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The preparation and reactions of the chloromethyl ether of 2, 3-butanediol monoacetate

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THE PREPARATION AND REACTIONS OF THE CHLOROMETHYL ETHER OF 2,3-BUTANEDIOL MONOACETATE

by

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TABLE OF CONTENTS

I. INTRODUCTION

The agricultural industry is periodically confronted with large surpluses of grain crops which initiate a decline in prices and create a generally unstable market. Furthermore, the industry is plagued with enormous quantities of residues such as hulls, bran, straws and corn cobs. The major portions of these materials are either inefficiently utilized or entirely wasted.

One of the most promising means of utilizing grain surpluses as well as farm wastes is to convert them by fermentation to chemicals valuable to other industries. The most common of these processes is the yeast fermentation to produce ethyl alcohol. However, the production of one of the less exploited chemicals available by fermentation, 2,3-butanediol or 2,3-butylene glycol, has recently become of special interest as a possible outlet for farm surpluses and wastes. During the recent war, much effort was devoted to converting it to 1,3-butadiene, the basic raw material for the synthetic rubber industry. Although a successful process was developed for producing butadiene from 2,3-butanediol, this development came after the urgency of the situation had made it necessary to base the industrial production of butadiene on the petroleum and ethanol processes. The search for new commercial outlets for 2,3-butanediol continues.

One of the biggest problems which has prevented the

2,3-butanediol fermentation from becoming one of major industrial importance, has been the difficulty in recovering the relatively small amount of the water soluble, slightly volatile diol from the large amount of dissolved solids and suspended material in the dilute fermented beer. A very ingenious method to solve this problem is that proposed by Senkus (104). According to this process, the butanediol in the fermented mash is converted to its dioxolane (4,5-dimethyl-1,3-dioxolane) by the addition of formaldehyde and an acid catalyst. The dioxolane is then removed from the reaction mixture as an azeotrope with water which distills (78-84°) and condenses to a diphasic mixture. The phases are separated and the butanediol is then liberated from the dioxolane in the oil layer by alcoholysis. When the dioxolane is heated with methanol and an acid catalyst, methylal distils; excess methanol is removed, and the butanediol is then purified by distillation of the residue.

It may be noted that by this procedure, 4,5-dimethyl-1,3-dioxolane is more readily available than the butanediol. Thus, any potential commercial applications of the dioxolane would indirectly be an outlet for farm surpluses and wastes through the butylene glycol fermentation.

The literature relating to the chemical reactions of dioxolanes contains a recent reference (36) to the splitting of dioxolanes with acetyl chloride. A variety of products is

obtained by this reaction and their nature depends upon the conditions employed. Under proper conditions a chloromethyl ether of a glycol monoacetate is obtained.

$$R_1R_2C-O \quad R_3R_4 + AcCl \rightarrow R_1R_2C-CR_3R_4$$
$$\underset{CH_2}{\overset{O \quad O}{\diagdown}} \qquad \qquad OAc \quad OCH_2Cl$$
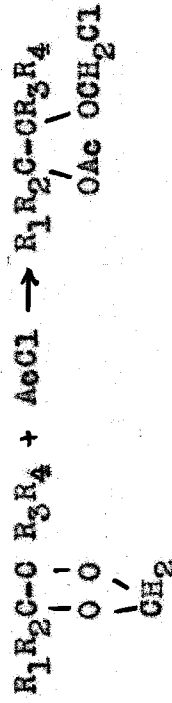
Chloromethyl ethers, because of the enhanced reactivity of the halogen atom adjacent to the negative oxygen atom, take part in many types of reactions.

It was the purpose of this investigation to apply the acetyl chloride cleavage of dioxolanes to 4,5-dimethyl-1,3-dioxolane and to prepare a few of the multitude of possible derivatives of the chloromethyl ether of butanediol monoacetate, a compound which should be expected as one of the products of the cleavage reaction. Through a consideration of their chemical and physical properties, one should be able to predict possible applications of these derivatives in the chemical industry.

II. MATERIALS AND METHODS

The 2,3-butanediol used in this investigation was gener-
ously furnished by the Northern Regional Research Laboratory,
Peoria, Ill. This material, which was a technical grade
product obtained from the Aerobacter aerogenes fermentation,
has been reported to contain approximately 90% meso-butane-
diol and approximately 10% dextrorotatory glycol as well as
traces of diacetyl, acetylmethylcarbinol and water. It was
purified by distillation in vacuo (5-7mm) through an 18-inch
jacketed Widmer column. Small fractions of the distillate
were removed periodically and the refractive index was deter-
mined. The optically active diol and volatile impurities
were removed in the first part of the distillation as was
indicated by the low refractive index. When these materials
had been removed the refractive index of the distillate
increased rather sharply and the material which distilled,
with a refractive index of 1.4360 - 1.4370 at 25°, was col-
lected for use in this study. When seeded with a few crystals
of pure meso-2,3-butanediol it crystallized and remained a
solid at room temperature. From a consideration of the
physical data in Table I and the work of Neish (80) who used
a similar distillation procedure to prove the purity of the
levorotatory butanediol produced in the Aerobacillus polymyxa
fermentation, the product used in this study may be assumed to
be meso-2,3-butanediol of high purity.

TABLE I

The Physical Properties of the 2,3-Butanediols

Compound	b.p. (742mm)	m.p. (°C)	n_D^{25}
meso-2,3-Butanediol	181.7 (133)	34.0 (133)	1.4366 (16)
dl-2,3-Butanediol	176.7 (133)	7.6 (133)	1.4308 (16)

Unless otherwise specified, all other chemicals employed were of reagent grade. Most of the organic chemicals employed were Eastman "White Label" and were used without further purification. Those of questionable purity were redistilled, and a fraction boiling over a three degree range was collected for use.

Refractive index: Refractive indices were determined with a Zeiss Abbe Refractometer. Measurements were made at 25°.

Density: Densities were determined by the conventional method with a pycknometer.

Molecular refraction: The molecular refractions were determined in the usual manner from observed measurements of refractive index and density and the molecular weight. The calculated values were obtained from the data for atomic and structural refractive constants (55).

Saponification equivalent: The conventional determination of saponification equivalent using hot alcoholic alkali (106) could not be employed when a majority of the compounds prepared were analyzed. Low results were obtained, apparently

because of the liberation of formaldehyde which yielded formic acid in the presence of hot alkali.

