Rates and Equilibria in the Reaction of γ-Butyrolactone with Alcohols. A Convenient Synthesis of 4-Hydroxybutyrates[1]

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The acid-catalyzed alcoholysis of γ-butyrolactone yields an equilibrium mixture of the lactone and the corresponding 4-hydroxybutyrates. Methyl, ethyl, and isopropyl esters of 4-hydroxybutyric acid were isolated in 10–50% yield. The relative rates of the acid-catalyzed reaction of γ-butyrolactone with alcohols decrease in the order: methyl > ethyl > isopropyl. The equilibrium constants and the equilibrium concentrations of the corresponding 4-hydroxybutyrates have been determined.

An authentic sample of ethyl 4-hydroxybutyrate was required for identification of the product formed in the hydroboration of ethyl 3-butenoate.[3] Only a few scattered references to this ester were found in the literature. Curtius had reported that a compound, obtained by treating ethyl 4-aminobutyrate with nitrous acid, might have been ethyl 4-hydroxybutyrate.[4] However, the material was not characterized.[5] Cherbuliez reported the preparation of ethyl 4-hydroxybutyrate by the same method, but did not report any physical constants or attempts to characterize the material.[6] Spencer prepared ethyl 4-hydroxybutyrate from sodium ethoxide and γ-butyrolactone,[7] but did not attempt to isolate it owing to reported instability of analogous compounds.[8] However, ethyl 4-hydroxybutyrate, prepared by a reductive desulfurization of a monothio ester, $C_6H_5CH_2SCO(CH_2)_2CO_2C_2H_5$, has been isolated in 52% yield, and properly characterized.[9] Trichlorophenyl 4-hydroxybutyrate was the only other ester of unsubstituted 4-hydroxybutyric acid located in the literature.[10] However, several 2- and 4-alkyl-substituted 4-hydroxybutyrates have been prepared.[11–14]

The observation that ethyl 4-hydroxybutyrate, obtained *via* the hydroboration–oxidation of ethyl 3-butenoate, is a relatively stable material suggested the desirability of developing a simple synthesis of esters of this type. Acid-catalyzed esterification of γ-butyrolactone appeared to offer a simple solution to the synthetic problem.

Results

Preliminary experiments showed that γ-butyrolactone reacted with ethanol in presence of a small quantity of sulfuric acid. A product peak, presumably due to ethyl 4-hydroxybutyrate, was detected by gas chromatography. The concentration of the product increased until approximately one-half of the γ-butyrolactone had reacted. No further disappearance of γ-butyrolactone was observed, indicating that an equilibrium had been achieved. The reaction of γ-butyrolactone with methyl and isopropyl alcohols proceeded in a similar manner.

Relative rates of acid-catalyzed reaction of γ-butyrolactone with methyl, ethyl, and isopropyl alcohol were then determined. In each case the alcohol solutions, 2 *M* in γ-butyrolactone and 0.05 *N* in sulfuric acid, were stirred at 25 ± 0.5°. At various time intervals, aliquots were withdrawn, neutralized with solid carbonates, and analyzed by gas chromatography. The results are presented in Figure 1.

The rates of alcoholysis decreased in the following order: methyl > ethyl > isopropyl. At equilibrium the conversion of γ-butyrolactone to the corresponding hydroxy ester was 73% for methyl, 61% for ethyl, and 48% for isopropyl alcohol. The equilibrium constants for the three alcoholysis reactions were calculated, using the equilibrium concentrations of γ-butyrolactone and the hydroxy esters and estimated equilibrium concentrations of alcohols. The results are listed in Table I.

TABLE I

EQUILIBRIUM PRODUCT COMPOSITION AND EQUILIBRIUM CONSTANTS FOR ACID-CATALYZED ALCOHOLYSIS OF γ-BUTYROLACTONE AT 25°

	Equilibrium product composition			
Alcohol	Hydroxy ester, %	Lactone, %[a]	Ester/lactone	K_{25}[b], M^{-1}
Methyl	73	27	2.7	0.136
Ethyl	61	39	1.9	0.117
Isopropyl	48	52	0.92	0.091

[a] Initial concentration of γ-butyrolactone was 2 *M* in each case. [b] For the reaction: $\underbrace{OCH_2CH_2CH_2C{=}O}$ + ROH ⇆ $HOCH_2CH_2CH_2CO_2R$.

The possibility of isolating ethyl 4-hydroxybutyrate was then explored. After equilibrium had been attained, the solution was stirred for several hours with calcium carbonate to neutralize the catalyst. Excess alcohol was removed *in vacuo*, and the residue was distilled under reduced pressure. The initial distillate consisted largely of γ-butyrolactone. Although the hydroxy ester had been concentrated in the residue, further distillation gave only γ-butyrolactone and ethanol. Evidently the hydroxy ester was decomposing during distillation.

