

Preparation of 1,3-Propanediol and Its Methyl Derivatives by Grignard Reactions or by LiAlH_4 Reduction

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This paper describes the preparation of 12 methyl-substituted 1,3-propanediols from methyl derivatives of ethyl β -hydroxypropionate. The syntheses of 2,4-pentanediol and its 3-methyl and 3,3-dimethyl derivatives by hydrogenating 2,4-pentanedione or its 3-methyl and 3,3-dimethyl derivatives are also discussed.

Three general methods have been used to prepare 1,3-propanediol and its methyl derivatives. The first starts from an aldol, the second from a methylated 1,3-dioxane and the third from ethyl β -hydroxypropionate or one of its methyl derivatives.

1. Aldol as initial reactant. The condensation of two keto compounds forms the initial step of this procedure. The second step involves reduction or Grignard synthesis. Because the yields of aldols are usually relatively low, aldolization is the limiting stage in this procedure.

When two aldehydes are condensed in the presence of sodium or magnesium amalgam, the reduction may take place concurrently¹ and the product is an 1,3-alkanediol. 2,2-Dimethyl-1,3-propanediol is commonly prepared by the Cannizzaro reaction.²⁻⁵

The aldol condensation is carried out in very mild conditions, usually at room temperature. The reaction is catalyzed by, for instance, potassium hydroxide, barium hydroxide, potassium carbonate, sodium acetate, and salts of organic bases. More recently, anion exchange resins have been used as catalysts.⁶⁻¹⁰

The reactivities of carbonyl compounds decrease in the order $\text{CH}_2\text{O} > n$ -aldehydes $> \alpha$ -branched aldehydes $>$ ketones. Consequently, when an aldehyde is condensed with a ketone, the former acts as a carbonyl compound and the latter as a methylene compound. The yield of ketol depends on the mole ratio of the initial reactants and on the concentration of the catalyst.¹¹⁻¹³

Reduction of aldols. Aldols are usually hydrogenated in the presence of Raney nickel or copper chromite. The latter is used in fairly mild conditions, 125–150°C and 100 atm. hydrogen pressure, and the yields are high. The

hydrogenation catalyzed by Raney nickel is more likely to lead to side-reactions,¹⁴ although Dubois¹² prepared some 1,3-alkanediols in good yield by hydrogenating aldols in ethanol at atmospheric pressure using this catalyst. In some cases also LiAlH_4 has been used as the reducing agent.^{15,16}

Grignard reactions of aldols. Several side-reactions, such as addition, reduction, and enolization, may occur in these Grignard reactions. Therefore the yields are generally poorer than those of the above reaction.

Table 1. Methyl-substituted 1,3-propanediols prepared by the reduction of aldols.

I is formaldehyde, II isobutyraldehyde, III methyl ethyl ketone, IV acetaldehyde, V acetone, VI 3-methylbutanone-2, VII propionaldehyde, VIII 1,3-propanediol, IX 2-methyl-1,3-propanediol, X 2,2-dimethyl-1,3-propanediol, XI 1,3-butanediol, XII 2-methyl-1,3-butanediol, XIII 3-methyl-1,3-butanediol, XIV 2,2-dimethyl-1,3-butanediol, XV 2,3-dimethyl-1,3-butanediol, XVI 2,2,3-trimethyl-1,3-butanediol, XVII 2,4-pentane-diol, XVIII 2-methyl-2,4-pentane-diol, XIX 3-methyl-2,4-pentane-diol, XX 2,3-dimethyl-2,4-pentane-diol, XXI 2,4-dimethyl-2,4-pentane-diol, XXII 3,3-dimethyl-2,4-pentane-diol, XXIII 2,3,3-trimethyl-2,4-pentane-diol, XXIV 2,3,4-trimethyl-2,4-pentane-diol, XXV 2,3,3,4-tetramethyl-2,4-pentane-diol.