The following method is a slight modification of that of Kunz (51), and it was employed in the analysis of all esters prepared:

Approximately 0.5 g. of the ester to be analyzed was dissolved in 50 ml. of acetone in a 250 ml. Erlenmeyer flask. After cooling in an ice bath 100 ml. of 0.1N KOH was added slowly, with stirring. The stoppered flask was stored 16 hours in a refrigerator at approximately 0°. The excess alkali was then titrated with 0.250N HCl. A control analysis of the acetone was run simultaneously. The saponification equivalent was determined from the following equation:

Saponification equivalent =

$$\frac{\text{weight of sample} \quad x \quad 1000}{\left[\text{ml. HCl(blank)} - \text{ml. HCl(sample)}\right]\text{Normality HCl}}$$

Chlorine analysis: The following rapid method was devised for the determination of the active chlorine in the chloromethyl ethers:

Approximately 0.5 g. of the chloromethyl ether was added to 50 ml. of water at room temperature in a 250-ml. Erlenmeyer flask. A drop of phenolphthalein was added and 1N NaOH was introduced until the indicator became pink and remained so for several minutes. The solution was then treated with only sufficient 0.5N H_2SO_4 to decolorize the indicator. Five ml. of 2 per cent dextrin solution and 10 drops of dichlorofluorescein

indicator were added and the solution was titrated to the pink end-point with standard silver nitrate solution according to the method of Fajans (132) for the determination of soluble chloride.

The per cent chlorine is obtained as follows:

$$\% \ Cl = \frac{Vol. AgNO_3 \times Normality \ AgNO_3 \times .035456}{weight \ sample} \times 100$$

III. PREPARATION OF THE CHLOROMETHYL ETHER OF 2,3-BUTANEDIOL MONOACETATE BY THE REACTION OF 4,5-DIMETHYL-1,3-DIOXOLANE AND ACETYL CHLORIDE

A. Review of Literature

There are numerous references in the literature to the synthesis of 1,3-dioxolanes from glycols and aldehydes. By the classical method, the equimolar quantities of aldehyde and glycol were heated in the presence of an acid catalyst to allow the reaction to reach equilibrium. After neutralizing the catalyst the dioxolane was recovered by extraction of the reaction medium and distillation of the extract (91, 126, 17, 41, 22, 23). Backer (5) and more recently Neish and MacDonald (82) have prepared dioxolanes of 2,3-butanediol by this procedure.

Salmi and co-workers (95,98) improved this procedure by conducting the reaction in the presence of an inert solvent capable of forming an azeotrope with water. The water formed as a product of the reaction was removed continuously as a component of the azeotropic mixture. Excellent yields were obtained because the equilibrium reaction was forced to completion. In certain instances (97) the dioxolane which was produced formed a suitable azeotropic mixture with the water of reaction and the use of an entrainer was obviated. Senkus (104), as mentioned earlier, applied the latter method to the recovery of 2,3-butanediol from fermentation beers.

Until recent years the chemistry of the 1,3-dioxolanes

has been virtually unexplored. Leutner (60, 61) has compared the rates of hydrolysis of various substituted dioxolanes in acid solution. The pyrolysis of several dioxolanes was studied by Bilger and Hibbert (7) and this work has been pursued more recently relative to the dioxolanes derived from 2,3-butanediol (81). Legault and Lewis (57) related the rate of oxygen absorption by the ether linkages of dioxolanes to their structures. Sussman and Gresham (121) reported the acid catalyzed alcoholysis of 1,3-dioxolane. Products were alkoxymethoxyethanols, $ROCH_2OCH_2CH_2OH$. Similarly the reaction of dioxolane with acetals yielded 1,2-bis-(alkoxymethoxy)-ethane, $ROCH_2OCH_2CH_2OCH_2OR$ (37). A patent by Gresham (38) described the polymerization of 1,3-dioxolane in the presence of acids, boron triflouride or Friedel-Crafts catalysts. Polymers of the structure $(-OCH_2OCH_2CH_2-)_x$ were obtained. A series of patents assigned to E. I. DuPont de Nemours then followed which enlarged on this basic discovery. By conducting the polymerization in the presence of various chain interrupting agents, such as acids, acid anhydrides, amides, esters and alcohols (67, 68), their unsaturated derivatives (69), carbon monoxide (35), or unsaturated hydrocarbons (39), useful modified polymers were obtained. Senkus (103) reacted several 1,3-dioxolenes including 4,5-dimethyl dioxolane with a molar equivalent of acetic anhydride and obtained good yields of products of the type $RCOOCHRCHROCH_2OOCR$.

In the course of investigating the polymerization of 1,3-dioxolanes in the presence of chain interrupting agents, Gresham (36) found that dioxolanes and acyl halides react with the formation of simple to high molecular weight compounds depending on the conditions used. When equimolar quantities of reactants were mixed and heated several hours, a chloromethyl ether of a glycol monoacetate was reported in 75-80% yields. In the presence of H_2SO_4 and a six-fold excess of the dioxolane, the product was a high molecular weight viscous liquid. This is not only the sole report of cleavage of dioxolanes with acid halides but the only reported synthesis of a chloromethyl ether of a glycol monoester.

Basis for such a reaction, however, is found in the cleavage of ethers by acyl halides catalyzed by zinc chloride (18, 54, 77, 125, 124) or ferric chloride (130). The products are an alkyl halide and an ester. Thus

$$RCOCl + EtOEt \longrightarrow RCOOEt + EtCl$$

The effect of structure on the nature of the products derived from the splitting of mixed ethers has been studied extensively (71, 72, 73, 74).

With even more bearing on the reaction of acyl halides and dioxolanes, is the cleavage of acyclic acetals by acetyl chloride. Mylo (79) reported the use of copper bronze as a catalyst for the reaction and later Strauss (118, 120) and co-workers found thionyl chloride more ideal as the catalyst.

The following type of reaction was observed:

$$C_6H_5CH(OR)_2 + AcCl \xrightarrow{\text{cat.}} C_6H_5CHClOR + AcOR$$

Post (88) observed a similar reaction when simple aliphatic acetals were reacted with benzoyl chloride. No catalyst was required.

B. Experimental

1. Preparation of 4,5-dimethyl-1,3-dioxolane

The method used to prepare the 4,5-dimethyl dioxolane was based on the procedure of Senkus (104). Senkus' method was excellent for converting 2,3-butanediol to the dioxolane in high yields, but he was primarily interested in the crude oil containing not only the dioxolane, but also formaldehyde, methylal, and water. This mixture was obtained when the acidified butanediol beer was treated with formaldehyde, distilled and the resulting azeotrope condensed and separated. It contained only 84-87% of the dioxolane and was used without further purification in the recovery process described. The novelty of the procedure described below is the purification of the crude dioxolane and its recovery in good yields. The major problem was the separation of excess formaldehyde from the dioxolane.

Procedure: In a 2-liter round bottom flask 450g. of meso-2,3-butanediol was mixed with 250 ml. of 37% formaldehyde.

Ten milliliters of 1:1 sulfuric acid was dissolved in 250 ml.
more of formaldehyde and this solution was added gradually
to the reaction mixture. The contents of the flask, which
had warmed slightly on mixing, was heated to boiling and an
azeotrope, which was diphasic when condensed, distilled over
the range 80-84°. When most of this azeotrope had been dis-
tilled, as was indicated by a rise in vapor temperature, the
aqueous phase from the distillate was returned to the reaction
flask and the distillation continued to recover the dioxolane
which had dissolved. An additional amount of azeotrope was
then collected and separated into oil and aqueous phases.
The aqueous phase was again returned to the reaction flask
and the oil layers combined. The last portion of the dioxolane
was removed from the reaction mixture by collecting the dis-
tillate over the range 84-97° and saturating it with anhydrous
potassium carbonate. The salt layer was discarded and the
small amount of oil layer which was salted out was combined
with the other portions of oil.