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(2) Research assistant on an investigation supported by the Ethyl Corp.

(3) H. C. Brown and K. A. Keblys, *J. Am. Chem. Soc.*, **86**, 1795 (1964).

(4) T. Curtius and E. Mueller, *Ber.*, **37**, 1261 (1904).

(5) The reported boiling point of this material was 10–15° lower than the reported boiling point of γ-butyrolactone. Our studies have revealed that all simple 4-hydroxybutyrates possess higher boiling points than γ-butyrolactone.

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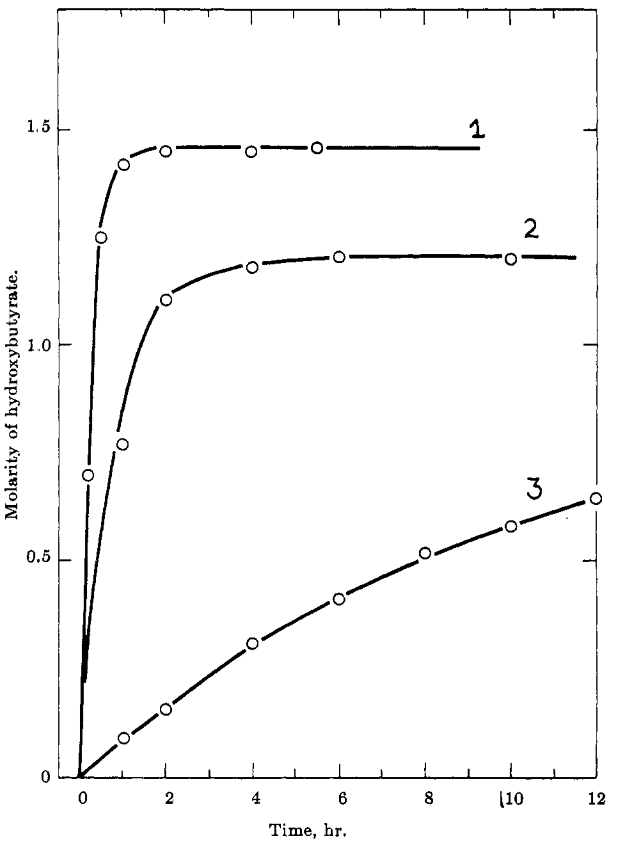

Figure 1.—Relative rates of acid-catalyzed alcoholysis of γ-butyrolactone at 25°: curve 1, methanol; curve 2, ethanol; and curve 3, 2-propanol.

It appeared possible that the neutralization of the reaction mixture had been incomplete, and that the residual acid had catalyzed the reverse reaction. However, a prolonged contact of the reaction mixture with calcium carbonate still failed to achieve a complete neutralization. The product again decomposed during distillation. Treatment of the reaction mixture with lithium carbonate appeared to give a more complete neutralization of the catalyst, but final distillation still gave only γ-butyrolactone and ethanol. In this case the decomposition might have been catalyzed by lithium 4-hydroxybutyrate formed during the attempted neutralization.

Finally, an ethanolysis reaction mixture, after treatment with calcium carbonate and evaporation of excess alcohol, was dissolved in ether and washed with a dilute sodium carbonate solution. After drying and evaporation of solvent, the residue was distilled rapidly at 0.2 mm, using a short-path apparatus and an ice-cooled receiver. Fractionation of the flash distillate gave ethyl 4-hydroxybutyrate, about 98% pure, in 53% yield.

Methyl and isopropyl 4-hydroxybutyrates were isolated, using the same procedure. The formation of small quantities of higher boiling materials was observed in the methanolysis and ethanolysis reactions, but these were not characterized. In the case of the reaction involving isopropyl alcohol, a higher boiling component was isolated from the reaction mixture. Infrared, microanalysis, and molecular refractivity indicated that this material was 3-carboisopropoxypropyl 4-hydroxybutyrate, a dimeric species, presumably formed by a reaction of γ-butyrolactone with isopropyl 4-hydroxybutyrate.

The yields and physical constants of the isolated 4-hydroxybutyrates are listed in Table II.

Discussion

The relative rates of acid-catalyzed alcoholysis of butyrolactone decrease in the following order: methyl > ethyl > isopropyl. This trend of relative rates parallels closely the trend observed in the esterification of acetic acid with these alcohols.[15] Furthermore, the observed relative reactivities of these alcohols with γ-butyrolactone are in qualitative agreement with the reactivities predicted by Taft's substituent constants for the alkyl components in acid-catalyzed esterifications.[16]

The observed difference in γ-butyrolactone alcoholysis rates was noticeably greater than the difference in the calculated equilibrium constants for the three alcoholysis reactions studied. A similar phenomenon had been observed in numerous esterification reactions[15] and has been explained by the argument that steric factors are much more important in the transition state than in either the products or the reactants.[17]

The yields of 4-hydroxybutyrates isolated from the alcoholysis reaction mixtures were rather low. Nevertheless, the acid-catalyzed reaction of γ-butyrolactone with primary and secondary alcohols provides a simple method for the preparation of 4-hydroxybutyrates.