Product	Yield from aldol %	Aldol condensa- tion or aldol	Yield %	Total yield of the diol	Ref.
X	50	I + II	—	50 ^a	4
X	64	I + II	—	64 ^a	5
XI	87	Acetaldol	—	—	17
XI	39 ^b	Acetaldol	—	—	15
XII	81	I + III	15	12	18
XII	92	I + III	19	17	12
XIV	—	IV + II	—	13	19
XVII	70	IV + V	84	59	12
XVIII	82	Diacetonealcohol	—	—	12
XVIII	78	Diacetonealcohol	—	—	17
XVIII	93	Diacetonealcohol	—	—	20
XIX	80	IV + III	—	—	12
XIX	60	IV + III	37	22	21
XIX	—	IV + III	—	33	22
XIX	66	IV + III	85	56	17
XXII	25 ^b	IV + VI	40	10	16

^a Cannizzaro reaction. ^b Reduction with LiAlH_4 .

Table 2. Methyl-substituted 1,3-propanediols prepared from aldols by the Grignard reaction.

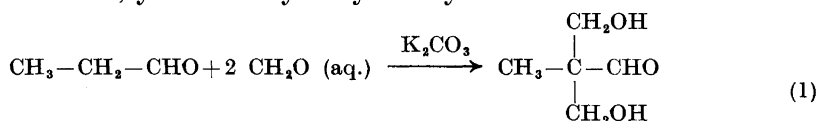
Product	Yield from aldol %	Aldol condensa- tion or aldol	Yield %	Total yield of the diol	Ref.
XIII	46	I + V	32	15	23
XV	42	I + III	38	16	24
XVII	high	Acetaldol	—	—	25
XVII	70	Acetaldol	—	—	15
XIX	50	IV + VII	—	—	26
XXI	70	Diacetonealcohol	—	—	27

Table 3. 1,3-Propanediol and its methyl derivatives which may be prepared by reduction (R) or Grignard reaction (G) from aldols.

1,3-Alkanediol	Method	Aldol condensation	Yield %	Ref.
VIII	R	I + IV	?	28
IX	R	I + VII	Nil	2, 3, 29, 30
XVI	G	I + VI	> 32 ^a	20
XX	G	IV + III	37	21
XXIII	G	III + VI	40	16

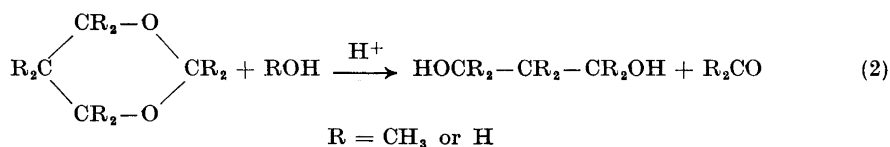
^a Estimated.

The preparation of eleven methyl-substituted 1,3-propanediols from aldols has been reported earlier. Moreover, other aldol condensations have been studied.^{2,3,16,20,21,28-30} The second of these condensation reactions, which are presented in Table 3, yields a dihydroxy aldehyde:



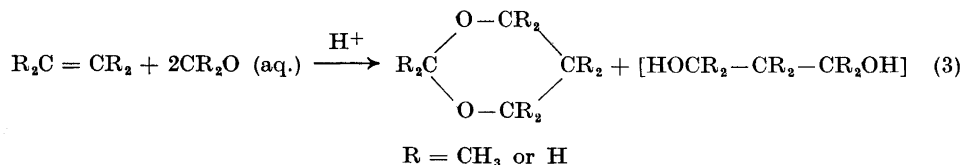
Consequently, starting from aldols it is possible to prepare, in addition to 1,3-propanediol, fourteen of its methyl derivatives.

2. *1,3-Dioxane as initial reactant.* The hydrolysis of 1,3-dioxanes is reversible and is carried out in acidic media. Sulfuric acid in 2 % concentration has been used to catalyze both the hydrolysis and the alcoholysis.³¹



The yield increases if the formed aldehyde or ketone is removed from the reaction mixture. 1,3-Dioxanes derived from formaldehyde are usually decomposed by methanolysis, since the formed dimethoxymethane boils at 42°C.³²⁻³⁴ The use of less volatile alcohols may lead to the cleavage of water from the diols.^{35,36}

1,3-Dioxanes have been prepared by the Prins reaction:^{31,37,38}



This reaction yields simultaneously a 1,3-dioxane (main product) and the corresponding 1,3-alkanediol; also an unsaturated alcohol may be formed.

