

# Reactions of Lactones with Alcohols in a Diazomethane-Ether Solution

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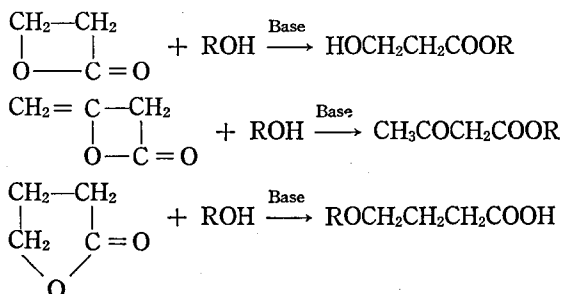
**Abstract:** The reaction of  $\beta$ -propiolactone(1), ketene dimer(2) or  $\gamma$ -butyrolactone(3) with methanol, ethanol, 1-propanol and 1-butanol in the diazomethane-ether solution has been carried out. The reaction of (1) with alcohols, as well as the base catalyzed reaction, gives alkyl hydracrylate. In the same manner, (2), after reacting with alcohols gives alkyl acetoacetate. However, (3), after reacting with alcohols, gives alkyl  $\gamma$ -oxybutyrate. Alkyl  $\gamma$ -oxybutyrate is reported to be impossible to be obtained by the base catalyzed reaction. The effects of time, temperature and diazomethane concentration on the proportions of products are demonstrated.

## 1. Introduction

As a part of the investigation of the reactions of lactones <sup>(1), (2)</sup>, a ring-enlargement of lactone by the use of diazomethane is studied. It has been studied by many workers that carbocyclic ketones react with diazomethane to give the ring-enlarged ketones <sup>(3)</sup>. Therefore, it occurred to us that ring-enlarged  $\gamma$ -butyrolactone might be prepared by the treatment of (1) with diazomethane. This reaction under the same conditions, however, did not give the expected product. When the alcohol solvent was used to activate diazomethane, the alcohol reacted with (1) to give alkyl hydracrylate, and diazomethane was conversely acted as the activating catalyst of alcohol in this reaction.

Then the reactions of lactones with alcohols, when catalyzed by diazomethane, are studied. Although azlactone <sup>(4)</sup>, enollactone <sup>(5)</sup> and  $\delta$ -valerolactone <sup>(6)</sup> have been found to form derivatives of ester under similar condition when diazomethane is

SCHEME 1



present, but four- and five-membered ring lactones have not been used. Therefore  $\beta$ -propiolactone, ketene dimer and  $\gamma$ -butyrolactone are used here as four- and five-membered ring lactones.

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On the other hand, the reaction of (1)<sup>(7)</sup>, (2)<sup>(8), (9)</sup> or (3)<sup>(10)</sup> with alcohols have been investigated with base or acid catalysis (Scheme I). (1) and (2) easily form polymer by strong base and acid, and these, therefore, must be alcoholized very slowly to avoid polymerization. It was supposed that the reaction with diazomethane would be occurred at rather mild experimental condition, and polymerization of these lactones would decrease more with diazomethane than with base and acid catalyses.

## 2. Results and Discussion

### 2.1 The Reaction of $\beta$ -Propiolactone with Diazomethane

Heterocyclic ring of lactone contains carbonyl group and oxygen, and a lot of the chemical reactivities of lactone are occurred when carbonyl-oxygen bond or alkyl-oxygen bond is broken. However, it seems to be that the reactivity of carbonyl group of lactone may be raised by using appropriate catalysts, such as Lewis acid type, and then, the lactone may react with diazomethane giving enlarged lactone.

TABLE I  
REACTIONS OF  $\beta$ -PROPIOLACTONE WITH DIAZOMETHANE

$\beta$ -P.L. (g)	D.M. (g)	Catal. (g)		Temp. (°C)	Time (hr)	Polymer (g)	Product (g)
20.0	10.0			10	1 week	12.0	
14.4	5.5	BF <sub>3</sub>	2.5	-15	2	3.1	
17.3	10.0	BF <sub>3</sub>	17.3	0	17	12.8	2 <sup>(b)</sup>
10.0	6.0	AlCl <sub>3</sub>	0.5	5	44	1.5	
15.0	5.8	LiCl	0.5	20	27	7.3	
10.0	5.0	NaOH	0.2	10	30	2.4	
7.0	3.0	ZnCl <sub>2</sub>	0.1	10	15	0.5	
37.0	8.0 <sup>(a)</sup>	CH <sub>3</sub> OH	120cc	30	5	5.0	12 <sup>(c)</sup>

(a) Diazomethane was prepared by decomposition of N-nitrosomethyl urethane.