The oil was treated with a slight excess (35 ml.) of
1:3 ammonium hydroxide to convert the formaldehyde to
hexamethylene tetramine. The mixture was then saturated with
anhydrous potassium carbonate and the oil layer was dried over
night with Drierite. The dried product was distilled through
a 12-in. jacketed Vigreux column. Approximately 50 g. of
distillate was collected between 42 and 68°. This was a

mixture of methylal and methanol which is obtained by acidi-
fying commercial formaldehyde. No definite boiling point was
observed over the range 68-98°, and the 40 g. fraction col-
lected was apparently a mixture of methanol and 4,5-dimethyl
dioxolane. The main product then distilled from 98-102°,
with the major portion boiling at 100-102°. The refractive
index at 25° was 1.4035. The yield in the several prepara-
tions by this procedure was 87-90%. Senkus gives the fol-
lowing physical constants for pure meso-4,5-dimethyl dioxolane:

B.p. 101.5° (750 mm.), n_D^{20} 1.4055.

2. Reaction of 4,5-dimethyl dioxolane and acetyl chloride

Reaction without catalyst. Three hundred and thirty-
five grams (10% excess) of freshly distilled Baker and
Adamson's acetyl chloride (49-52°) was placed in a one-liter
three neck flask. Three hundred and ninety-seven grams of
the 4,5-dimethyl dioxolane was added dropwise over a period
of $3\frac{1}{2}$ hours while refluxing on an oil bath at 65° and stir-
ring mechanically. The temperature was raised to 85° and the
reaction continued another hour. After standing overnight at
room temperature, the colorless reaction mixture was distilled.
Almost all the starting materials were recovered unchanged.

When small equimolar portions of Baker and Adamson
acetyl chloride (not redistilled) and 4,5-dimethyl dioxolane
were mixed and warmed, an exothermic reaction occurred.

Apparently there was a sufficient quantity of some impurity
in the acetyl chloride to catalyze the reaction. Possibili-
ties were the hydrogen chloride, which was removed upon redis-
tillation, and compounds of phosphorous. The latter element
is present to the extent of 0.15% in the acetyl chloride.

Reaction in the presence of hydrogen chloride. Three
hundred and sixty-six grams of freshly distilled acetyl
chloride was vigorously refluxed on an oil bath at 80°. Two
milliliters of concentrated HCl was added to 433 g. of 4,5-
dimethyl dioxolane and this solution was added over a period
of 2½ hours to the acetyl chloride. The mixture was then
refluxed 11 hours on a 110° oil bath. A test sample showed
that about 35% of the reaction mixture was still distillable
when heated to 110°. It was also noted that an addition of
more HCl did not produce an immediate increase in reaction
rate but that the addition of a small amount of sulfuric
acid initiated a rapid, spontaneous reaction. Accordingly,
50 ml. of the reaction mixture was treated with 2 ml. of con-
centrated sulfuric acid in a one-liter flask, and after the
spontaneous reaction had occurred the remainder of the reaction
mixture was added with stirring while the bath temperature was
maintained at 120°. The addition required 1½ hours and the
heating was continued an additional hour. Four and one-half
grams of anhydrous sodium acetate was added to neutralize the
catalyst and the reaction mixture was distilled through a

Vigreux column. The excess acetyl chloride was removed and
the residue distilled in vacuo. Approximately 100 g. of an
ester containing no halogen distilled at 44-47° (1.5 mm.).
It was insoluble in and heavier than water and the refractive
index at 25° was 1.4128. Although not identified, it may
have been meso-2,3-butanediol diacetate which has the con-
stants b.p. 66° (5.5 mm.), n_D^{24} 1.4130 (151). The main product
then distilled over the range 62-68° (3 mm.). This was the
chloromethyl ether of 2,3-butanediol monoacetate (2-chloro-
methoxy-3-acetoxybutane). Its identification and physical
properties are discussed in the next section. The yield was
461 g. or 61.5% of theory.

Reaction in the presence of phosphoric acid. Two
hundred and sixty-seven grams of 4,5-dimethyl dioxolane con-
taining 0.75 ml. of phosphoric acid was added over a period
of 1¼ hours to 226.5 g. (10% excess) of freshly distilled
acetyl chloride containing 0.5 ml. of phosphoric acid while
stirring and refluxing vigorously on an oil bath. At the end
of the addition, the internal reaction temperature had risen
from 49° to 78°. The bath temperature was gradually increased
to 120° and at the end of an hour the internal temperature
rose to 115°. Refluxing had ceased and the reaction mixture
was colored a light brown. The temperature was maintained
four hours longer and the catalyst was then neutralized by
the addition of 3 g. of anhydrous sodium acetate. The excess

acetyl chloride (15 g.) was removed by distillation and the pressure was lowered to 1.5 mm. Careful fractionation yielded 5.5 g. of a forerun (35-40°). The distillation temperature rose and the main product was collected over the range 56-59° (1.5 mm.). A yield of 420 g. or 89.0% of the theoretical yield of 2-chloromethoxy-3-acetoxy butane was obtained. It was a colorless liquid and possessed a mild pleasant odor. It hydrolyzed upon contact with moisture to yield pungent and sharp formaldehyde and hydrogen chloride. A sample purified by redistillation had the following properties:

b.p. 63.5-64.5° (2 mm.), n_D^{25} 1.4335, d_4^{25} 1.0975.

Analysis. Calculated for $C_7H_{13}O_3Cl$: Cl, 19.68%; MR_D 42.82. Found: Cl, 19.68%; MR_D 42.88.

The structure was confirmed by its ease of hydrolysis in the cold,

$$CH_3CH(OAc)CH(OCH_2Cl)CH_3 + H_2O \rightarrow CH_3CH(OAc)CHOHCH_3 + HCl + HCHO$$
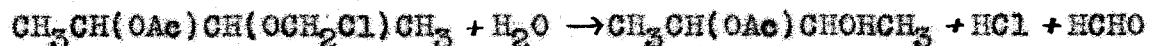
and by its synthesis from butanediol monoacetate, which is the reversal of the reaction above. The synthesis of 2-chloromethoxy-3-acetoxy-butane from 2,3-butanediol monoacetate was studied in some detail to investigate its feasibility when compared with the synthesis starting with 4,5-dimethyl dioxolane just described.