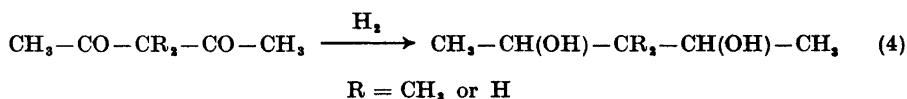
Because the above reaction does not seem to succeed with acetone as reactant, this procedure may lead, in addition to 1,3-propanediol, to ten of its methyl derivatives (*cf.* Ref. 31). The required alkenes are listed in Table 4.

Table 4. Ethene and its methyl derivatives which can be used in the preparation of 1,3-dioxane and its methyl derivatives.

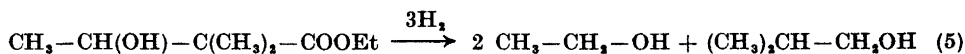
Compound		b.p. °C/760 mm Hg
Ethene	$\text{CH}_2=\text{CH}_2$	-105
Propene	$\text{CH}_3\text{CH}=\text{CH}_2$	-47.8
Methylpropene	$(\text{CH}_3)_2\text{C}=\text{CH}_2$	-6.6
<i>cis</i> -2-Butene	$\text{CH}_3\text{CH}=\text{CHCH}_3$	+3.7
<i>trans</i> -2-Butene	$\text{CH}_3\text{CH}=\text{CHCH}_3$	+0.9
2-Methyl-2-butene	$\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)_2$	+39
2,3-Dimethylbutene	$(\text{CH}_3)_2\text{C}=\text{C}(\text{CH}_3)_2$	+73

Only two of these compounds are liquids at room temperature and hence suitable for preparation of 1,3-alkanediols under usual conditions. Therefore this procedure is not very suitable for laboratory use, although large-scale preparations can be performed.

3. *Ethyl β -hydroxypropionate and its methyl derivatives as initial reactants.* Starting from β -hydroxy esters it is possible to prepare 1,3-propanediol and fourteen methyl-substituted 1,3-propanediols. The remaining three methyl derivatives may be synthesized by the reaction:



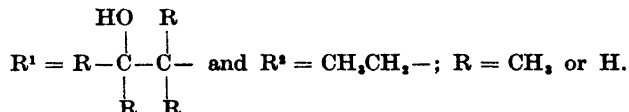
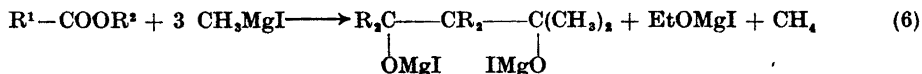
The reduction of β -hydroxy esters. β -Hydroxy esters can be reduced to the corresponding 1,3-alkanediols by catalytic hydrogenation in the presence of either copper chromite or Raney nickel and by lithium aluminium hydride. In the catalytic method only copper chromite gives reasonable yields,^{14,39} but a relatively high temperature (200–250°C) and pressure (200–300 atm.) are required. However, degradation of β -hydroxy esters may occur in these conditions.⁴⁰ Adkins and Folkers⁴¹ have reported that at 250°C and 220 atm. the reduction of ethyl α,α -dimethyl- β -hydroxybutyrate leads to isobutanol in a yield of 98 % of theory:



Adkins⁴⁰ found that this reduction succeeded at 80–150°C when the amount of catalyst was equal to that of the ester.

The reduction of β -hydroxy esters is now mostly carried out with LiAlH_4 . The yields are usually fairly good, the reaction is rapid and only simple equipment is required.⁴²

Grignard reactions of β -hydroxy esters. β -Hydroxy esters react with methylmagnesium iodide as follows:



When either R^1 and R^2 or both are bulky, their steric effect may lead to Claisen condensation and to cleavage of the ester.⁴³ Hydrolysis of the complex formed in reaction (6) leads to an 1,3-alkanediol.