(b) distilled mixture.

(c) Methyl hydracrylate.

As is shown in Table I, (1) did not react with diazomethane when catalysts are present, and substantially all these reactions gave only solid and liquid of polyesters of (1). In spite of using a boron trifluoride, which is described to be the best catalyst in ring-enlarged reaction<sup>(11)</sup>, this reaction gave a small amount of products at 0°C for 17 hr., and the products contained no  $\gamma$ -butyrolactone (by the retention times of gas chromatograph). when methanol was used as catalyst, (1) reacted not with diazomethane but with methanol to formed methyl hydracrylate in a 44% yield. The result, as would be expected, was not obtained, That is tentatively ascribed not to be increased the reactivity of carbonyl group in lactone ring by catalysts, and the oxygen bond is broken by catalysts because of the higher reactivity of oxygen bond more than carbonyl group.

## 2.2 The Reaction of $\beta$ -Propiolactone with Alcohols

It has been studied by Gresham *et al.* that reaction of (1) with alcohols forms two products, depending on the catalysis, alkyl hydracrylate with base catalysis and  $\beta$ -alkoxy acid with acid catalysis.

The reaction of (1) with alcohols, when catalyzed by diazomethane, gave alkyl hydracrylate, as well as base catalyzed reaction. Reaction products were confirmed by the identification of infrared spectra and retention times of gas chromatograph with those of samples, which were prepared according to the directions of Gresham *et al.*

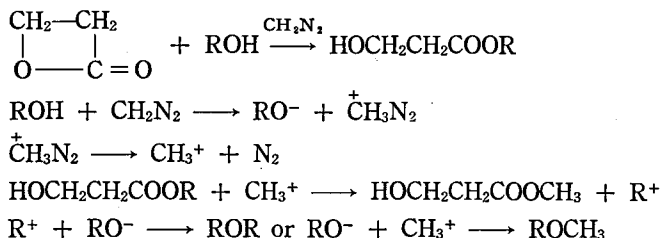
TABLE II  
REACTIONS OF  $\beta$ -PROPIOLACTONE WITH ALCOHOLS

Alcohol		$\beta$ -P.L. (g)	D.M. (g)	Temp. (°C)	Time (hr)	HOCH <sub>2</sub> CH <sub>2</sub> COOR		methyl Hydracrylate yield(g)
R	(g)					b. p. (°C/mm)	yield, g(%)	
CH <sub>3</sub>	26	8		30	17		0	
CH <sub>3</sub>	26	8	1.4	30	17		9.0 (79)	
CH <sub>3</sub>	26	8	2.7	30	17	81/20	9.3 (82)	
CH <sub>3</sub>	26	8	5.3	30	17		8.3 (71)	
CH <sub>3</sub>	26	8	2.7	20	17		6.5 (56)	
CH <sub>3</sub>	26	8	2.7	30	48		9.1 (80)	
C <sub>2</sub> H <sub>5</sub>	36.8	8	5.3	30	67	79/12	3.7 (31)	0.7
<i>n</i> -C <sub>3</sub> H <sub>7</sub>	60	14.4	2.6	30	17	85/9	5.2 (20)	0.8
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	74	14.4	2.6	28	17	69/1.4	5.7 (20)	0.8

As is shown in Table II, the reaction product of (1) with methanol was obtained in good yield, as much as base catalyzed reaction. However, the reaction products of (1) with the other alcohols were obtained less than with methanol, and contained a certain quantity of methyl hydracrylate, which increased when diazomethane was added more. When the reaction temperature rised above 30°C, diazomethane was removed for a while, and the amount of products decreased. When it was falled below 20°C, the a mount decreased also. The yields of alkyl hydracrylate were scarcely obtained depending upon the quantity of diazomethane, and then, the diazomethane fairly remained in ether solvent, in spite of these conditions, such as at 30°C for 17 hr.