The major difficulty in the isolation procedure appears to be the complete neutralization of the acid catalyst. The greatest loss of the product occurs during the evaporation of excess alcohol. If traces of acid (or of base) are present at that point, the rapid decrease in the alcohol concentration might be expected to shift the equilibrium to the lactone side, causing the decomposition of the hydroxy ester.

Furthermore, at low alcohol concentrations during the evaporation stage, an acid-catalyzed reaction between the hydroxy ester and γ-butyrolactone is possible. This side reaction occurred to an appreciable extent during the isolation of isopropyl 4-hydroxybutyrate, as evidenced by isolation of a substantial quantity of a dimeric species.

Undoubtedly, a considerable improvement in yields of the hydroxy esters might be attained by proper modifications of the isolation procedure and by a more efficient fractionation. Such refinements, however, were beyond the scope of the present study.

As indicated by the constants, the equilibrium of the alcoholysis reactions lies largely on the lactone–alcohol side. As a result, a large excess of alcohol is needed in order to attain a reasonable conversion of the lactone. Therefore, from a synthetic point of view, the alcoholysis reaction appears to be limited to readily available alcohols and lactones.

It might be pointed out that ethyl 4-hydroxybutyrate has been obtained in good yield by hydroboration of ethyl 3-butenoate.[3] Particularly in cases where the lactone alcoholysis route might prove difficult, the

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(17) J. Hine, "Physical Organic Chemistry," 1st ed, McGraw-Hill Book Co., New York, N. Y., 1956, p 276.

Table II

Summary of Data for Isolated 4-Hydroxybutyrates

4-Hydroxy- butyrate	Yield,[a] %	Conversion,[b] %	Bp, °C (mm)	$n^{20}D$	d^{20}_{20}	Molar refractivity		Mp of derivative,[d] °C
						Calcd[c]	Found	
Methyl	13	10	45.6 (0.2)	1.4295	1.075	28.34	28.36	75.0–75.5
Ethyl[e]	53	30	57–58 (0.4)	1.4291	1.036	32.99	32.89	63.0–63.5
Isopropyl	22	12	64 (0.4)	1.4270	0.993	37.81	37.67	52.0–53.0
Dimer[f]	27	14	100 (0.4)	1.4460	1.072	57.81	57.81	. . .

[a] Isolated, based on the amount of hydroxy ester at equilibrium, as determined by gas chromatography. [b] Based on butyrolactone used. [c] Calculated using atomic refractivities given by A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1957, p. 1035. [d] 3,5-Dinitrobenzoate. [e] Lit.[9] bp 99–103° (15 mm), 3,5-dinitrobenzoate mp 62–63°. [f] $HO(CH_2)_3CO_2(CH_2)_3CO_2CH(CH_3)_2$.

hydroboration reaction provides a convenient alternate route to 4-hydroxybutyrates.

Experimental Section

Materials.—Methanol and isopropyl alcohol were purified by distillation from magnesium. Ethanol was distilled from sodium and diethyl phthalate. All alcohols were at least 99% pure by gas chromatography.

γ-Butyrolactone from Eastman Organic Chemicals was purified by distillation: bp 70–71° (6 mm), $n^{20}D$ 1.4370; lit.[18] bp 70–71° (5 mm), $n^{20}D$ 1.4365.

Gas Chromatographic Analysis.—Solutions of γ-butyrolactone and 4-hydroxybutyrates were analyzed using a 2.5-ft column packed with Sorbitol (4%) and Silicone 703 (16%) on regular firebrick, operated at 115–120° with a 100-cc/min flow of helium. The decomposition of 4-hydroxybutyrates on this column ranged from 1 to 3 mole %. All other columns tried caused more extensive and irreproducible decomposition of the hydroxybutyrates.

Relative Rates of Alcoholysis.—The following procedure was used for the reactions of γ-butyrolactone with ethyl and isopropyl alcohols. γ-Butyrolactone (8.60 g, 0.100 mole) was mixed with enough standardized sulfuric acid–alcohol solution to make the final acid concentration 0.05 *N*, then diluted to 50.0 ml with alcohol, and stirred at 25 ± 0.5°. Periodically, 2.0-ml samples were withdrawn, shaken with 0.5 g of lithium carbonate, filtered, and analyzed immediately by gas chromatography. A blank experiment showed that γ-butyrolactone solutions in ethyl and isopropyl alcohol, stirred 2 hr with lithium carbonate, did not contain any hydroxy ester.