IV. THE PREPARATION OF THE CHLOROMETHYL ETHER OF 2,3-BUTANEDIOL MONOACETATE BY THE REACTION OF 2,3-BUTANEDIOL MONOACETATE, FORMALDEHYDE AND HYDROGEN CHLORIDE

A. Review of Literature

Winstein and Lucas (131) have reported the preparation of erythro-butanediol monoacetate in 80% yield by the sulfuric acid-catalyzed reaction of meso-butanediol and acetic anhydride at moderate temperature. The compound was also produced by the reaction of trans-2,3-epoxybutane and acetic acid at room temperature. The physical properties for the monoacetate reported are for the product of the latter reaction. Morrell, Geller and Lathrop (101) found that the reaction of butanediol and a stoichiometric amount of acetic anhydride gave the pure monoacetate in small preparations, while in larger preparations as much as 15% diacetate was formed which was difficult to separate. The synthesis of meso-2,3-butanediol diacetate from butanediol and acetic acid has been studied extensively in recent years (101, 78). The kinetics of this reaction have been investigated (105) and the reaction is reported to consist of two successive second order reactions, the first of which is the formation of the butanediol monoacetate from butylene glycol and acetic acid. The heat of activation for this step is calculated to be somewhat less than the succeeding conversion of the monoacetate to the diacetate.

The conversion of alcohols to their chloromethyl ethers

is a well-known reaction. The conventional method was first reported by Henry (40). The alcohol is treated with an excess of 40% formaldehyde solution, cooled to 0° and hydrogen chloride gas is bubbled in. When saturated with gas, the two layers which have formed are separated and the oil layer is dried and distilled. Since the reaction is a reversible one, several modifications have been made to increase the yield; all of these were designed to drive the reaction toward completion by removing water or reducing its solubility in the product. DeSonay (115) saturated the liquid with calcium chloride. Litterscheid (65) substituted formaldehyde polymers for aqueous formaldehyde and recently several patents (33, 2) described the reaction of paraformaldehyde, glycols and anhydrous hydrogen chloride in the presence of solvents, such as benzene, ether, methylene chloride or chloroform, immiscible with water but miscible with the product. Lichtenberger and Martin (62, 63) have also applied the reactions to glycols including 2,3-butanediol to produce bis(chloromethoxy) ethers. The reaction has been successfully extended to various substituted alcohols including phenyl alkanols (94), chlorohydrins (8, 27, 96, 64), and nitroalcohols (44). However, there has been no report of a glycol monoester being subjected to this reaction.

B. Experimental

1. Preparation of erythro-2,3-butanediol monoacetate

The method used to prepare the butanediol monoacetate
was the acid catalyzed esterification of butanediol with
acetic acid. If successful, this would be the most econom-
ical method of preparation. The procedure adopted was based
on the batch method of Schniepp, Dunning and Lathrop (101)
for the preparation of 2,3-butanediol diacetate, using an
entrainer to remove the water of esterification azeotropi-
cally. In consideration of the earlier mentioned observations
of Shlechter, Othmer and Marshak (105), the acetic acid was
added dropwise while the water was removed continuously in
order to direct the esterification toward production of the
monoester.

Procedure using n-butyl acetate as an entrainer: Three
moles (270 g.) of meso-2,3-butanediol was added to a one-liter
three-neck flask and a solution of 1.8 ml. of concentrated
sulfuric acid in 135 ml. of n-butyl acetate was added. The
flask was equipped with a high speed mechanical stirrer, a
dropping funnel and a modified Dean-Stark distilling trap
(4). The contents of the flask were heated to 75-80° and three
moles (180 g.) of glacial acetic acid was added dropwise over
a period of $2\frac{1}{2}$ hours. A vacuum (approx. 85 mm.) was main-
tained in the system so that the water-butyl acetate azeotrope

distilled rapidly into the trap. As the phases separated, the water collected in the trap and the butyl acetate was returned to the reaction. These conditions were maintained until the distillate was homogeneous. Forty-nine milliliters of aqueous phase was collected. Anhydrous sodium carbonate (5.2 g.) was added to the reaction mixture to neutralize the catalyst; the mixture was then distilled through a 12-in. Vigreux column. The n-butyl acetate and more azeotrope distilled at 42-47° (30 mm.). The pressure was reduced to 6 mm. and the distillation was conducted to dryness without fractionation. This distillate was then fractionated through the same column at atmospheric pressure. Several grams of yellow liquid distilled below 140°, which probably included diacetyl and some residual butyl acetate. About seven grams of distillate was collected with a boiling range of 140-176° and then the major products of the reaction distilled. They distilled over the range 176-185° and, although no definite fractions could be collected, the distillate was resolved into three portions. A total yield of 353.6 g. was obtained. The physical constants, yields and saponification equivalents of these fractions are given in Table IIA.

After consideration of this data and that for pure monoacetate, diacetate and diol which are presented in Table III, it was apparent that the last fraction contained considerable butanediol diacetate as an impurity. Although the saponifica-

tion equivalents of fractions 1 and 2 indicated the presence of approximately 5% of butanediol, the corresponding refractive index did not. It seemed possible that some butanediol monoacetate had been further esterified to the diacetate by ester exchange with the n-butyl acetate entrainer. For this reason, the esterification was repeated using benzene as an entrainer.

Procedure using benzene as an entrainer: Reaction of four moles of 2,3-butanediol and four moles of acetic acid in the presence of 2.4 ml. of sulfuric acid was conducted in accordance with the previous procedure; however, 180 ml. of benzene was substituted for the n-butyl acetate. Since benzene forms an azeotrope with acetic acid, it was necessary to add additional acetic acid to replace that which distilled into the decanter with the benzene and dissolved in the aqueous phase; the amount was determined by titration of the water layer with alkali. The product was worked up as before and once again it distilled over a broad range (178-188°). It was resolved into four fractions and their physical data and analyses are presented in Table IIB. The presence of both the unesterified glycol and of the diacetate is obvious in this synthesis and their resolution into pure compounds would be most difficult.

TABLE II

PROPERTIES OF PRODUCTS FROM THE ESTERIFICATION OF BUTANEDIOL WITH AN EQUIMOLAR AMOUNT OF ACETIC ACID

A. Butyl acetate as an entrainer

Fraction	Boiling range, °C.	Weight, grams.	Saponification equivalent	n_D^{25}
1	176-182	115.3		1.4208
2	182-183.5	162.3	139.2*	1.4209
3	183.5-185	76.0	120.0	1.4188

*Fractions 1 and 2 combined for analysis.