On the basis of these results, the diazomethane almost fancies as the activating agent on alcohol through their mechanism, as is assumed by Wieland and Rothhaupt. At the same time, it seems to be that a very small amount of diazomethane attracts hydrogen of hydroxyl group of alcohol, and gives methyl cation by evolving nitrogen, and then, alkyl group of obtained alkyl hydracrylate is replaced by methyl cation (Shown in Scheme II). A small amount of dimethyl ether was contained in exhaust gas of reaction (1) with methanol.

## SCHEME II



As is shown in Fig. 1, the yields of product increased with more concentration of alcohol. This result may be explained when the polymerization of (1) decrease and the equilibrium in ester exchange reaction is shifted to the right owing to the excess alcohol.

Compared with base catalyzed reaction, our method improves in easy controlling for mild reaction and in easy treatment after the end of reaction because the catalyst is removed according as the solvent is removed, but the other yields than that by treatment with methanol do not prove consistently successful.

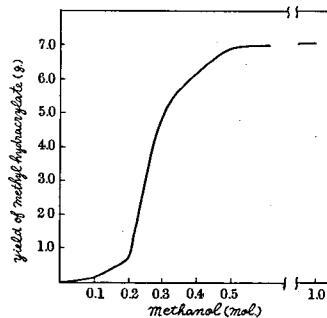


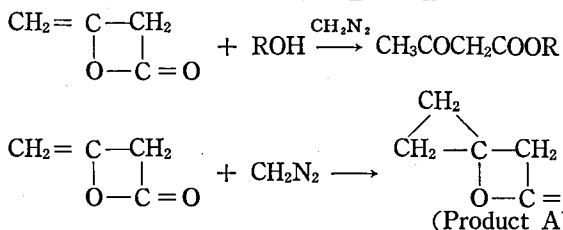
Fig. 1 Reaction of methanol with 0.1 mol. of B.P.L. at 27°C for 17 hr.

## 2,3 The Reaction of Ketene Dimer with Alcohols

It has been investigated by Boese that reaction of (2) with alcohols gives alkyl acetoacetate with sodium or base as catalyst.

The reaction of (2) with alcohols, when catalyzed by  $\text{[diazomethane]}$ , similarly gave alkyl acetoacetate (Shown in Scheme III). These products were confirmed by the identification of these infrared spectra and retention times of gas chromatograph with those of samples, which were prepared according to the directions of Boese.

## SCHEME III



As is shown in Table III, the reaction of (2) with alcohols was occurred in the similar reaction system to reaction of (1), that is, methyl acetoacetate was obtained better than the other esters, and was contained in the other esters, and its yield was increased with more added  $\text{[diazomethane]}$ . However, reaction of (2) differed from reaction of (1) and (3), the yellow color of diazomethane in a solution being colorless at the end of treatment with alcohol. Diazomethane acted not only as catalyst but as reaction agent.

TABLE III  
REACTIONS OF KETENE DIMER WITH ALCOHOLS

Alcohol		K. D. (g)	D. M. (g)	Temp. (°C)	Time (hr)	CH <sub>3</sub> COCH <sub>2</sub> COOR		Methyl Acetoace- tate yield(g)	Product A (g)
R	(g)					b. p. (°C/mm)	yield, g(%)		
		8.4	5.6	27	17			2.1	0.2
		8.4	5.6	28	48			2.2	0.2
CH <sub>3</sub>	36.0	8.0		25	17		0		0.0
CH <sub>3</sub>	25.6	8.4	1.4	25	17		4.6 (40)		0.2
CH <sub>3</sub>	25.6	8.4	2.6	25	17	63/13	6.6 (57)		0.2
CH <sub>3</sub>	25.6	8.4	5.6	25	17		6.9 (59)		0.6
C <sub>2</sub> H <sub>5</sub>	33.6	8.4	2.6	25	17	65/10	3.9 (30)	0.7	0.8
<i>n</i> -C <sub>3</sub> H <sub>7</sub>	60.0	8.4	2.6	28	17	71/10	4.4 (30)	0.9	0.9
<i>i</i> -C <sub>3</sub> H <sub>7</sub>	48.0	8.4	2.6	25	17	67/10	1.7 (12)	0.5	0.8
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	74.0	8.4	2.6	28	17	84/12	4.2 (26)	0.7	1.0