The reduction of 2,4-pentanedione and its methyl derivatives. This reduction is usually carried out by catalytic hydrogenation in the presence of Raney nickel or copper chromite in the temperature range 100–150°C and at a pressure of 100 atm. Ethanol has been found to be a suitable solvent.^{14,44} When the temperature rises above 150°C, alcoholysis of the diketone may occur.¹⁴



If the temperature rises above 200°C, the second hydroxyl group of the formed diol is displaced by a hydrogen atom. For instance, Burdick and Adkins⁴⁵ reported that the product of the reduction of β -hydroxypropionate contained 56 % 2-butanol and 32 % 1-butanol.

Pohoryles *et al.*¹⁵ reported that the reduction of 1,3-diketones by LiAlH_4 did not succeed. They analyzed the product of the hydrogenation of 2,4-pentanedione and found it to have the following composition: 2-Hydroxypentene-3 70.5 %, 2,4-pentanediol 2.5 %, 2,4-pentanedione 19.0 %.

EXPERIMENTAL

Grignard reaction. Methylmagnesium iodide (0.5–2.4 mole) was prepared in the usual manner in a three-necked bottle equipped with a mechanical stirrer, a funnel, and a reflux condenser. The condenser was fitted with a calcium chloride tube. β -Hydroxy ester (0.15–0.68 mole) in an equal volume of anhydrous ether was added through the funnel during 2 h, after which the mixture was refluxed and stirred for 1 h. The cooled reaction mixture was poured into a mixture of ice and saturated ammonium chloride solution. The formed precipitate was dissolved by adding more ammonium chloride solution. The ether layer was separated and the aqueous layer extracted three to five times with 150-ml portions of ether. The ether solutions were combined and dried with anhydrous sodium sulfate. The ether was removed by distillation and residual liquid was fractionated in a Vigreux column at reduced pressure.

Reduction. 0.20–0.50 mole of LiAlH_4 was dispersed in 200 ml of anhydrous ether. The mixture was cooled to 0°C in a cold bath (ice-NaCl), after which 0.15–0.40 mole of

a β -hydroxy ester in anhydrous ether (1:1, v/v) was added during 1 h through a funnel into the mechanically stirred solution. The mixture was refluxed for 1 h. The excess LiAlH_4 was decomposed by adding carefully 100 ml of water through the funnel into the stirred mixture in the ice bath. The formed white precipitate was separated from the ether layer and decomposed with ice-cold 20 % sulfuric acid. The resulting aqueous solution was extracted three times with 100 ml of ether. The combined ether layers

Table 5. Data on the preparation of methyl-substituted 1,3-propanediols from methyl derivatives of ethyl β -hydroxypropionate by the Grignard reaction.

XXVI is ethyl β -hydroxypropionate, XXVII ethyl β -hydroxybutyrate, XXVIII ethyl β -methyl- β -hydroxybutyrate, XXIX ethyl α -methyl- β -hydroxypropionate, XXX ethyl α -methyl- β -hydroxybutyrate, XXXI ethyl α,β -dimethyl- β -hydroxybutyrate, XXXII ethyl α,α -dimethyl- β -hydroxypropionate, XXXIII ethyl α,α -dimethyl- β -hydroxybutyrate, and XXXIV ethyl α,α,β -trimethyl- β -hydroxybutyrate.

1,3-Diol	Ester,	moles	CH_3I , moles	Mg, moles	Yield moles	%
XXI	XXVIII	0.151	0.501	0.503	0.043	29
XV	XXIX	0.567	2.42	2.43	0.189	34 ^a
XX	XXX	0.678	2.22	2.20	0.406	60
XXIV	XXXI	0.500	1.60	1.65	0.302	60
XXIII	XXXIII	0.215	0.801	0.823	0.171	80
XXV	XXXIV	0.287	1.00	1.03	0.077	27

^a Impure; this diol is obtained in a high yield and very pure from XXX by reduction with LiAlH_4 .⁴⁹

were dried with anhydrous potassium carbonate and the ether was removed by distillation. The residual clear oil was fractionated in a Vigreux column at reduced pressure.

