[Contribution from the Department of Chemistry, Canisius College]

DIOXOLANONES. I. SYNTHESIS OF ETHERS OF α-HYDROXY ACIDS

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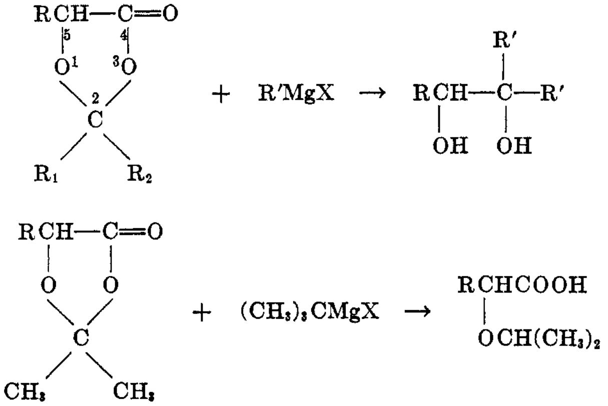
The reaction between non-bulky alkyl and aryl Grignard reagents and 1,3-dioxolan-4-ones, prepared from α-hydroxy acids and carbonyl compounds, generally yields 1,2-diols (1, 2). The acetone derivatives of α-hydroxy acids react with the bulky *tert*-butyl Grignard reagent to yield the α-isopropoxy acid



(2). It was of interest to determine whether the synthesis of the ethers of α-hydroxy acids, generally an involved procedure based on the Williamson reaction, can be more readily accomplished by the reaction of the *tert*-butyl Grignard reagent with the appropriate 1,3-dioxolan-4-one.

2,5-Dimethyl-2-ethyl- and 5-methyl-2,2-pentamethylene-1,3-dioxolan-4-one were prepared by the reaction of lactic acid and 2-butanone and cyclohexanone, respectively, in the presence of benzene and a catalytic amount of *p*-toluenesulfonic acid. 2-Isopropyl-5-methyl-1,3-dioxolan-4-one was prepared from lactic acid and methallyl alcohol by the method previously reported (3). Attempts to prepare the benzaldehyde and cinnamaldehyde derivatives of lactic acid were unsuccessful. de Bruyn and van Ekenstein have reported that attempts to prepare the benzaldehyde derivative were unsuccessful due to the reversibility of the reaction on distillation of the product (4).

The reaction between 2-isopropyl-5-methyl-1,3-dioxolan-4-one and *tert*-butylmagnesium chloride gave 2-isobutoxypropionic acid. The structure of the

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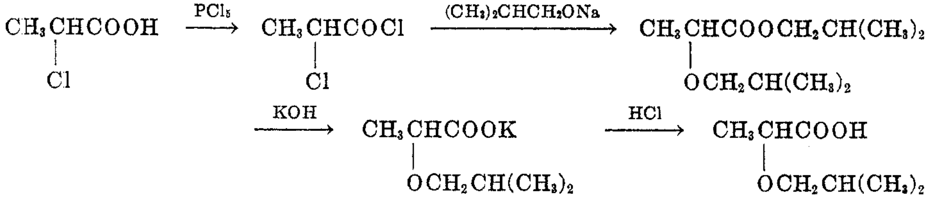
product was established by an unequivocal synthesis based on the following series of reactions:

