The Behavior of β-Aryl-β-hydroxybutyric Acids in Dilute Aqueous Acids[1,2]

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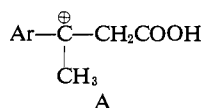
β-(p-Methylphenyl)-β-hydroxybutyric acid (IV) and β-(p-methoxyphenyl)-β-hydroxybutyric acid (V) have been resolved. The rate of racemization of IV and V in dilute sulfuric acid solution shows typical carbonium ion characteristics. In extremely dilute acid (~0.001 M sulfuric acid) the major reaction is decarboxylation and dehydration to form the 2-arylpropene. In 1 M sulfuric acid the most rapid reaction is true racemization. The variation in rate of the decarboxylation reaction is studied. Some further characteristics of the synchronous decarboxylation and dehydration are discussed.

Introduction

In the previous paper[1] it was shown that β-phenyl-β-hydroxybutyric acid (I) decomposes in strong sulfuric acid solutions to give a mixture of the unsaturated acids, trans-β-methylcinnamic acid (II) and 3-phenyl-3-butenoic acid (III), as well as simultaneously giving α-methylstyrene, carbon dioxide, and water.

In as much as the variation in rate for the synchronous decarboxylation and dehydration reaction[5] was much less sensitive to the sulfuric acid concentration in the medium, we have extended these studies to very dilute acid solutions, conditions under which decarboxylation should occur largely to the exclusion of the simple dehydration reactions.

We also desired to compare the rate of generation of the carbonium ion (A) with the rate of the decarboxylation reaction. For these purposes somewhat more reactive analogs of I will give convenient rates of reaction, and we have therefore studied the behavior of

$$\underset{\underset{\underset{A}{CH_3}}{\overset{|}{\underset{|}{}}}}{Ar—\overset{\oplus}{C}—CH_2COOH}$$

β-(p-methylphenyl)-β-hydroxybutyric acid (IV) and β-(p-methoxyphenyl)-β-hydroxybutyric acid (V) in very dilute sulfuric acid.

Experimental Section[6]

β-(p-Methylphenyl)-β-hydroxybutyric Acid (IV). Prepared by the Reformatsky reaction,[7] crude ethyl β-(p-methylphenyl)-β-hydroxybutyrate was saponified directly without prior distillation. A solution of 50 g. of ester in 200 ml. of 2.5 M methanolic potassium hydroxide was allowed to stand at room temperature for 3 days. The solution was diluted with 300 ml. of water and extracted with several small portions of ether, and the aqueous phase was chilled and acidified with cold 10% sulfuric acid and promptly extracted with ether (300 ml.). Evaporation of the ether afforded 29 g. (66%) of crude β-(p-methylphenyl)-β-hydroxybutyric acid. Several crystallizations from ether afforded pure IV, m.p. 72.5–74° (lit.[8] m.p. 73–74°).

Resolution of β-(p-Methylphenyl)-β-hydroxybutyric Acid. Brucine (120 g., 0.31 mole) was added to a boiling solution of β-(p-methylphenyl)-β-hydroxybutyric acid (65 g., 0.33 mole) in 800 ml. of ethyl acetate. The resulting solution quickly deposited crystals on cooling, m.p. 163–167°. After ten recrystallizations from ethyl acetate the melting point of the brucine salt was found to remain constant at 178–180° dec., $[\alpha]^{23}D$ −17.3° (c 0.10, chloroform).

Decomposition of the brucine salt with iced 10% hydrochloric acid, extraction with ether, evaporation of the solvent, and crystallization of the residual oil from benzene–hexane afforded (+)-β-(p-methylphenyl)-β-hydroxybutyric acid ((+)-IV) as long needles, m.p. 76–77° (cf. racemate, m.p. 72°), $[\alpha]^{23}D$ +11.9° (c 0.10, chloroform).

β-(p-Methoxyphenyl)-β-hydroxybutyric Acid (V). Ethyl β-(p-methoxyphenyl)-β-hydroxybutyrate was prepared by the Reformatsky reaction.[7] The crude, undistilled ethyl β-(p-methoxyphenyl)-β-hydroxybutyrate (50 g.) was hydrolyzed directly by heating under reflux with a solution of 14 g. of KOH, in 60 ml. of methanol, and 10 ml. of water. After the methanol had been removed, the basic solution was extracted twice with 50-ml. portions of ether and then clarified with Nuchar. The solution was acidified with cold, dilute H_2SO_4 and quickly extracted three times with 50-ml. portions of ether, and the combined ether extracts were washed several times with distilled water, then dried with anhydrous $MgSO_4$. The solution was filtered and the solvent was removed with a rotary evaporator to yield a light yellow oil. The last traces of solvent were removed under vacuum (5 mm.). After 1 hr. of pumping, the oil solidified. The yield of the crude material was 26 g. (60%). Four crystallizations from benzene–petroleum ether (b.p. 30–60°) afforded pure V, m.p. 80.4–81.6°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 63.05; H, 6.67.