Experimental data are presented in Tables 5 and 6. Commercially available diols except 2,2-dimethyl-1,3-propanediol were not synthesized. The preparation of ethyl

Table 6. Data on the preparation of methyl-substituted 1,3-propanediols by reduction of methyl derivatives of ethyl β -hydroxypropionate.

1,3-Diol	Ester,	moles	LiAlH_4 , moles	Yield moles	%
XIII	XXVIII	0.150	0.201	0.048	32
IX	XXIX	0.317	0.40	0.047	15
IX (in Ref. 49)		0.5	0.7	—	54
XII	XXX	0.395	0.50	0.132	34
X	XXXII	0.187	0.340	0.088	47
XIV	XXXIII	0.241	0.550	0.061	25
XIV (in Ref. 49)		0.479	0.625	—	88
XVI	XXXIV	0.301	0.474	0.137	46
XV (in Ref. 49)	XXX	0.415	0.625	0.336	81

esters of β -hydroxypropionic acid and its methyl derivatives are described in another paper.⁴⁶

The methylation of 2,4-pentanedione. One mole of 2,4-pentanedione was added to a vigorously stirred mixture containing 2.2 moles of sodium methoxide and 800 ml of

anhydrous ether. The stirring was continued for 1 h, after which 2.2 moles of methyl iodide was added during 1 h and the resulting mixture was refluxed for about 48 h. The formed sodium iodide was removed by filtration and the ether was distilled off. The remaining liquid was fractionated through a Hempel column. The above procedure was repeated replacing 2,4-pentanedione by the product from the first run. After removing the formed sodium iodide, the ether was distilled off again. On fractionation in a Hempel column, the residue gave 77 g of a product (60 % of theory), which boiled at 170–171°C/761 mm Hg and had a refractive index n_D^{20} of 1.4367. Gas chromatographic analysis yielded only one peak.

The reduction of the methylated 2,4-pentanedione. The methylated 2,4-pentanedione was reduced both by catalytic hydrogenation and with LiAlH_4 . The former was carried out in ether solution at 100 atm. in the presence of Raney nickel. The heating was discontinued at 165°C, but the temperature continued to rise to 185°C. The reduction was complete when the bomb had cooled to room temperature (about 20 h). The reaction mixture was removed from the hydrogenation vessel and the solvent (Et_2O) was distilled off. The residue was fractionated at reduced pressure.

The reduction with LiAlH_4 was done as described above. The data in Table 7 show that the latter procedure gives a much better yield than the former. Obviously the temperature was too high in the catalytic hydrogenation and consequently,^{45,47} the following side-reaction may have occurred:

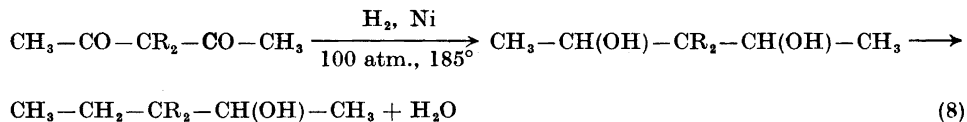


Table 7. Data on the reduction of the methylated 2,4-pentanedione.

Method	LiAlH_4 moles	Dione moles	P atm.	t °C	Yield, % of theory	B.p. °C/mm Hg	n_D^{20}	d_4^{20}
LiAlH_4	0.79	0.60	—	0	68	112–3/17	1.4443	0.9561
Raney Ni	—	1.09	100	165–85	16	108–14/17	1.4410	—

Identification of the product of the reduction of the methylated 2,4-pentanedione. The isomeric 1,3-dioxanes prepared from this product and those prepared earlier⁴⁸ from 3-methyl-2,4-pentanediol were compared by gas chromatographic analysis. The isomeric 1,3-dioxanes formed from each diol were found identical by comparing gas chromatograms of (1) the isomeric 1,3-dioxanes prepared from the product of the reduction of the methylated 2,4-pentanedione, (2) the isomeric 1,3-dioxanes prepared from 3-methyl-2,4-pentanediol, (3) a 1:1 (v/v) mixture of (1) and (2). As the retention times were equal in every case, the synthesized 1,3-diol consisted predominantly of 3-methyl-2,4-pentanediol. Thus only monomethylation of 2,4-pentanedione occurs when the above method is used.