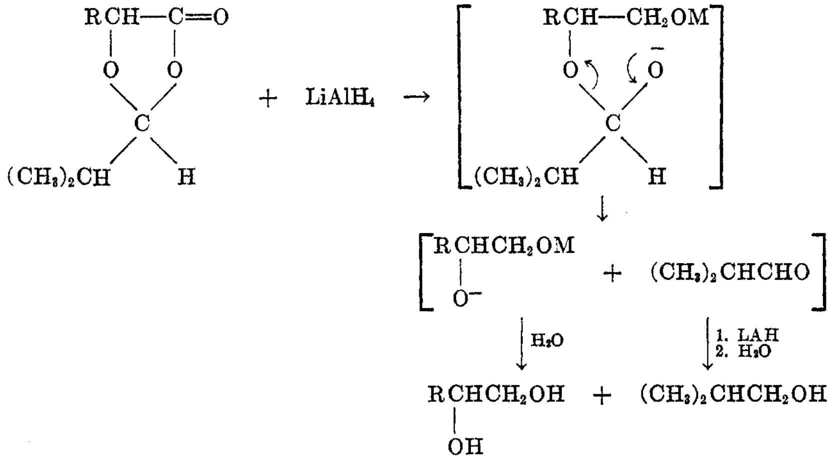


$$CH_3\underset{\underset{\displaystyle Cl}{|}}{C}HCOOH \xrightarrow{PCl_5} CH_3\underset{\underset{\displaystyle Cl}{|}}{C}HCOCl \xrightarrow{(CH_3)_2CHCH_2ONa} CH_3\underset{\underset{\displaystyle OCH_2CH(CH_3)_2}{|}}{C}HCOOCH_2CH(CH_3)_2$$

$$\xrightarrow{KOH} CH_3\underset{\underset{\displaystyle OCH_2CH(CH_3)_2}{|}}{C}HCOOK \xrightarrow{HCl} CH_3\underset{\underset{\displaystyle OCH_2CH(CH_3)_2}{|}}{C}HCOOH$$

2-(1-Methylpropoxy)propionic acid and 2-cyclohexyloxypropionic acid were similarly prepared from the dioxolanones.

The reaction between 2-isopropyl-5-methyl-1,3-dioxolan-4-one and lithium aluminum hydride gave isobutyl alcohol and propylene glycol, analogous to the behavior of the less-branched Grignard reagents. Although the $\text{—O}\overset{|}{\underset{|}{\text{C}}}\text{O—}$ grouping, as in acetals and dioxolanes, is generally resistant to attack by the complex metal hydride it has been shown that the presence of a contiguous reducible group results in the cleavage of the $\text{—O}\overset{|}{\underset{|}{\text{C}}}\text{O—}$ grouping (5).

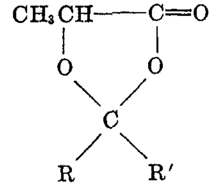


EXPERIMENTAL

2,5-Dimethyl-2-ethyl-1,3-dioxolan-4-one. In a 3-necked, 500-ml. flask equipped with a mechanical stirrer, thermometer, Dean-Stark tube, and reflux condenser, a mixture of 108 g. (1 mole) of 85% lactic acid, 110 g. (1.5 moles) of 2-butanone, 3 g. of *p*-toluenesulfonic acid monohydrate, and 100 ml. of benzene was refluxed for 3.25 hours at 80–90°. At the end of this time, the theoretical amount of water had been collected and 10 g. of anhydrous sodium acetate was added to the reaction mixture. After filtration and removal of the benzene and unreacted 2-butanone by distillation *in vacuo*, 40 g. (27.9% yield) of crude product was collected at b.p. 48–53° (5 mm.). Redistillation gave 23 g. of product, b.p. 50–51° (4 mm.).

TABLE I

1,3-DIOXOLAN-4-ONES



R	R′	Yield, %	b.p.,		d_4 (°C.)	n_D (°C.)	MRD		C		H	
			°C.	mm.			Calc'd	Found	Calc'd	Found	Calc'd	Found
i-C_3H_7	H	72	70–72[a]	13	1.0145 (25.4)[a]	1.4174 (25)[a]	35.62	35.73	58.31	58.14	8.39	8.23
C_2H_5	CH_3	28	50–51	4	1.0140 (24)	1.4167 (23.5)	35.62	35.70	58.31	58.16	8.39	8.52
C_5H_{10}[b]		78	84–86	2	1.0869 (22)	1.4565 (25)	42.66	42.72	63.51	63.79	8.32	8.06

[a] Reported (3) b.p. 71.0–71.3° (14 mm.), $d_4^{24.8}$ 1.0168, $n_D^{24.8}$ 1.4198. [b] Pentamethylene.