Resolution of β-(p-Methoxyphenyl)-β-hydroxybutyric Acid. Brucine (150 g., 0.38 mole) was added to a

(1) Previous paper: D. S. Noyce and R. A. Heller, *J. Am. Chem. Soc.*, 87, 4325 (1965).

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(3) National Institutes of Health Postdoctoral Fellow, 1959–1961.

(4) Dow Fellow in Chemistry, 1964–1965.

(5) D. S. Noyce, P. A. King, and G. L. Woo, *J. Org. Chem.*, 26, 632 (1961).

(6) Melting points are corrected; boiling points are uncorrected.

(7) C. R. Hauser and D. S. Breslow, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 408.

(8) H. Rupe and F. Wiederkehr, *Helv. Chim. Acta*, 7, 663 (1924).

boiling solution of β-(p-methoxyphenyl)-β-hydroxy-butyric acid (80 g., 0.38 mole) in 1 l. of ethyl acetate. Upon standing at room temperature crystals were deposited slowly (120 g.), m.p. 128–135°. The melting point of the brucine salt was raised to 133–135° after two recrystallizations from ethyl acetate and remained constant after three further recrystallizations, $[\alpha]^{26}D$ −23.6° (c 0.07, chloroform).

The brucine salt was decomposed with *iced* 5 % hydrochloric acid in the presence of ether, to avoid any substantial racemization during hydrolysis. Evaporation of the ether extracts afforded (+)-V as a slowly crystallizing oil. By fractional crystallization from benzene–carbon tetrachloride and a few additional recrystallizations to constant rotation, (+)-V was obtained, as rosettes, m.p. 69.5–70.5° (*cf.* racemate, m.p. 80–81°), $[\alpha]^{25}D$ +7.40° (c 0.10, chloroform). Hydrolysis of the brucine salt after only two recrystallizations gave acid of relatively high rotation, $[\alpha]^{23}D$ +4.7° (c 0.20, chloroform).

Racemization Studies. A. In 50% Dioxane–50% Aqueous Sulfuric Acid. Due to limited solubility of the starting material in this medium, the concentrations of the optical solutions were made up to give initial rotations of 0.4–1.0°. The racemizations were followed in a center-filled 4-dm. jacketed polarimeter tube with an O. C. Rudolph polarimeter. Rotations were taken through the first 75 % of reaction when the clarity of the solution permitted this. When decarboxylation occurred as a competing reaction the low solubility of the decarboxylated material resulted in turbidity in the solution, and the amount of starting material had to be kept to a minimum, using material of highest optical purity, so that readings could be made throughout most of the first half-life. The formation of carbon dioxide interfered with the visibility of the image and the gas had to be shaken out periodically.

B. In 5% Dioxane–95% Aqueous Sulfuric Acid. In this medium it was impossible to follow the kinetics of racemization directly in the polarimeter tube. The solubility of the starting material was such as to result in only minute initial rotations; more adverse was the fact that the decarboxylated material was even less soluble in this medium and when formed in any quantity imparted turbidity to the solution. It was impossible to obtain readings to any significant extent of reaction. Instead the following aliquot technique was employed. (i) For the racemization of the (+)-V, the acid (2.0 g.) of good optical purity was dissolved in 62.5 ml. of dioxane and the solution was made up to 1250 ml. with the requisite strength of sulfuric acid. The resulting solution was apportioned to five 250-ml. volumetric flasks and immersed into a 45° constant temperature bath. A period necessary for temperature equilibration, previously determined, was allowed before the first sample was withdrawn at zero time. The volumetric flask was immersed in an ice bath and after sufficient cooling the solution was extracted with two 100-ml. portions of chloroform. The extracts were dried and concentrated to about 4 ml. at which time the only remaining solvent was dioxane. To prevent prolonged heating necessary for complete removal of the remaining dioxane, the optical solution was made up in dioxane by further addition of dioxane. The solution was filtered for optical clarity and the optical rotations

were measured in a 2-dm. polarimeter tube. Data over the first 60 % reaction were generally obtained. Since the initial rotations were comparatively large (as high as 1.5°) very good first-order plots were obtainable by this method. (ii) The *p*-methyl acid, (+)-IV, was more soluble in this medium and 100-ml. aliquots were used. Extractions were carried out with three 50-ml. portions of chloroform and the solvent was completely evaporated since mild heating *in vacuo* did not effect racemization or decarboxylation of (+)-IV. The optical solutions were then prepared by dissolving the remaining oil in chloroform. For the run at 25° the extractions were carried out while the aqueous solution was at ice temperature to prevent further reaction during work-up. Good kinetic data were obtainable.