The molecular refractivities calculated for 3-methyl- and 3,3-dimethyl-2,4-pentanedioles are 32.91 and 37.53 and those calculated from the experimental data (Table 7) 32.87 and 36.75, respectively. These values confirm that the product consisted predominantly of 3-methyl-2,4-pentanediol.

The gas chromatographic analyses were carried out on a Perkin-Elmer F 11 gas chromatograph. The column packing contained Apiezon L-grease (1 part) on Chromosorb P (9 parts). The temperature was 120°C and the gas flow pressures were nitrogen 0.2, oxygen 2.0 and hydrogen 1.0 kp/cm².

RESULTS AND DISCUSSION

1,3-Propanediol and fourteen of its methyl derivatives can be prepared both from aldols and from ethyl β -hydroxypropionate and its methyl derivatives, whereas the hydrolysis of 1,3-dioxanes is a less effective method for their preparation.

All of the prepared 1,3-alkanediols are listed in Table 8 together with their total yields, which can be compared with those obtained when they were prepared from aldols. The commercially available diols except 2,2-dimethyl-1,3-propanediol and 3-methyl-2,4-pentanediol were not synthesized in this work.

Table 8. Total yields of 1,3-propanediol and its methyl derivatives obtained by the aldol method and by the methods used in this work.

1,3-Diol	The aldol method		This work
	Total yield, %	Ref.	Total yield, %
VIII ^c	—	—	—
IX	— ^a	—	5 (20 ^b)
X ^c	11	4	23
XI ^c	—	—	—
XII	17	12	15
XIII	15	23	14
XIV	13	19	15 (58 ^b)
XV	16	24	13 (58 ^b)
XVI	20 ^d	24	34
XVII ^c	—	—	—
XVIII ^c	—	—	—
XIX	22—56	12, 17, 21, 22, 26	41 ^e
XX	19 ^d	21, 26	27
XXI	70 ^f	27	13
XXII	10	16	— ^g
XXIII	20 ^d	16, 26	48
XXIV	— ^a	—	43
XXV	— ^a	—	20

^a The corresponding aldols cannot be prepared. ^b From Ref. 49. ^c Commercially available products. ^d Estimated. ^e From 3-methyl-2,4-pentanediol. ^f From diacetonealcohol. ^g Not prepared in this work.

The data in Table 8 show that the total yields in this work were either nearly equal to or higher than those obtained using the aldol method. The total yields of both methods may obviously be improved by investigating the successive steps in detail. However, the method used in this study seems to be more promising than the aldol method, since the aldol condensation forms the critical stage in the latter. Moreover, the former method is fairly simple and is favored by the small number of initial reactants required.

Recently Launosalo and Pihlaja⁴⁹ have reported that the yields in the reduction of β -hydroxy esters with LiAlH_4 improve greatly if the ether extrac-

Table 9. Physical constants of the prepared methyl-substituted 1,3-propanediols compared with those presented earlier.