B. Benzene as an entrainer

1	178-180	96.5	154.1	1.4220
2	180-182	156.9	148.5	1.4220
3	182-184	159.0	131.3	1.4210
4	184-188	52.5	113.1	1.4180

TABLE III

meso-2,3-BUTANEDIOL AND ITS ESTERS

Compound	Boiling point, °C.	n_D^{25}	Saponification equivalent
meso-2,3-Butanediol	181.7 (133)	1.4366 (16)	---
erythro-2,3-Butanediol monoacetate	178-183 (105)	1.4215 (131)	132
meso-2,3-Butanediol diacetate	193 (101)	1.4132 (16)	87
meso-2,3-Butanediol-meso-2,3-butanediol diacetate, CBM (77.6% diol)	177.6 (85)		

2. Reaction of erythro-2,3-butanediol monoacetate, formaldehyde and hydrogen chloride

Procedure without water-immiscible diluent: One-half mole (66 g.) of the crude erythro-2,3-butanediol monoacetate (Fraction 2, Table IIA.) was added to a 500-ml. three-neck flask and cooled in an ice bath. Fifteen grams of trioxymethylene was added and this reaction mixture was stirred mechanically. Approximately 5 g. of sodium chloride was added to salt out the product from the water formed in the reaction. Anhydrous hydrogen chloride was bubbled into the reaction mixture until it was saturated. About two and one-half hours was required for completion of the reaction. No aqueous layer had formed, although the trioxymethylene had reacted. The salt was still undissolved. Anhydrous calcium chloride to dry the product was added and hydrogen chloride was evolved copiously. A portion of the hydrated calcium chloride became syrupy and dissolved. Gaseous carbon dioxide was bubbled through to remove some excess hydrogen chloride. The calcium chloride was filtered off and the filtrate was distilled in vacuo. A considerable amount of polymerized formaldehyde collected in the condenser. The main products were 4,5-dimethyl dioxolane and acetic acid. The desired 2-chloromethoxy-3-acetoxy butane was not obtained. A solid mass of calcium salts was in the residue. After consideration of the nature of the products, it appeared plausible that the water

formed in the reaction had to some extent, hydrolyzed the acetoxy- group of the desired product and the dioxolane was formed when the resultant 3-chloromethoxy-2-butanol underwent ring closure with elimination of hydrogen chloride.

Procedure in presence of carbon tetrachloride: One mole

of crude erythro-butanediol monoacetate (Fraction 3, Table IIB) was dissolved in 500 ml. of carbon tetrachloride and cooled in an ice bath. One mole of trioxymethylene and sixty grams of anhydrous sodium sulfate were added and anhydrous hydrogen chloride was bubbled in while the mixture was stirred. Four hours were required to saturate the mixture. Two layers had formed. The carbon tetrachloride layer was decanted from the sticky mass of salts and the latter was washed several times with carbon tetrachloride. The combined washings and solvent layer were dried over sodium sulfate. Carbon dioxide was bubbled through to remove the excess hydrogen chloride. After standing overnight, the sodium sulfate was filtered off and the filtrate was distilled. Carbon tetrachloride was removed at atmospheric pressure. The pressure was then reduced to 2 mm. and the product distilled through the Vigreux column over the range 56-65°. A yield of 129.5 g. of crude product was obtained. An analysis for active halogen indicated that the crude product, if 2-chloromethoxy-3-acetoxy-butane, was 80.3% pure. This is 58.7% of the theoretical amount of pure compound. The product was very difficult to purify by redis-

tillation because the impurities, mainly the butanediol diacetate which contaminated the starting material, distilled in the same range. A pure fraction was obtained for analysis and had the following physical constants:

b.p. 61.5-62.5° (2 mm.), n_D^{25} 1.4340.

Analysis. Calculated for $C_7H_{13}O_3Cl$: Cl, 19.68%
Found: Cl, 20.12%.

These data agree well with those presented previously for 2-chloromethoxy-3-acetoxy-butane prepared by the cleavage of 4,5-dimethyl dioxolane with acetyl chloride.

V. REACTIONS OF THE CHLOROMETHYL ETHER OF
2,3-BUTANEDIOL MONOACETATE

A. Review of Literature

Chloroethers react with alcohols to form acetals and liberate hydrogen chloride. Although this reaction has been studied (58), it has been of little preparative value. The presence of free hydrogen chloride initiates an alcoholysis of the product which diminishes the yield:

$$(1) \quad ROCH_2Cl \ + \ R'OH \rightleftharpoons ROCH_2OR' \ + \ HCl$$

$$(2) \quad ROCH_2OR' \ + \ R'OH \overset{HCl}{\rightleftharpoons} ROH + R'OCH_2OR'$$
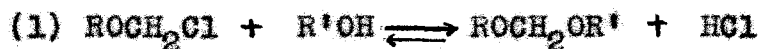
This reaction, however, has been useful in modifying polymers containing free hydroxyl groups. Polyvinyl alcohol (48) and phenol-aldehyde (100) polymers have been treated in this fashion. The more satisfactory method of conducting this reaction is to use the sodium alkoxide or phenoxide instead of the alcohol or phenol. This is the classical method of Henry (40), Favre (28), and Breslauer and Pictet (11). It has been extended to a large variety of phenols by Reychler (93) and to a variety of alcohols and phenols by Sabetay and Schving (94) and more recently by Reppe and Bauer (92). In all cases an acetal and sodium chloride are produced. The method is excellent for the preparation of mixed acetals.

Chloromethyl ethers and α-chloro ethers in general react with the metallic salts of carboxylic acids. Although there were several earlier reports (129, 30), the first detailed

study was made by Clarke, Fox and Mack (15). The products
were the metallic chloride and a carboxylic-acid ester of a
hemiacetal. The reaction with monochloromethyl ether was

$$CH_3OCH_2Cl + MOOCR \longrightarrow MCl + CH_3OCH_2OOCR$$
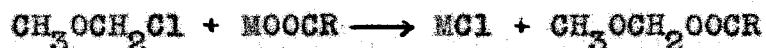
Sodium salts gave better yields than lead salts. The products
were hydrolyzed to formaldehyde, the free acid and methanol.
The stability toward water increased with increasing molecular
weight of the acid. It is likely that such increased stabil-
ity of the product was due, in part, to the lower miscibility
of it with water. The method was later modified and extended
to other chloroethers by Farren, Fife, Clark and Garland (27).
Products were obtained in 80-90% yield. Walker (127) prepared
the chloromethyl ethers of several simple alcohols and ethy-
lene glycol and reacted these with a number of sodium salts
including the acetate, formate, propionate, butyrate, benzoate,
phthalate and salicylate. The products, all liquids, were
tested for resistance to hydrolysis. Several were recommended
for plasticizers. The phthalates and salicylates could not be
distilled because of decomposition. These were purified by
simply washing out the sodium salts in the product with water
and drying with calcium chloride.

The reaction of metallic cyanides with α-chloroethers
has been reported. Gauthier (31) found that potassium cyanide
would not react with α-chloroethers as it does with simple
alkyl halides. It was necessary to use mercuric cyanide or

better cuprous cyanide. The cyanide and chloroether were
mixed to form a paste and the reaction was spontaneous. After
heating several hours on an oil bath, the product was distilled
from the salts and rectified. Yields of 70-80% were obtained
with chloromethyl ethers. However, poorer yields were
realized when the chlorine atom was secondary. The products,
α-alkoxy nitriles, were all liquids. Henze and co-workers
(42) modified the reaction by conducting it in the presence
of anhydrous ether. Lingo and Henze (64) used benzene as the
diluent and extended the reaction to a number of α-chloroethers
derived from ethylene chlorohydrin. Clark and Henze (14) made
a similar study related to ethylene bromohydrin. Allen and
Henze (1) prepared a nitrile from the chloromethyl ether of
1,3-glycerol dichlorohydrin and studied its reactions. More
recently Salmi, Leimu and Kallio (96) have prepared the
chloromethyl ethers of several chlorohydrins and studied the
nitriles obtained from them. The reaction has been extended
to the bis(chloromethyl) ethers of glycols (3). Speer and
Henze (116) used a suspension of silver cyanide in benzene to
react with sec.-butyl-α-chloroethyl ether.