Product Isolation under Conditions of Kinetic Experiments. 5% Dioxane Medium. A. From β-(p-Methoxyphenyl)-β-hydroxybutyric Acid. Experiment 1 was carried out in 0.001 M H_2SO_4 at 45.00°. The acid (2.20 g.) was dissolved in 50 ml. of dioxane and made up to 1 l. with sulfuric acid of about pH 2.8. After standing at 45° for 9 hr. (about 6 half-lives), the solution was cooled in the refrigerator overnight. The precipitated hydrocarbon was filtered and dried to give 920 mg. (61 % of theory) of 4-methoxy-α-methylstyrene (VIII), m.p. 31–33°. Sublimed material had m.p. 33–34° (lit.[9] m.p. 33°).

Experiment 2 was carried out in 0.01 M H_2SO_4. A solution of V (2.22 g.) was maintained at 45° in 5 % dioxane–95 % aqueous sulfuric acid solution (0.01 M) for 2.5 hr. (5 half-lives). After cooling, the precipitated solid was filtered and dried to give 0.32 g. of 4-methoxy-α-methylstyrene (20 % of theory). The aqueous mother liquors were extracted with a large quantity of chloroform, the extracts were dried, and the solvent was evaporated. The residual oil showed no carbonyl absorption in the 6-μ region but showed absorption due to a hydroxyl group in the 3-μ region. The total oil, chromatographed on Woelm III neutral alumina and eluted successively with 10 % ether–90 % benzene and 25 % ether–75 % benzene, afforded a colorless oil (900 mg., 53 %) whose infrared spectrum was very similar to that of the crude material. The strong absorption maximum at 11.3 μ, due to the vinyl hydrogen out-of-plane deformation vibrations, present in the hydrocarbon, was absent. The presence of a strong OH stretching vibration indicated that this compound was the hydrated olefin, 2-(p-methoxyphenyl)-2-propanol (IX). Total recovery of the product of reaction amounted to 73 %.

The absence of hydroxy acid among the products of reaction suggests that the measured rate at which optical activity is lost is in fact the rate of the synchronous decarboxylation and dehydration reaction. This process of course destroys both optical activity and the hydroxy acid. It is alternatively possible that a true racemization reaction and the synchronous decarboxylation and dehydration reaction have very similar rates under these particular conditions. Such a situation would mean that almost all the hydroxy acid would be destroyed during the time allowed for this reaction to proceed (several half-lives for the rate of loss of optical rotation). This interpretation sets both an upper and lower limit on the rate of decarboxylation

(9) A. Klages, *Ber.*, 37, 3995 (1904).

under these conditions, and these differ by only a factor of 2.

In order to demonstrate that the alcohol IX is not a direct product from the decarboxylation reaction, the olefin VIII was submitted to similar reaction conditions. After 4 hr. in 0.01 M sulfuric acid at 45°, VIII was substantially transformed to IX, and only 50% of VIII was recovered and 40% of IX isolated. These results are in complete accord with the recent detailed kinetic studies of Schubert, Lamm, and Keeffe.[10]

In a control experiment, it was shown that the hydroxy acid did not decarboxylate under conditions of work-up.

B. From β-(p-Methylphenyl)-β-hydroxybutyric Acid (IV). Experiment 3 was carried out in 0.44 M sulfuric acid at 45°. The acid (2.0 g.) was dissolved in 25 ml. of dioxane and made up to 500 ml. with 0.47 M sulfuric acid. The solution was heated at 45° for 3 hr. (a period of 6 half-lives, based on the measured rate of loss of optical activity under these conditions). The cloudy solution was extracted with five portions of chloroform, the extracts were dried over sodium sulfate, and the solvent was evaporated. The infrared spectrum of the remaining oil showed absorption due to carboxyl group but was not identical with the infrared spectrum of pure hydroxy acid.

A chloroform solution of this oil was extracted with five portions of 10% sodium bicarbonate (50 ml.) and the extracts were acidified to pH 1 while being iced. Extraction of the aqueous solution with chloroform and work-up in the usual manner afforded 0.65 g. (33% of theory) of an oil which solidified. The infrared spectrum of this solid was superimposable on authentic hydroxy acid IV.

The remaining chloroform solution was dried and concentrated to give 0.70 g. (52% of theory) of an oil. The infrared spectrum of this oil showed no carboxyl group absorption, but showed hydroxyl group absorption in the 3-μ region. This oil appears to be a mixture of 4-methyl-α-methylstyrene (VI) and 2-(4-methylphenyl)-2-propanol (VII).