TABLE II

ETHER ACIDS AND p-BROMOPHENACYL ESTERS[a]

$CH_3\underset{OR}{\underset{\mid}{C}H}COOH$ R	Yield, %	b.p. or m.p.		d_4 (°C.)	n_D (°C.)	MR_D		Neutral Equivalent		C		H	
		°C.	mm.			Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
i-C_4H_9	70	97–99	5	0.9673	1.4164	37.71	37.98	146.2	144.6	57.50	57.39	9.65	9.49
Ester		54–55		(24.4)	(25)					23.28[b]	23.68[b]		
sec-C_4H_9	70	87–88.5	4.5	0.9795	1.4199	37.71	37.77	146.2	146.9	57.50	57.79	9.65	9.40
Ester[c]				(24)	(24)								
C_6H_{11}[d]	63	117–119[e]	1.5	1.0493	1.4589	44.74	44.97	172.2	176.0	62.77	63.05	9.39	9.15
Ester		68–69		(22)[e]	(25)[e]					21.64[b]	22.02[b]		

[a] The p-bromophenacyl esters were prepared from p-bromophenacyl bromide according to the procedure in Shriner and Fuson, *Identification of Organic Compounds*, 2nd Edition, John Wiley and Sons, New York, N. Y., 1940, p. 132. [b] Bromine analysis. [c] The product had a crude melting point of 43–110°. Several attempts to purify the material gave uncrystallizable oils. [d] Cyclohexyl. [e] Reported (6) b.p. 145° (12 mm.), d^{25} 1.060, n_D^{25} 1.4615.

5-Methyl-2,2-pentamethylene-1,3-dioxolan-4-one. In a similar manner, the reaction of 212 g. (2 moles) of 85% lactic acid, 295 g. (3 moles) of cyclohexanone, 5 g. of p-toluenesulfonic acid monohydrate, and 270 ml. of benzene, after 3.5 hours refluxing gave 265 g. (78% yield) of a colorless liquid, b.p. 85–89° (2 mm.). Redistillation gave 192 g. of product, b.p. 84–86° (2 mm.).

Attempted synthesis of 2-phenyl-5-methyl-1,3-dioxolan-4-one. In a similar manner, 318 g. (3 moles) of 85% lactic acid, 477 g. (4.5 moles) of benzaldehyde, 8 g. of p-toluenesulfonic acid monohydrate, and 400 ml. of benzene were refluxed for 8.5 hours to yield 92 g. of water. However, after neutralization with 27 g. of anhydrous sodium acetate, vacuum-distillation gave 385 g. of benzaldehyde, b.p. 65–66° (14 mm.).

Attempted synthesis of 5-methyl-2-styryl-1,3-dioxolan-4-one. In a similar manner, 159 g.

(1.5 moles) of 85% lactic acid, 300 g. (2.25 moles) of cinnamaldehyde, 4 g. of *p*-toluenesulfonic acid monohydrate, and 250 ml. of benzene, after refluxing 9 hours gave 47 g. of water and 295 g. of cinnamaldehyde.

2-Isopropyl-5-methyl-1,3-dioxolan-4-one was prepared according to the procedure of Gaylord (3) from methallyl alcohol and lactic acid.

2-Isobutoxypropionic acid. A solution of 48 g. (0.33 mole) of 2-isopropyl-5-methyl-1,3-dioxolan-4-one in 170 ml. of ether was added over a period of 0.75 hour to the *tert*-butyl Grignard reagent prepared from 24.4 g. (1 mole) of magnesium turnings and 91 g. of *tert*-butyl chloride. After refluxing for an additional one-half hour the reaction mixture was decomposed with 340 ml. of concentrated hydrochloric acid and 1700 g. of ice. Distillation of the dried ether layer and extracts gave 34 g. (70% yield) of crude material, b.p. 97–99° (5 mm.). Redistillation gave 25 g. of product, b.p. 89° (3 mm.).

The *p-bromophenacyl ester* of 2-isobutoxypropionic acid, prepared in the usual manner and recrystallized from aqueous ethanol, had m.p. 54–55° which was not depressed by admixture with the corresponding derivative of the authentic acid prepared by an unequivocal method.