1,3-Diol	B.p. °C/mm Hg	d_4^{20}	n_D^{20}	M.p.	Method	References
XIII	103/13	0.9633	1.4463	—	R	This work
	104/14	—	1.4415	—	R	50
	95/7	0.9763	1.4420	—	H	51
	107—9/15	0.980	1.4430	—	H	52
	110—15/20	0.980	1.4420	—	H	33
	—	0.991	1.4459	—	A	33
IX	100/8	0.9955	1.4466	—	R	This work
	107—9/12	—	—	—	— ^a	53
	110—1/14.5	1.0297 ^b	—	—	— ^a	54
	90—3/4	—	1.4436	—	R1	55
	83—4/3	—	1.4430	—	R2	56
	213—4/760	1.0290	1.4445	—	—	57
	75—6/0.3	1.0273	1.4499 ^c	—	—	58
	118—20/18.5	—	1.4423	—	R1	49
XII	98—100/6	0.9866	1.4507	—	R	This work
	92/6	0.9919	1.4478	—	H	51
	114—5/16	0.9870	1.4464	—	H	59
	68/0.8	0.9915	1.448	—	H	33
	115—6/20	—	1.4461	—	AM	18
	102—103/14	—	—	—	AM	12
	111—2/17	—	—	—	R1	60
X	103—4/14	—	—	126—7	R	This work
	105—110/7	—	—	127—8	AM	53
	—	—	—	126—8	AM	4
	—	—	—	128	— ^d	5
	—	—	—	128—9	AM	5
XIV	106—8/8	0.9703	1.4490	—	R	This work
	121/20	—	1.4408	—	AM	19
	71—2/0.5	—	1.4475	—	R1	61
	125—7/25—6	—	1.4482	—	R	49
XV	109—112/12	0.9630	1.4531 ^e	—	G	This work
	95/12	0.9680	1.4460	—	G	62
	95—5.5/7	0.9980	1.4489	—	AM	24
	109—110/	—	—	—	—	—
	10—11	0.9644	1.4473	—	R	49
XX	108—112/7	0.9346	1.4478	—	G	This work
XXI	89/14	0.9104	1.4339	—	G	This work
	64/2	—	1.4378	—	AM	63
	89/5	0.9164	1.4327	—	AM	27
	113/35	0.9206	1.4375	—	AM	64
	100/17	—	1.4327	—	G1	65
XVI	subl.	—	—	127—9	R	This work

Table 9. Continued.

XXIII	subl.	—	—	87	G	This work
XXIV	94/16	0.9097	1.4376	—	G	This work
XXV	94/3	—	—	65—7	G	This work
	113/11	—	—	75—6	G1	66
	125/20	—	—	74	G1	21
	118/11	—	—	76.5	G1	67

R, by the reduction of β -hydroxy esters; R1, other reductions with LiAlH_4 ; R2, by hydrogenation with Raney Ni; G by the Grignard reaction of β -hydroxy esters; G1, other Grignard reactions; H, by the hydrolysis of the corresponding 1,3-dioxane; A, by the alcoholysis of the corresponding 1,3-dioxane; AM, by the aldol method.

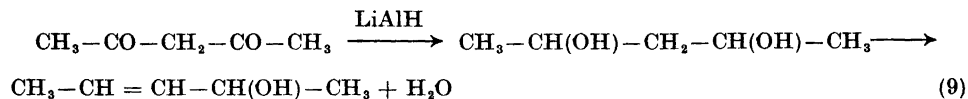
^a From the diacetate of the diol; ^b at 0°C; ^c at 4°C; ^d from pentaerythritol; ^e impure.

tion is carried out continuously in a liquid-liquid extraction apparatus (Table 8).

The physical constants of the prepared diols are presented in Table 9 together with previously reported values.

Pohoryles *et al.*¹⁵ reported that LiAlH_4 cannot be used to reduce 2,4-pentanedione. They obtained 2,4-pentanediol in a yield of only 2.5 % of theory when using tetrahydrofuran as solvent. Krynitsky *et al.*⁶⁸ proposed that LiAlH_4 reacts with the keto form of an enolizable compound. The reduction of 3-methyl-2,4-pentanedione with LiAlH_4 in this work yielded the corresponding diol in a yield of 68 % of theory and no side-products were formed. Conant and Thompson⁶⁹ observed that the degree of enolization of pure 2,4-pentanedione is 76–80 % and that of 3-methyl-2,4-pentanedione 30–31 %.

Consequently, it may be possible to reduce 2,4-pentanedione with LiAlH_4 by increasing the reaction time, since the reduction rate depends on the keto-enol equilibrium. The poor yield in the work of Pohoryles *et al.*¹⁵ may have been due to the solvent, which boiled at 65–66°C, since they obtained an unsaturated compound in 70.5 % yield:



Thus the experimental data of Pohoryles *et al.*¹⁵ may be regarded as too meagre to validate their conclusion.

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