Experiment 4 was carried out in 1.84 M sulfuric acid at 25°. The procedure used was very similar to that above. A solution of 2.05 g. of the hydroxy acid was held at 25° for 3 hr. (6 half-lives); the solution was only faintly cloudy at this time. Work-up afforded 1.95 g. of a semisolid. Extraction procedures as above afforded 1.45 g. (71%) of solid hydroxy acid, m.p. 68–70°, whose infrared spectrum was superimposable on that of an authentic sample. The neutral fraction gave 0.19 (*ca.* 11%) of an oil whose infrared spectrum indicated that it consisted of a similar mixture as above, containing hydrocarbon and its hydration product. This experiment indicates that the rate of decarboxylation is much less than that of racemization (by a factor of at least 20). The measured racemization rate at this acidity, therefore, is essentially unaffected by the decarboxylation reaction.

Measurement of H_0 and pH Values. The analytical solutions for measurement of H_0 were prepared by dissolving the requisite amount of indicator in 25 ml. of dioxane, freshly purified, and by diluting with 25 ml. of sulfuric acid of the requisite strength. The resulting

solution showed a 1–2% volume contraction, which was taken into account in calculating the final concentration of the indicator. The measured H_0 values are listed in Table I.

Table I. H_0 Values of 50% Dioxane–50% Aqueous Sulfuric Acid Mixtures

Concn. of H_2SO_4, M^a	$\left[\dfrac{BH^+}{B}\right]$	H_0	$\Delta H_0{}^b$
0.05	1.05ᶜ	2.41	1.25
0.25	0.19ᵈ	1.72	1.12
0.52	0.52ᵈ	1.27	1.07
0.98	1.55ᵈ	0.80	1.00
1.46	4.00ᵈ	0.39	0.84
1.46	0.165ᵉ	0.49	0.94
2.07	0.332ᵉ	0.19	1.09
2.54	0.80ᵉ	−0.19	0.96
3.35	4.16ᵉ	−0.91	0.64

ᵃ Final concentration. *ᵇ* H_0 in aqueous sulfuric acid minus H_0 in 50% dioxane–50% aqueous sulfuric acid. *ᶜ* Indicator, 3-nitroaniline, pK_a = 2.43. *ᵈ* Indicator, 4-nitroaniline, pK_a = 0.99. *ᵉ* Indicator, 2-nitroaniline, pK_a = −0.29.

A plot of H_0 *vs.* molarity of sulfuric acid parallels that for purely aqueous sulfuric acid up to about 1 M, with a difference in acidity function of about one unit. This is qualitatively similar to the reported H_0 values of perchloric acid in 60% dioxane.[11]

Rate of Carbon Dioxide Evolution. From β-(p-Methoxyphenyl)-β-hydroxybutyric Acid in Aqueous Sulfuric Acid. For solubility purposes the sulfuric acid solutions used for these determinations contained 5% (by volume) of dioxane. The apparatus was similar to one previously described by Bartlett and Jones.[12] It consisted of a 40-ml. reaction flask connected by means of a ball joint to a mercury manometer. The manometer was constructed of glass capillary tubing (1 mm.), which was connected to a mercury reservoir (20-mm. glass tubing). The manometer was equipped with a three-way stopcock that could be opened to a vacuum pump. The assembly was mounted on a fiberboard backplate and placed over a constant temperature bath. A typical kinetic determination involved attaching the reaction flask containing approximately 32 ml. of the mineral acid solution, pulling a partial vacuum to expel the dissolved gases, closing the system and allowing it to come to thermal equilibrium, opening the system and adding the sample (60 mg. dissolved in 0.1 ml. of dioxane), all joints sealed, reducing pressure (approximately 50 mm. internal pressure), and beginning rapid stirring (magnetic stirrer).

After approximately 10 min., the initial zero point reading was taken and thereafter at appropriate time intervals manometer readings were taken as the internal pressure increased. The pressure change was in each case approximately 120 mm. (0.2 ml. volume increase) after 10 half-lives. In all experiments no gas leakage was observed and all infinite time readings were constant. Rate constants were obtained graphically by plotting log % unreacted *vs.* time. In these experi-

(10) W. M. Schubert, B. Lamm, and J. R. Keeffe, *J. Am. Chem. Soc.*, **86**, 4727 (1964).

(11) D. V. Banthorpe, E. D. Hughes, C. K. Ingold, and J. Roy, *J. Chem. Soc.*, 3294 (1962).

(12) P. D. Bartlett and R. H. Jones, *J. Am. Chem. Soc.*, **79**, 2158 (1957).

ments it should be noted that only approximately one-third of the released carbon dioxide enters the gas phase (the remainder staying in solution). Using the value listed by Edsall and Wyman[13] for the solubility of carbon dioxide in water (25°) the yield of carbon dioxide can be calculated. The pressure increase observed (120 mm.) is found to correspond to an essentially quantitative evolution of gas if a 60-mg. sample is used (with approximately a 14-ml. gas space above the solution).