Then the treatment of (2) with diazomethane, when no alcohol is used, has been studied. The reaction products could be isolated by means of neither fractional distillation, except a foremer, nor column chromatograph. The infrared spectra and retention times of gas chromatograph of both of a foremer and methyl acetoacetate were identical, but this process has not been studied yet. It is understood that the other products were contained two kinds of substances by means of gas chromatograph with P. E. G. column. One of them (Product A) will be  $\beta$ -propiolactone- $\beta$ -spiro-cyclopropane, because the yield of product A increases with lower reactivity of alcohol, as well as the double bond in azlactone occurs. Upon another reason, it will be suggested that  $\beta$ -lactone and cyclopropane may be existed in the infrared spectrum of product A (Absorption peaks were displayed at 1805 and 1005 cm<sup>-1</sup>). Another product is too small a quantity to investigate its structure.

#### 2.4 The Reaction of $\gamma$ -Butyrolactone with Alcohols

It has been studied by Reppe *et al.* that reaction of (3) with alcohols gives  $\gamma$ -alcohoxy butyric acid with base catalysis. However, the reaction of (3) with alcohols, when catalyzed by diazomethane, gave alkyl  $\gamma$ -oxybutyrate (Shown in

TABLE IV  
REACTIONS OF  $\gamma$ -BUTYROLACTONE WITH ALCOHOLS

Alcohol		$\gamma$ -B. L. (g)	D. M. (g)	Temp. (°C)	Time (hr)	HOCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> COOR	
R	(g)					b. p. (°C/mm)	yield, g(%)
		8.6	2.6	30	17		0
CH <sub>3</sub>	32	8.6	2.6	30	17		4.6 (39)
CH <sub>3</sub>	32	8.6	5.6	30	17	51.5/0.8	4.5 (38)
CH <sub>3</sub>	32	8.6	1.3	27	51		5.3 (45)
C <sub>2</sub> H <sub>5</sub>	36.8	8.6	2.6	30	17	48/0.4	4.5 (34)
<i>n</i> -C <sub>3</sub> H <sub>7</sub>	60	8.6	2.6	30	17	56/0.2	4.9 (35)
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	74	8.6	2.6	30	17	66/0.1	5.6 (35)

Table V).

The reaction products displayed major absorption peaks in the infrared spectra at 3400, 1735, 1165 and 1055  $\text{cm}^{-1}$ , and their elemental analyses were identified with alkyl  $\gamma$ -oxybutyrate.

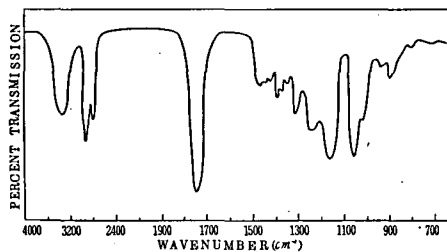
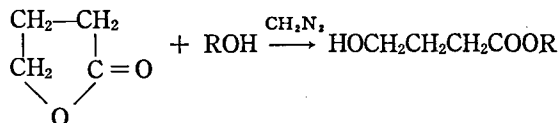


Fig. 2 Infrared spectrum of *n*-propyl  $\gamma$ -oxybutyrate.

On the other hand, alkyl  $\alpha$ - and  $\beta$ -oxybutyrate have been already prepatated, but alkyl  $\gamma$ -oxybutyrate have not been known so much. (3) is easily hydrolyzed in alkali solution, gives alkali solt of  $\gamma$ -butyric acid, and appeared slowly from  $\gamma$ -oxybutyric acid at room temperature or quickly in acid <sup>(2)</sup>.

The procedure of Reppe *et al.* has been treated at high temperature with base catalysts, therefore, (3) will be acted rather as type of oxy acid than as type of lactone. Then these procedure do not give these esters, but give  $\gamma$ -alchooxy butyric acid through the solt of  $\gamma$ -alchooxy butyric acid. Under reaction condition at low temperature, (3) would be reacted as well as the other lactones (Scheme IV).