Owing to a rapid reaction rate, a modified procedure was used for the methanolysis reaction. To a 2.0 *M* solution of γ-butyrolactone in methanol was added from a calibrated dropper enough concentrated sulfuric acid to make the solution 0.05 *N* in acid. Since it was found that lithium carbonate catalyzed the methanolysis reaction, calcium carbonate was used to neutralize the aliquots before analysis by gas chromatography.

The results of these experiments are presented in Figure 1.

Preparation of Ethyl 4-Hydroxybutyrate.—γ-Butyrolactone (20.0 g, 0.23 mole) was dissolved in 100 ml of ethanol. The solution was treated with 0.5 g of concentrated sulfuric acid and stirred 13 hr at room temperature. Then 3 g of calcium carbonate was added, and stirring was continued for 1 hr. After filtration, excess ethanol was evaporated *in vacuo*. The remaining solution was diluted with 100 ml of ether, washed with 15 ml of 1% sodium carbonate, 15 ml of water, and 15 ml of saturated sodium chloride solution, then dried over magnesium sulfate. Ether was evaporated *in vacuo* and the remaining material was distilled rapidly at 0.2 mm using a short-path apparatus and an ice-cooled receiver. The flash distillate was fractionated using a 3-in. Vigreux column. The first two fractions contained 83 and 50% γ-butyrolactone, respectively. The last three fractions, 9.32 g, 53% yield, collected at 57–58° at 0.4 mm, consisted of ethyl 4-hydroxybutyrate, 97–98% pure by gas chromatography, $n^{20}D$ 1.4291, d^{20}_{20} 1.0361, infrared bands at 2.97 and 8.67 μ. The hydroxy ester was soluble in water and benzene and insoluble in hexane.

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.42; H, 8.98.

The 3,5-dinitrobenzoate of the product, recrystallized from ether–hexane, melted at 63.0–63.5°, lit.[9] mp 62–63°.

Anal. Calcd for $C_{13}H_{14}N_2O_8$: C, 47.85; H, 4.33; N, 8.59. Found: C, 48.00; H, 4.40; N, 8.47.

Methyl 4-Hydroxybutyrate.—By the procedure described above, methyl 4-hydroxybutyrate was prepared from 35.0 g (0.41 mole) of γ-butyrolactone and 175 ml of methanol. Final fractionation afforded 4.36 g (13%) of methyl 4-hydroxybutyrate, 97–98% pure by gas chromatography, collected at 45–46° at 0.2 mm: $n^{20}D$ 1.4295; d^{20}_{20} 1.0744; infrared bands at 3.03, 5.80, and 8.65 μ. The hydroxy ester was soluble in water and benzene and insoluble in hexane.

Anal. Calcd for $C_5H_{10}O_3$: C, 50.85; H, 8.54. Found: C, 50.87; H, 8.70.

The 3,5-dinitrobenzoate derivative, recrystallized from ether–hexane, melted at 75.0–75.5°.

Anal. Calcd for $C_{12}H_{12}N_2O_8$: C, 46.16; H, 3.88; N, 8.97. Found: C, 46.01; H, 3.71; N, 9.18.

Isopropyl 4-Hydroxybutyrate.—By the procedure described above, isopropyl 4-hydroxybutyrate was prepared from 30.0 g (0.35 mole) of γ-butyrolactone and 175 ml of isopropyl alcohol. Final fractionation afforded 10.7 g (22% yield) of isopropyl 4-hydroxybutyrate, 97–98% pure by gas chromatography, collected at 62–66° at 0.4–0.5 mm: $n^{20}D$ 1.4270; d^{20}_{20} 0.9926; infrared bands at 3.00, 5.80, and 8.54 μ. The hydroxy ester was soluble in water, benzene, and hexane.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.39; H, 9.36.

The 3,5-dinitrobenzoate derivative, recrystallized from ether–hexane, melted at 52–53°.

Anal. Calcd for $C_{14}H_{16}N_2O_8$: C, 49.41; H, 4.74; N, 8.23. Found: C, 49.64; H, 4.70; N, 8.51.

There was also isolated 5.9 g of a viscous oil by rapid distillation at 100–110° at 0.4 mm. The distillate was stirred at 40° at 1 mm until the refractive index was constant. The remaining material, $n^{20}D$ 1.4460, d^{20}_{20} 1.0723, on examination by gas chromatography, showed only two very small and tailing peaks corresponding to the isopropyl ester and butyrolactone. The infrared spectrum revealed no major differences from the spectrum of isopropyl 4-hydroxybutyrate. The molecular refractivity, calculated for $HO(CH_2)_3CO_2(CH_2)_3CO_2CH(CH_3)_2$, was 57.81; the experimental value was 57.78.

Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.98; H, 8.63.

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