Stability of β-(p-Methoxyphenyl)-β-hydroxybutyric Acid in Benzene Solution. A small quantity (512 mg.) of the pure hydroxy acid was dissolved in 150 ml. of benzene. The solution was heated under reflux for approximately 5 days. At the end of this period the solution was allowed to cool to room temperature and remain at this temperature for an additional 30 days. The benzene solvent was removed to yield a colorless oil that crystallized on standing. The infrared spectrum of the recovered material was identical with that of pure β-(p-methoxyphenyl)-β-hydroxybutyric acid. The melting point of the recovered material (without further purification) was 81.6–82.8° (authentic sample m.p. 80.5–81.6°).

Results

Racemization of (+)-IV. In 1.82 M sulfuric acid (+)-β-(p-tolyl)-β-hydroxybutyric acid racemizes at a convenient rate, the pseudo-first-order rate constant at 25° being 3.60×10^{-4} sec.$^{-1}$. This is a true racemization rate, as the product after 6 half-lives was almost entirely racemic IV, m.p. 68–70°. There was formed only about 10% of 2-(p-tolyl)-2-propene (VI) and 2-(p-tolyl)-2-propanol) in this time by decarboxylation. Thus racemization is some 20 times faster than decarboxylation.

In 0.44 M sulfuric acid at 45°, the rate of loss of optical activity is essentially a true racemization rate, as evidenced by the fact that substantial quantities of racemic IV may be isolated after 6 half lives, and only 50% of the theoretical amount of VI (and/or VII) is formed in this time.

The studies of Noyce and Heller[1] are in full accord with these results. Extrapolating the rates of dehydration from that study [(I → II) or (I → III)] to these acidities, using the correlation of rates with the acidity function, H_0, and finally using a ρ–σ^- correlation to predict the rate of dehydration of IV under these conditions, gives a predicted rate of dehydration of IV at 25° at $H_0 = -0.65$ of log $k_{-H_2O} = -5.6$ to -5.9 (or log $k_{-H_2O} = -4.5$ to -4.8 at 45°), depending on the choice of ρ. Thus, racemization is about 100 times faster than dehydration (see also below). This result is qualitatively similar to that obtained in the dehydration of β-phenyl-β-hydroxypropionic acid[14] where k_α/k_{-H_2O} was 50.

The rate of racemization is clearly a strongly acid-catalyzed reaction as shown by the data in Table II on the rate of racemization of IV under differing conditions.

At low sulfuric acid concentrations, the process by which decarboxylation occurs becomes progressively more competitive with the racemization through the

(13) J. T. Edsall and J. Wyman, "Biophysical Chemistry," Vol. I, Academic Press Inc., New York, N. Y., 1958, p. 555.
(14) D. S. Noyce and C. A. Lane, *J. Am. Chem. Soc.*, **84**, 1635 (1962).

Table II. Racemization of
β-(p-Methylphenyl)-β-hydroxybutyric Acid (IV)

Run	Concn. of H_2SO_4, M^a	H_0	k, sec.$^{-1}$	log $k + H_0$
A.	5% Dioxane–95% aqueous sulfuric acid at 25.00°			
1	1.82^b	-0.65	3.60×10^{-4}	
		At 45.00°		
2	0.19	$+0.72$	2.02×10^{-4}	
3	0.44^c	$+0.25$	3.75×10^{-4}	
B.	50% Dioxane–50% aqueous sulfuric acid at 25.00°			
4	1.25^d	0.63	1.22×10^{-5}	-4.28
5	1.46	0.49	1.75×10^{-5}	-4.27
6	2.07	0.19	7.70×10^{-5}	-3.92
7	2.54	-0.19	1.86×10^{-4}	-3.92
		At 45.00°		
8	0.05	$+2.41$	$3.8 \pm 0.2 \times 10^{-6}$	-3.00
9	0.25	1.72	1.54×10^{-5}	-3.09
10	0.527	1.27	4.27×10^{-5}	-3.10
11	0.750	1.10	7.15×10^{-5}	-3.13
12	1.00	0.80	1.20×10^{-4}	-3.12
13	1.25^d	0.63	2.16×10^{-4}	-3.04

^{a} Final sulfuric acid concentration. ^{b} Isolated product; almost exclusively IV (see Experimental Section). ^{c} Isolated product; largely IV; some decarboxylation (see Experimental Section). ^{d} E_a = 27 kcal.

carbonium ion A. Thus, it appears that below sulfuric acid concentrations of ca. 0.1 M the loss of observed optical activity is due in large measure to the decarboxylation reaction, rather than to a strictly defined racemization. Examination of the behavior of V at lower acid concentrations is revealing (see below).