2-Chloropropionyl chloride was prepared from 375 g. (1.8 moles) of phosphorus pentachloride and 136 g. (1.25 moles) of 2-chloropropionic acid to yield 237.5 g. of product, b.p. 107–109°, contaminated with phosphorus oxychloride [reported (7) b.p. 109–110° (744 mm.)].

2-Isobutoxypropionic acid. 2-Chloropropionyl chloride, 64 g., was added over a period of 1.5 hours to a solution of sodium isobutoxide prepared from 410 g. (5.5 moles) of isobutyl alcohol and 35 g. (1.5 moles) of metallic sodium. The mixture was refluxed for five hours, a solution of 42 g. (0.75 mole) of potassium hydroxide in 42 g. of water was added, and refluxing was continued for 4.5 hours. The isobutyl alcohol was steam-distilled, 70 ml. of concentrated hydrochloric acid was added, and refluxing was continued for an additional hour. The reaction mixture was cooled, the aqueous layer was extracted with ether, and the combined organic and ether layers were dried over calcium chloride. Distillation gave 18 g. (24.5% yield based on impure acid chloride) of product, b.p. 95–96° (5 mm.), n_D^{25} 1.4165, d_4^{26} 0.9644, MR_D: Calc'd, 37.71; Found, 38.04.

The *p-bromophenacyl ester* of 2-isobutoxypropionic acid had m.p. 53.5–55°.

2-(1-Methylpropoxy)propionic acid was prepared as above in 70% yield from the *tert*-butyl Grignard reagent and 48 g. (0.33 mole) of 2,5-dimethyl-2-ethyl-1,3-dioxolan-4-one.

2-Cyclohexyloxypropionic acid was prepared as above from the *tert*-butyl Grignard reagent and 57.5 g. (0.33 mole) of 5-methyl-2,2-pentamethylene-1,3-dioxolan-4-one. The crude product, 35 g. (59% yield) had b.p. 116–118° (2 mm.). On redistillation the product had b.p. 117–119° (1.5 mm.). A duplicate run gave a 63% yield of product.

Reduction with lithium aluminum hydride. The hydride (19 g., 0.5 mole) was refluxed for two hours in 400 ml. of diethyl ether. A total of 72 g. (0.5 mole) of 2-isopropyl-5-methyl-1,3-dioxolan-4-one in 400 ml. of ether was added slowly over four hours with agitation while maintaining the temperature below 5°. After the addition was complete the reaction mixture was stirred for an additional hour and allowed to stand overnight before hydrolysis with 9.5 g. of water, 9.5 g. of 10% sodium hydroxide, and 28.5 g. of 10% sodium hydroxide. After filtration the cake was extracted with ether in a Soxhlet extractor and the ether was combined with the original filtrate. The combined ether extracts were dried over magnesium sulfate and distilled twice to give 19.5 g. (53% yield) of isobutyl alcohol and 15 g. (40% yield) of propylene glycol, b.p. 90–92° (17 mm.).

The *phenylurethan* of isobutyl alcohol had m.p. 84–85° and showed no depression on a mixture melting point with authentic material, m.p. 85.5°.

The *trityl ether* of propylene glycol had m.p. 163.5° which was not depressed when mixed with the corresponding derivative of authentic propylene glycol, m.p. 164–164.5°. Although the reported melting point is 176.5° (8) the analysis of the lower-melting material was satisfactory.

Anal. Calc'd for $C_{41}H_{36}O_2$: C, 87.86; H, 6.43.
Found: C, 87.69; H, 6.32.

Acknowledgment. We wish to acknowledge the assistance of John A. Snyder who carried out the lithium aluminum hydride reduction.

SUMMARY

Dioxolanones have been prepared from lactic acid and an aliphatic aldehyde, an aliphatic ketone, and an alicyclic ketone. The reaction between a dioxolanone and the *tert*-butyl Grignard reagent yields the ether of an α-hydroxy acid and appears to be a general method for the synthesis of such ethers. The reaction between a dioxolanone and lithium aluminum hydride results in cleavage to yield the glycol derived from the hydroxy acid and the alcohol derived from the carbonyl component.

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