Grignard reagents are known to react with α-chloroethers
by a coupling mechanism. An addition compound is first formed
and when this is decomposed by dilute acid, a magnesium halide
is produced. An alkyl or aryl group has replaced the α-chlo-
rine. The equation below illustrates the overall reaction.

$$ROCHClR' + R''MgX \longrightarrow ROCHR''R' + MgXCl$$
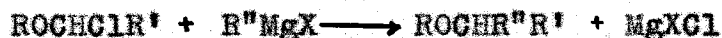
DeKok, Leendertse and Schoenmaker (128) have prepared a number of the simpler ethers from α-chloroethers in this manner. Yields were 60-85%. Gauthier (32) prepared a number of 1-alkoxy-4-propyl cyclohexanes from 1-chloromethoxy-4-propyl cyclohexane by coupling with appropriate Grignard reagents. Grignard reagents derived from unsaturated halides (134), alkoxy halides (86) and di-halides (20, 59) have been coupled with simple α-chloroethers. The coupling of α, β-dihalo-ethers with simple Grignard reagents has been studied extensively (46, 122, 26, 84, 83). In all such cases the β-halogen was unaffected and the α-halogen coupled smoothly. The chloromethyl ethers of several chlorohydrins have been coupled with Grignard reagents (8) and only the α-halogen reacted. Bis(halomethyl) ethers react with two moles of Grignard reagents to form the dialkyl ethers (87, 62, 63).

The reaction of α-chloroethers and amines is a vigorous one. Many α-chloroethers have been characterized by reacting them with tertiary amines to produce quaternary ammonium chlorides. (66, 50, 62). Tronov (123) used the reaction as a measure of halogen activity. The salts are generally very hygroscopic and difficult to crystallize. For analysis, they were converted to their auric chloride or platinic chloride complexes which were easily characterized. Kursanov and Setkina (52) prepared a series of chloromethyl ethers of high

molecular weight alcohols and formed the quaternary salts by the reaction with pyridine, trimethyl amine and dimethyl aniline. The products were used to impregnate cotton cloth for waterproofing. Later, (53) this impregnation of cellulose was reported to be a chemical reaction. A series of halomethyl ethers and hexamethylene tetramine were brought together and the salts were tested for antibacterial properties (75). Polymers were prepared by the reaction of bis(α-chloroethyl) ether and hexamethylenetetramine (10).

2-Aminothiazole, useful in the preparation of sulfathiazole has been prepared by the interaction of thiourea and an α-chloroether. 1,2-Dichloroethyl ethyl ether (12) as well as the corresponding butyl and isoamyl ethers have been used. The yields were very good in all cases. Swiss patents (113, 114) describe the preparation of surface active agents by condensing the chloromethyl ethers of high molecular weight aliphatic alcohols with thiourea. Polymeric waterproofing compounds (111, 112) are obtained when bis(chloromethyl) ether is condensed with thiourea and high molecular weight amides.

In the presence of the proper catalysts and solvents, α-haloethers add to an olefinic linkage. Chloromethyl methyl ether adds to propylene in the presence of zinc or bismuth chlorides and carbon disulfide to yield 1-methoxy-3-chlorobutane (21, 102). Straus and Thiel (119) investigated the addition of α-chlorobenzyl methyl ether to buta-

diene, cyclohexadiene and cyclopentadiene. The addition
occurred by a 1,4-mechanism. Dykstra (24) studied the cata-
lytic addition of chloromethyl ethers to vinyl acetylene. The
catylytic addition of α-chloro ethers to simple and conjuga-
ted olefins has been reported in several patents (25, 49, 76).
Staudinger and Tuerck (117) have patented a process for the
addition of α-haloethers to ketene. The products are the
expected β-alkoxy propionyl halides.

Simonsen has investigated the use of monochloromethyl
ether in syntheses involving the sodium derivatives of com-
pounds containing active methylene groups. The initial
coupling to the active methylene with the elimination of
sodium chloride was the general reaction in the case of
malonic ester (107) and several of its closely related deriv-
atives (109, 110, 90). Very interesting derivatives were
then obtained by subjecting the condensation products to fur-
ther syntheses. The coupling with ethyl acetoacetate (108)
occurred chiefly with the enolic form of the ester. The major
product was the ethyl ester of β-methoxymethoxy crotonic
acid. A similar observation was made by Lapworth and Mellor
(56) in regard to the α-alkyl acetoacetic esters. Bergmann
(6) condensed the sodium derivative of diphenylmethane with
monochloromethyl ether and obtained 1,1-diphenyl-2-methoxy-
ethane. An extensive series of α-chloroethers was condensed
with the sodium derivative of malonic ester by Hill and Keach

(90) and the barbiturates of the condensation products were synthesized.

Among the miscellaneous reactions of simple α-haloethers is the condensation with metals. The only report is a patent (99) which describes the coupling of two molecules by sodium, zinc or magnesium accompanied by the elimination of the chlorine as the metallic chloride. Monochloromethyl ether reacts with a mixture of nitric and sulfuric acids to give nitromethoxymethyl nitrate and nitromethoxymethoxymethyl nitrate (47). The addition of chloromethyl ethers to epiclorohydrin has also been reported (9), in the presence of mercuric chloride. The products are 1,3-dichloro-2-alkoxymethoxy-propane. The condensation of sodium thiosulfate and α-haloethers, especially those derived from high molecular weight alcohols, are reported to yield wetting and penetrating agents (19). The products are alkoxymethyl esters of sodium acid thiosulfate.

B. Experimental

1. Reaction of the sodium salts of carboxylic acids with 2-chloromethoxy-3-acetoxybutane

The appropriate sodium salt was ground in a mortar to pass through a 60 mesh screen and dried several hours in an oven at 110°. A five per cent excess of the sodium salt was placed in a three-neck flask equipped with dropping funnel

and reflux condenser and mechanically stirred. The chloroether was added gradually over a period of 10 to 15 minutes. When the reactions were spontaneous and highly exothermic a cold water bath was used to control the temperature. The reaction mixtures were then heated on a steam bath for three hours to complete the reaction. The reaction mixtures were thick pastes when first mixed but as the reaction progressed the masses liquefied. When cooled, anhydrous ether was added to dilute the mixture and the salts were filtered off. The residue was washed several times with ether and all the filtrates were combined. The excess sodium salt and by-product sodium chloride were dissolved and the small amount of residual oil obtained was added to the combined filtrates. The ether was removed by distillation and the product was then rectified in vacuo through a small Vigreux column equipped with an electrically heated jacket.