The data in 1.25 M sulfuric acid in the 50% dioxane medium (runs 4 and 13) allows an estimate of the activation parameters. Noteworthy is the high positive ΔS^* for the reaction of about $+10$ e.u.

The entropy of limiting S_N1 reactions in mixed aqueous solvents is generally strongly positive.[15] The entropy of activation for acid-catalyzed reactions of alcohols are generally about 10 e.u. less positive.[16] Thus, the results of the racemization experiments with IV are completely concordant with general carbonium ion theory.

Loss of Optical Activity of V. The rate at which V loses optical activity under a variety of conditions is recorded in Table III.

In solution of V in 0.001 M H_2SO_4, the predominant reaction is decarboxylation, as evidenced by the isolation of large quantities of 2-(p-anisyl)propene from reaction mixtures in this solvent. In 0.01 M sulfuric acid a mixture of 2-p-anisylpropene and 2-(p-anisyl)-2-propanol is isolated after 5 half-lives for the observed rate of loss of optical activity. This mixture results from the rehydration of the initially formed styrene.[17]

Comparing the observations made with IV and V in 0.05 M sulfuric acid at 45° in 50% aqueous dioxane (runs 8 and 19) one may obtain a value for ρ of -4.1 (using σ^- values for methyl and methoxyl). Such a value is of course concordant with a carbonium ion mechanism for the acid-catalyzed racemization of tertiary benzyl alcohols, and is further quite similar to the ρ value for the ionization of the chlorides from which σ^+ values were derived.

(15) S. Winstein and A. H. Fainberg, *ibid.*, **79**, 5937 (1957).
(16) R. E. Powell, *J. Phys. Chem.*, **58**, 528 (1954).
(17) For the rate of hydration of 2-(p-anisyl)propene, see ref. 10.

Table III. Rate of Loss of Optical Activity of β-(p-Methoxyphenyl)-β-hydroxybutyric Acid at 45.00°

Run no.	Concn. of H_2SO_4, M^a	pH	k, sec.$^{-1}$	log k + pH
	A. 50% Dioxane–50% aqueous sulfuric acid			
14	0.0009	...[b]	2.5 × 10^{-6}	...
15	0.00015	...[b]	2.1 × 10^{-6}	...
16	0.005	2.32	1.92 × 10^{-5}	2.39
17	0.010	1.96	4.62 × 10^{-5}	2.36[c]
18	0.018	1.70	8.75 × 10^{-5d}	2.36
19	0.050	1.26[e]	3.12 × 10^{-4f}	2.24
	B. 5% Dioxane–95% aqueous sulfuric acid			
20	ca. 0.001	2.72	1.41 × 10^{-4}	1.13
21	ca. 0.01	1.88	3.85 × 10^{-4}	1.53

[a] Sulfuric acid concentration after mixing. [b] pH value not meaningful; contribution from the self-ionization of the hydroxy acid to the total acidity. Readings of optical rotation could not be carried further than 35% reaction. [c] 40% of the theoretical amount of hydrocarbon, 2-(p-anisyl)propene, was isolated after 60% reaction, by dilution of the optical solution with ice and filtration. [d] From the measured rate of decarboxylation (see Table V) at this acidity in the same medium this observed rate is a sum which includes approximately a 50% contribution from decarboxylation. The corrected rate for racemization reaction is about 4.4 × 10^{-5}. [e] The measured H_0 value is 2.41 at this acidity. [f] 35% hydrocarbon isolated after 3 half-lives (90 min).

Decarboxylation of IV and V. With the information regarding the rate of racemization of optically active IV and V available it is instructive to further examine the decarboxylation process by which carbon dioxide, water, and the 2-arylpropene are formed. The rate of formation of carbon dioxide under a variety of conditions has been measured; the results are presented in Tables IV and V. Examination of these data further

Table IV. Rate of Decarboxylation of β-(p-Methylphenyl)-β-hydroxybutyric Acid (IV) in Dilute Aqueous Sulfuric Acid

Run no.	H_2SO_4, %	Solvent^a	Temp., °C	H_0	k, sec.$^{-1}$
27	4.55	50% D	44.70	+1.30	1.30 × 10^{-5}
28	4.57	H$_2$O	44.70	+0.16	1.28 × 10^{-4}
29	4.57	H$_2$O	44.70		1.19 × 10^{-4}
30	8.93	H$_2$O	44.70	−0.23	1.87 × 10^{-4}
31	14.75	5% D	44.70	−0.59	2.84 × 10^{-4}
32	20.18	5% D	44.70	−0.93	4.27 × 10^{-4}
33	7.48	5% D	24.91	−0.04[b]	6.83 × 10^{-6}
34	8.37	5% D	45.00	−0.04[b]	1.78 × 10^{-4}

[a] D = dioxane. [b] H_0 values measured using o-nitroaniline as indicator; E_a = 30.6 kcal., ΔS^* = 21.6 e.u.

supports the conclusion in the previous paper that the decarboxylation process is a characteristic of the hydroxy acid. A cursory extrapolation of the data for the simple dehydration reactions of β-aryl-β-hydroxybutyric acids shows that dehydration is too slow to be involved as a prior step. In the most concentrated sulfuric acid solutions used for the direct measurement of the rate of decarboxylation of IV (run 32) and of V (run 48) extrapolated rates for a dehydration of IV or V are from 5 to 20 times too slow.