#### SCHEME IV



In closing, it may be concluded from the results of this investigation that the methylation of these lactones and the synthesis of alkyl  $\gamma$ -oxybutyrate are satisfactory.

In addition, these reactions are ester exchange reaction, then, aliphatic ester was used in place of lactone. For example, the reaction of ethyl acetate, *n*-propyl acetate, *n*-butyl acetate or *n*-butyl stearate with methanol are studied, but the expected products were scarcely obtained in each reaction.

### 3. Experimental Section

#### Materials

$\beta$ -Propiolactone, obtained commercially, dried ( $\text{MgSO}_4$ ), and purified by fractional distillation.

Diazomethane is obtained from nitrosomethyl urea. Diazomethane and nitrosomethyl urea are prepared by a method given in "Organic Syntheses" <sup>(3)</sup>.

Ketene dimer, offered by DAICEL Ltd., dried ( $\text{MgSO}_4$ ), and purified by

fractional distillation.

$\gamma$ -Butyrolactone, obtained commercially, dried ( $\text{MgSO}_4$ ), and purified by fractional distillation.

The alcohols, obtained commercially, special grade (WAKO Ltd.).

#### Reactions of Lactones with Alcohols used Diazomethane Catalysis

In a 500-cc. round-bottomed flask, which was fitted with a reflux condenser protected by a calcium chloride drying tube, were placed 200cc. of absolute ether, 0.1 mole of lactone and 0.8 mole of alcohol, when the mixture was cooled to  $-10^\circ\text{C}$ , 2.7 g. of diazomethane, which was dried by potassium hydroxide for 2 hr. and sodium for 1 hr., was added. The temperature of the mixture was raised, and the reaction mixture was maintained at approximately  $30^\circ\text{C}$  for 17 hr. After ether and diazomethane were removed, residues were distilled at reduced pressure. Yields and the other data are listed in Table II, III, IV and V.

#### Methyl $\beta$ -Oxypropionate (Methyl Hydracrylate)

The oily residues from above reaction of (1) with methanol was distilled through a short column. Methyl  $\beta$ -oxypropionate was collected at  $81^\circ\text{C}$  (20 mm), at 82% yield.

#### Methyl Acetoacetate

The oily residues from above reaction of (2) with methanol was distilled through a short column. Methyl acetoacetate was collected at  $62.5^\circ\text{C}$  (13 mm), at 59% yield.

#### Methyl $\gamma$ -Oxybutyrate

The oily and transparent residues from above reaction of (3) with methanol were distilled through a short column. Methyl  $\gamma$ -oxybutyrate was collected at  $51.5^\circ\text{C}$  (0.75 mm), at 39% yield.

TABLE V  
ALKYL  $\gamma$ -OXYBUTYRATE

Alkyl	$n_D^{25}$	Carbon(%)		Hydrogen(%)	
		Calcd.	Found	Calcd.	Found
Methyl	1.4254	50.85	51.08	8.47	8.49
Ethyl	1.4250	54.53	54.80	9.15	9.21
<i>n</i> -Propyl	1.4280	57.51	57.21	9.65	9.66
<i>n</i> -Butyl	1.4313	59.98	60.23	10.07	10.02

#### Reaction of Diazomethane with Ketene Dimer

A solution of (2) (8.4 g.) and diazomethane (5.6 g.) in dried ether (200cc.) was kept at  $27^\circ\text{C}$  for 17 hr. After evaporation of the ether and excess (2), the residues were distilled through a short column under reduced pressure. There were obtained methyl acetoacetate (2.1 g.) and the mixture (0.3 g.), which could not be isolated by distillation. The mixture was displayed two peaks in gas chromatograph with P.E.G. column. The rear peak (product A) is described above, and the yield of

product A was 0.2 g. (calculated by a ratio of peak area of gas chromatograph).

### Acknowledgment

The author is gratefully indebted to the late Dr. Nakabayashi for his kind directions.

Acknowledgment is due to Dr. Okamiya, Shinshu University for valuable discussion, Mr. Tanaka, Shinshu University for infrared spectral data, Mr. Hayatsu, of the same college, for his help with the experiments, and DAICEL Ltd., for supplying ketene dimer.

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