4-Acetoxy-3-methyl-2-oxapentyl acetate. Forty-three grams of fused anhydrous sodium acetate and 90.2 g. of 2-chloro-methoxy-3-acetoxybutane were treated according to the general procedure. The distillation in vacuo yielded a forerun of about three grams as the temperature rose to 72° (1.5 mm.). The main fraction of 87.4 g. was collected at 72-73.5°(1.5 mm.). It was a colorless oil with mild pleasant odor. This was an 85.6% yield of 4-acetoxy-3-methyl-2-oxapentylacetate. The physical constants were as follows: b.p. 72-73.5° (1.5 mm.).

n_D^{25} 1.4200. The same compound was prepared by Senkus (103) by refluxing 4,5-dimethyl dioxolane with acetic anhydride. The physical constants reported by Senkus are b.p. 228-232° (750 mm.), n_D^{25} 1.4212.

4-Acetoxy-3-methyl-2-oxapentyl benzoate. 75.7 g. of sodium benzoate and 90.5 g. of 2-chloromethoxy-3-acetoxy-butane, treated according to the general procedure, yielded approximately 3 g. of oil distilling at 45-47° (1mm.) and then 1-2 g. of a white crystalline solid which sublimed into the condenser. The solid was soluble in sodium hydroxide solution and its melting point corresponded to that of benzoic acid. The major product, 4-acetoxy-3-methyl-2-oxa-pentyl benzoate, was collected over the range 143-145.5° (1mm.). The yield was 106.0 g. (79.8%). It was a colorless, almost odorless, slightly viscous oil possessing the following physical properties: b.p. 143-145.5° (1mm.), n_D^{25} 1.4889, d_4^{25} 1.1135.

Analysis. Calculated for $C_{14}H_{18}O_6$: Saponification equivalent, 108; MR_D, 68.19. Found: Saponification equivalent, 108.1; MR_D, 68.70.

bis(4-Acetoxy-3-methyl-2-oxapentyl)adipate. Sodium adipate was prepared by treating an aqueous suspension of adipic acid with concentrated sodium hydroxide solution until the acid had completely dissolved and the solution was pink to

phenolphthalein. The solution was treated with an equal volume of 95% ethanol to precipitate the disodium salt. The precipitated salt was filtered, dissolved in the minimum amount of water and reprecipitated with ethanol. It was filtered and dried at 110°.

Fifty and one-half grams of disodium adipate and 90.5 g. of 2-chloromethoxy-3-acetoxybutane, treated according to the general procedure, yielded a small forerun at 45-47° (2 mm.); bis(4-acetoxy-3-methyl-2-oxapentyl)adipate then distilled over the range 205-213° (0.5 mm.). The yield was 82.5 g. (76.2%). The product was a viscous, colorless, odorless oil which was insoluble in water. There was a residue of approximately 10 g. which was difficult to distill through the column because the high still temperature required caused decomposition. The fraction collected at 210-213° was the largest and was reserved for the determination of physical constants and analysis. The data obtained follow: b.p. 210-213° (0.5 mm.), d_4^{25} 1.1094, n_D^{25} 1.4458.

Analysis. Calculated for $C_{20}H_{34}O_{10}$: Saponification equivalent, 135; MR_D, 104.44. Found: Saponification equivalent, 134.6, MR_D 104.21.

4-Acetoxy-3-methyl-2-oxapentyl stearate. One hundred grams of sodium stearate (Fischer Scientific Technical Grade) and 53 g. of 2-chloromethoxy-3-acetoxybutane yielded, beside the usual small forerun, about 15-20 g. of stearic acid which

distilled at 172-175° (1mm.) and solidified in the condenser. The main product (52.2 g.) was collected over the range 196-204° (0.5 mm.). The first part of the distillate was an oil but the last part to distill was a soft, low melting wax. The yield of crude 4-acetoxy-3-methyl-2-oxapentyl stearate was 41.3%. When cooled in an ice bath the entire mass solidified. It was diluted with absolute ethanol and recrystallized three times from this solvent. A white wax, insoluble in water but soluble in all common organic solvents was obtained. It melted at 36-37° and when warmed with dilute acid, formaldehyde was evolved.

Since the compound was insoluble in the acetone-aqueous alkali mixture usually employed for the saponification equivalent analysis, it was necessary to modify the saponification procedure as follows:

The sample (0.2 g.) was dissolved in 15 ml. of 95% ethanol and 15 ml. of an alcoholic solution of sodium hydroxide (8 g. of sodium dissolved in 250 ml. of ethanol and 25 ml. of water) was added. This mixture was stored 24 hours in an ice box. It was then diluted with 25 ml. of water and titrated as usual with standardized hydrochloric acid. A blank was also run and the saponification equivalent calculated as before.

Analysis. Calculated for $C_{25}H_{48}O_5$: Saponification equivalent 214. Found: Saponification equivalent 213.

bis(4-Acetoxy-3-methyl-2-oxapentyl) phthalate. Disodium

phthalate was prepared similar to the disodium adipate
described above. The salt was dried at 150° for 2½ hours
to decompose any hydrate and then for 16 hours at 110°. Fifty-
five grams of disodium phthalate and 90.5 g. of 2-chloromethoxy-
3-acetoxybutane reacted very readily. The reaction mixture was
treated according to the general procedure and a very viscous
pale yellow oil was obtained. When distilled in vacuo the
usual forerun was obtained, however the product could not be
distilled at 0.5 mm. When the pot temperature had reached
195°, decomposition occurred; formaldehyde was copiously
evolved and phthalic anhydride sublimed into the column and
condenser. The same difficulty was experienced by Walker (127)
when attempting to distil phthalates of this type.

2. The reaction of carboxylic acid anhydrides with 2-chloro-methoxy-3-acetoxybutane

There is no mention in the literature of the reaction of
chloromethyl ethers with acid anhydrides. A preliminary test,
however, indicated the production of acetyl chloride when
acetic anhydride and 2-chloromethoxy-3-acetoxybutane were
heated together in the presence of an acid catalyst. A series
of reactions was carried out to investigate the nature of the
reaction.

The equivalent amounts of the acid anhydride and the
chloroether were mixed in a round bottom flask and 0.2% of
concentrated sulfuric acid was dissolved in the mixture. The

flask was equipped with a distilling head and heated to a temperature such that the acyl halide would distil in preference to the reagents. Since the reaction was suspected to be reversible, the acyl halide was removed continuously. A slow stream of air was passed through the reaction mixture to aid the distillation. When the distillation of acyl halide ceased, the catalyst was neutralized with anhydrous sodium acetate and the reaction mixture was fractionated _in vacuo_ through the Vigreux column. The products were found to be identical with those produced by the action of the corresponding sodium salt on the 2-chloromethoxy-3-acetoxybutane.