Discussion. The data obtained in this study provide additional insight into the details of the complex network of reactions involved in the decomposition of β-aryl-β-hydroxy acids in acidic media.

The relevant relationships are most easily summarized

Table V. Rate of Decarboxylation of β-(p-Methoxyphenyl)-β-hydroxybutyric Acid (V) in Dilute Sulfuric Acid

Run no.	Concn. of H_2SO_4, M	Solvent^a	Temp., °C	H_0	k, sec.$^{-1}$
36	0.141	5% D	25.00	+0.86	1.40 × 10^{-4}
37	0.254	H$_2$O	25.00	+0.44	1.57 × 10^{-4}
38	0.258	5% D	25.00	+0.55	1.79 × 10^{-4}
39	0.460	5% D	24.91	+0.34	2.13 × 10^{-4}
40	0.460	5% D	24.91	+0.34	2.15 × 10^{-4}
41	0.532	5% D	25.00	+0.18	2.33 × 10^{-4}
42	0.730	5% D	24.91	+0.08	2.62 × 10^{-4}
43	0.730	5% D	24.91	+0.08	2.27 × 10^{-4}
44	0.730	5% D	24.91	+0.08	2.80 × 10^{-4}
45	0.800	5% D	24.91	−0.04	2.72 × 10^{-4c}
46	0.800	5% D	24.91	−0.04	2.80 × 10^{-4c}
47	0.800	5% D	24.91	−0.04	2.85 × 10^{-4c}
48	1.05	5% D	25.00	−0.24	3.00 × 10^{-4}
49	0.73	5% D	15.00	−0.05	4.63 × 10^{-5c}
50	0.85	5% D	34.83	−0.03	1.15 × 10^{-3c}
51	None	H$_2$O	44.70	...	~9.00 × 10^{-5}
52	0.018	50% D	44.70	~3.0^b	4.4 × 10^{-5}
53	0.010	H$_2$O	44.70	~1.7	4.42 × 10^{-4}
54	0.460	5% D	45.00	+0.41	3.12 × 10^{-3}

[a] D = dioxane. [b] pH = 1.70. [c] E_a = 28 kcal., ΔS^* = +21 e.u.

graphically, by reference to Figures 1 and 2 for the behavior of compounds IV and V.

The direct, true racemization rate for (+)-IV is represented by the dashed line (--⊕--) in Figure 1. Experimental points are given by the plus symbols. The slope of the line log k vs. H_0 is 1.1. This slope is very similar to that obtained for other carbonium ion reactions proceeding from benzyl alcohols. For example, Deno, Kish, and Peterson[18] report that the dehydration of cumyl alcohols shows unit slope correlation with H_0. In these laboratories it has been observed that the rate of racemization of β-phenyl-β-hydroxypropionic acid increases more rapidly than h_0; the slope of a plot of log k vs. H_0 is 1.17.[19] Similar results have been obtained in a study of the racemization of 1,2-diphenylethanol[20] and in studies of the O^{18} exchange reactions of t-butyl alcohol[21] and 1-phenylethanol.[22]

The rate of the acid-catalyzed dehydration of IV can be closely estimated on the basis of ample analogy and reasonable extrapolations. Extrapolation of the data of Noyce and Heller as well as some preliminary measurements by Gortler[23] provide a sound basis for the solid line and triangles.

Finally the rate profile for the decarboxylation reaction (circles in Figure 1) deserves additional comment. The reaction shows a very modest sensitivity to changing mineral acid concentration when it is compared with the other reactions in this system. In dilute acid (pH ~2) it becomes competitive with racemization; in more concentrated mineral acid (~40%) it is now competitive with dehydration.

