in the solvent of lowest dielectric constant. Thus, if the fundamental entropy change is  $-X$  in a solvent of low dielectric constant in which the solvation change associated with formation of the transition state is perhaps negligible, then in another solvent with higher dielectric constant the release of molecules from solvation

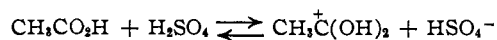
(24) R. A. Fairclough and C. N. Hinshelwood, *J. Chem. Soc.*, 538, 1573 (1937).

(25) C. P. Smyth and H. E. Rogers, *THIS JOURNAL*, 52, 1824 (1930).

(26) Reference 21, p. 416.

may contribute a degree of "disordering," *i.e.*, an entropy term  $+Y$ . The entropy of activation in the latter solvent then becomes  $-X + Y$ , which is less negative than  $-X$ . ( $\Delta S^\circ$  for the hexanoic acid: in water,  $\hat{=}$   $-16$ , in acetic acid,  $\hat{=}$   $-33$ , and similarly for the heptanoic acid.)

When small amounts of water are added, the solvent system obviously becomes very complicated; the water may promote ionization of the sulfuric acid, which is otherwise very incomplete<sup>27</sup>



Also, owing to the low polarity of the acetic acid, water molecules or oxonium ions may become partially segregated in the neighborhood of the keto-acid molecules; in that case the environment of the

(27) H. A. E. Mackenzie and E. R. S. Winter, *Trans. Faraday Soc.*, **44**, 159 (1948).

reactant will be unlike that in anhydrous acetic acid and may tend toward conditions prevailing in aqueous solutions. This would account for the reaction parameters in "wet" acetic acid having values between those observed in the anhydrous solvent and those in aqueous solution. Inhibition of the ring-closure by acetic anhydride is believed to be due to the presence of acetylium ion,  $\text{CH}_3\overset{+}{\text{C}}\text{O}$ ,<sup>28</sup> the latter must function as a strong acid and electrophilic reagent and may attack the basic centers of the keto-acid or the enolic double bond.

**Acknowledgments.**—The authors wish to thank Imperial Chemical Industries, Ltd., for a grant toward the cost of materials and Mr. P. R. Wood for some of the elementary analyses.

(28) H. Burton and P. F. G. Prall, *Quart. Revs.*, **6**, 314 (1952).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, YALE UNIVERSITY]

## Reactions of Nitrous Acid with *p*-Hydroxycinnamic Acid and its Derivatives<sup>1</sup>

BY CHRISTINE ZILOUDROU,<sup>2</sup> WILLIAM L. MEYER AND JOSEPH S. FRUTON

RECEIVED MARCH 21, 1957

*p*-Hydroxycinnamic acid reacts with  $\text{HNO}_2$  in dilute aqueous solution to form *p*-hydroxymandelaldehyde. With derivatives of *p*-hydroxycinnamic acid in which the carboxyl group is substituted (*e.g.*, the methyl ester), the predominant reaction is a nitration *ortho* to the phenolic hydroxyl. Because of the production of nitrite by the nitrate reductase of plants, the possibility exists that reactions of  $\text{HNO}_2$  with *p*-hydroxycinnamic acid and its derivatives may occur in plant tissues.

Previous studies in this Laboratory<sup>3,4</sup> have led to the finding that *N*-acetyldehydrotyrosine (*N*-acetyl-*p*-hydroxycinnamic acid) is readily converted by dilute  $\text{HNO}_2$  to *N*-acetyl-*p*-hydroxymandelic acid amide. This conversion was first observed<sup>3</sup> upon acidification of suspensions of *Escherichia coli* grown in a culture medium supplemented with acetyldehydrotyrosine. Subsequent studies<sup>4</sup> showed that the role of the bacteria is to reduce nitrate (a component of the basal medium<sup>5</sup>) to nitrite, presumably by the action of nitrate reductase<sup>6</sup>; upon acidification of the culture filtrate to *pH* 4 or less, a rapid non-enzymic reaction between  $\text{HNO}_2$  and acetyldehydrotyrosine ensues. Because of the widespread occurrence, among plants, of nitrate reductase and of *p*-hydroxycinnamic acid (*p*-coumaric acid) and its derivatives (*e.g.*, caffeic acid, coniferyl alcohol), the new reaction merited further study in relation to several problems of plant metabolism.

### Reaction of *p*-Hydroxycinnamic Acid with $\text{HNO}_2$ .

—In analogy with the action of  $\text{HNO}_2$  on acetyldehydrotyrosine, the expected product of the reaction with *p*-hydroxycinnamic acid is *p*-hydroxy-

mandelaldehyde, which does not appear to have been described previously; the isomeric 1,4'-dihydroxyacetophenone was prepared by Robinson.<sup>7</sup> Upon treatment of *p*-hydroxycinnamic acid with 2 equivalents of  $\text{HNO}_2$  at *pH* 2,  $\text{CO}_2$  is evolved with the formation of a product whose strong reducing properties, absorption spectrum, elementary analysis, and derivatives (2,4-dinitrophenylhydrazone, semicarbazone, phenyllosazone) support its identification as *p*-hydroxymandelaldehyde. On treatment with 2.5 moles of  $\text{NaIO}_4$  per mole of product, the expected amount of formic acid was released, and *p*-hydroxybenzaldehyde (identified as its phenylhydrazone) was formed. However, with a 1:1 molar ratio of periodate to product, 50% of the expected formic acid was released more rapidly than the rest, suggesting that the *p*-hydroxymandelaldehyde is present in aqueous solution as a dimer that is slowly cleaved during the reaction with periodate. This possibility is supported by the fact that the semicarbazone isolated from aqueous solution gave an elementary analysis in agreement with the values calculated for a derivative of a dimer.

The rate of the reaction of *p*-hydroxycinnamic acid with nitrite is markedly dependent on *pH*. At 30°, in the presence of 0.11 *M* citric acid-sodium citrate buffer containing  $4 \times 10^{-3}$  *M* nitrite (introduced as sodium nitrite) the apparent first-order rate constants (in  $\text{min.}^{-1}$ ) for the disappearance of *p*-hydroxycinnamic acid (initial concentration,  $4 \times 10^{-4}$  *M*) were found to be: *pH* 5.1, 0.0010; *pH* 4.1, 0.0068; *pH* 2.9, 0.092. At lower *pH*

(1) This work was supported by grants from the Rockefeller Foundation and from the National Science Foundation.

(2) Postdoctoral Fellow of the Greek Fellowship Foundation.

(3) J. S. Fruton, S. Simmonds and V. A. Smith, *J. Biol. Chem.*, **169**, 267 (1947).

(4) G. Taborsky, P. S. Cammarata and J. S. Fruton, *ibid.*, **226**, 103 (1957).

(5) C. H. Gray and E. L. Tatum, *Proc. Natl. Acad. Sci.*, **30**, 404 (1944).

(6) A. Nason, in W. D. McElroy and B. Glass, "Inorganic Nitrogen Metabolism," Johns Hopkins Press, Baltimore, Md., 1956, p. 109.

(7) R. Robinson, *J. Chem. Soc.*, 1464 (1928).