(18) N. C. Deno, F. A. Kish, and H. J. Peterson, *J. Am. Chem. Soc.*, 87, 2157 (1965); cf. H. J. Peterson, Dissertation, Pennsylvania State University, 1960; *Dissertation Abstr.*, 21, 2489 (1961).
(19) D. S. Noyce and C. A. Lane, *J. Am. Chem. Soc.*, 84, 1635 (1962).
(20) D. R. Hartter, Dissertation, University of California, Berkeley, 1964; cf. D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Am. Chem. Soc.*, 86, 3583 (1964).
(21) R. H. Boyd, R. W. Taft, Jr., D. P. Wolf, and D. R. Christman, *ibid.*, 82, 4729 (1960).
(22) E. Grunwald, A. Heller, and F. S. Klein, *J. Chem. Soc.*, 2604 (1957).
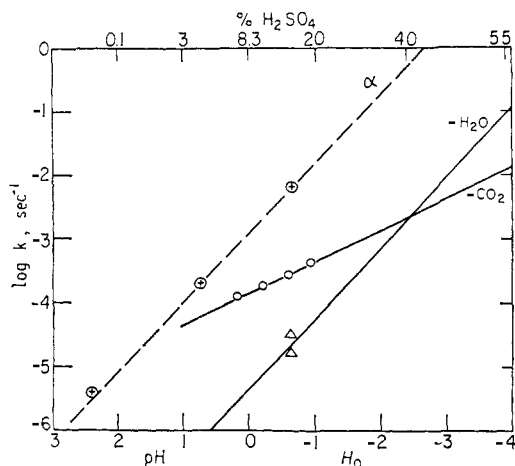(23) L. B. Gortler, unpublished observations.

Figure 1. Reactions of β-(p-methylphenyl)-β-hydroxybutyric acid at 45°: $\oplus$ - -, rate of racemization; $\bigcirc$——, rate of decarboxylation–dehydration; $\triangle$——, rate of dehydration.

Figure 2. Reactions of β-(p-methoxyphenyl)-β-hydroxybutyric acid at 25°: $\oplus$ - -, rate of racemization; $\bigcirc$——, rate of decarboxylation; $\triangle$——, rate of dehydration.

A very similar picture (Figure 2) may be constructed for the behavior of V, similar in all respects and qualitatively identical. The only differences are in the numerical magnitudes of the rates, and in the regions of mineral acid concentration in which they are of appropriate magnitude for direct measurement.

Conclusion. The decarboxylation of β-hydroxy acids exhibits several unusual characteristics. First, the reaction is relatively insensitive to the mineral acid content of the medium, with the slopes of log k *vs.* H_0 plots being near 0.3 for V, and somewhat larger for IV.

Second, the reaction is strongly inhibited by nonhydroxylic or nonpolar solvents. The rate in 50% dioxane is markedly suppressed (compare runs 27 and 28; runs 52 and 53) and V survives extended boiling in benzene unscathed. Such observations suggest a very polar transition state for the decarboxylation process.

The direct product of the synchronous loss of water and carbon dioxide is the olefin. The olefin may be isolated if the solution is not sufficiently acidic to catalyze the hydration of the substituted olefin more rapidly than it is formed.

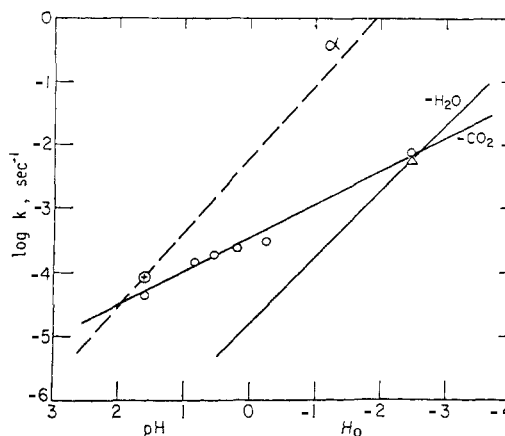Mechanistically, these observations suggest a very important role for a species which is zwitterionic in

nature, either C or D as a critical intermediate, closely

$$
\begin{array}{cc}
\overset{+}{O}H_2 & \\
| & \overset{+}{} \\
Ar\!-\!\overset{|}{C}\!-\!CH_2CO_2^- & Ar\!-\!\overset{|}{C}\!-\!CH_2CO_2^- \\
| & | \\
CH_3 & CH_3 \\
C & D
\end{array}
$$

related to the activated complex for dehydration. Such a suggestion has been made from these laboratories in a preliminary communication.[24] A close analogy to the situation studied by Liang and Bartlett,[25] the decomposition of β-isovalerolactone, is apparent. Related to this latter situation is the observation of Pressman and Lucas[26] that the decomposition of β-hydroxyisovaleric acid at 100° in dilute mineral acid solution gives rise to isobutylene (and *t*-butyl alcohol) in competition with the formation of dimethylacrylic acid by simple dehydration.

In the following paper we point out the relationship of these observations to the well-known decarboxylation of cinnamic acids in mineral acid solution.

(24) D. S. Noyce, G. L. Woo, and P. A. King, *J. Org. Chem.*, **26**, 632 (1961).
(25) H. T. Liang and P. D. Bartlett, *J. Am. Chem. Soc.*, **80**, 3585 (1958).
(26) D. Pressman and H. J. Lucas, *ibid.*, **62**, 2069 (1940).