4-Acetoxy-3-methyl-2-oxapentyl acetate. Forty-two grams of 2-chloromethoxy-3-acetoxybutane and 23.8 g. of acetic anhydride were mixed with 0.2 ml. of concentrated sulfuric acid and treated according to the general procedure described. Acetyl chloride was distilled from the reaction at 49-52°. Approximately 15 g. was collected in 2 hours. After neutralization of the catalyst with 0.34 g. of sodium acetate, fractional distillation of the reaction mixture yielded 42 g. (88.5%) of product collected over the range 69-71° (1mm.). The physical properties were: b.p. 69-71° (1 mm.), n_D^{25} 1.4203, d_4^{25} 1.0648. These data agree very well with those obtained for the 4-acetoxy-3-methyl-2-oxapentyl acetate prepared previously by the action of sodium acetate on the chloroether and with the data of Senkus (103) previously quoted. The

observed molecular refraction was 48.65; the calculated is 48.71.

To determine whether the acetoxy-group of the 2-chloro-methoxy-3-acetoxybutane was involved in the reaction, butyric anhydride was substituted for acetic anhydride in the reaction and the nature of the acyl halide produced was investigated.

4-Acetoxy-3-methyl-2-oxapentyl butyrate. Sixty-one and one-half grams of butyric anhydride and 70 g. of 2-chloro-methoxy-3-acetoxybutane treated in the presence of 0.25 ml. of sulfuric acid according to the general procedure gave 36 g. (87.5%) of butyryl chloride (101-104°). The catalyst was neutralized with 0.2 g. of sodium acetate. When the reaction mixture was fractionated in vacuo about 9 g. of unreacted butyric anhydride was collected at 47-50° (1mm.). The product, a colorless, almost odorless oil, then distilled over the range 81-87° (1mm.). The major portion was collected at 82-85° and was reserved for the determination of physical data and analysis. The crude yield was 73.1 g. (81.3%). The physical constants of the 4-acetoxy-3-methyl-2-oxapentyl butyrate were: b.p. 82-85° (1mm.), n_D^{25} 1.4240, d_4^{25} 1.0268.

Analysis. Calculated for $C_{11}H_{20}O_5$: Saponification equivalent 116.0; MR_D 57.94. Found: Saponification equivalent 114.5, MR_D 57.85.

4-Acetoxy-3-methyl-2-oxapentyl benzoate. Fifty-six and one-half grams of benzoic anhydride was mixed with 45.1 g. of

2-chloromethoxy-3-acetoxybutane and 0.25 ml. of sulfuric acid
and the reaction carried out according to the general procedure.
Because of the high boiling point of benzoyl chloride, the
reaction was run at 5-7 mm. pressure. The benzoyl chloride
distilled at 65-67° over a period of one hour. It was contam-
inated with some of the unreacted chloroether which could not
be efficiently separated without a fractionating column.
Approximately 15 g. was collected. The catalyst was neutra-
lized with 1.35 g. sodium benzoate and the reaction mixture
was fractionated in vacuo. Several grams of benzoic acid
sublimed at 90-110°(0.5 mm.). Thirty-five grams (52.7%) of
crude 4-acetoxy-3-methyl-2-oxapentyl benzoate distilled over
the range 130-137°. Its identity with that produced by the
interaction of sodium benzoate and the chloroether was veri-
fied through its physical constants: b.p. 132-135° (0.5 mm.),
n_D^{25} 1.4895. Almost one-half (27.5 g.) of the benzoic anhydride
was recovered unchanged. It distilled at 155-165° (0.5 mm.).

3. Reaction of cuprous cyanide with 2-chloromethoxy-3-acetoxy-butane

    a. 2-cyanomethoxy-3-acetoxybutane. Forty-eight grams
(5% excess) of cuprous cyanide and 90.5 g. of 2-chloromethoxy-
3-acetoxybutane were mixed to form a paste in a three-neck
flask equipped with reflux condenser and mechanical stirrer.
The mixture was heated gently on a steam bath to initiate the
reaction and then it was necessary to moderate it with a cold

TABLE IV

PHYSICAL CONSTANTS OF SOME 4-ACETOXY-3-METHYL-2-OXAPENTYL ESTERS.

$$CH_3CH(OAc)CH(CH_3)OCH_2OOCR$$

R	Method of Prep. (2)	Yield %	b.p. °C.	mm.	n^{25}_D	d^{25}_4	Sapon. equiv. Calc'd.	Sapon. equiv. Obs.	MR_D Calc'd.	MR_D Obs.
CH_3-	1	85.6	72-35	1.5	1.4200	--	--	--	--	--
	2	85.5	69-71	1.0	1.4203	1.0648	--	--	48.71	48.65
$CH_3CH_2CH_2-$	2	81.3	82-5	1.0	1.4240	1.0237	116.0	114.5	57.94	58.02
$C_{17}H_{35}-$	1	41.3	(1)		--	--	214	213	--	--
C_6H_5-	1	78.8	143-5.5	1.0	1.4889	1.1135	108	108.1	68.19	68.70
	2	52.7	132-5	0.5	1.4895	--	--	--	--	--
$-(CH_2)_4-$	1	76.2	210-3	0.5	1.4458	1.1094	133	134.6	104.44	104.21

(1) M.p. 36-37°

(2) Method 1. Prepared by action of sodium salt on 2-chloromethoxy-3-acetoxybutane.

Method 2. Prepared by action of acid anhydride on 2-chloromethoxy-3-acetoxybutane.

water bath. Finally, the mixture was heated for four hours
on a steam bath. After cooling, the reaction mixture was
diluted with 75 ml. of anhydrous ether and filtered from the
cuprous chloride and excess cyanide. The salts were washed
three times with 50 ml. portions of ether. The ether extract,
when added to the filtrate, precipitated a brown tar. The
ether solution was decanted from the tar and then distilled.
After the ether had been removed, the product was fractionated
by distillation in vacuo. A small forerun was collected over
the range 42-73°. The 2-cyanomethoxy-3-acetoxybutane then
distilled at 73-75° (1mm.). It was a colorless liquid,
insoluble in water, with a faint pleasant odor. The yield
was 70.1 g. (82.3%). Its physical properties were; b.p. 73-75°
(1 mm.), n_D^{25} 1.4255, d_4^{25} 1.0368.

Analysis. Calculated for $C_8H_{13}O_3N$: N, 8.17% MR_D, 42.19.
Found: N, 7.83%; MR_D, 42.43.

The hydrolysis of both the nitrile and acetoxy group of
2-cyanomethoxy-3-acetoxy butane would give the δ-hydroxy acid,
2-carboxymethoxy-3-hydroxybutane, $CH_3CH(OH)CH(OCH_2COOH)CH_3$.

δ-Hydroxy acids of this type, related to glycollic acid, have
not been isolated but exist as mixtures of the lactone and acid
or their polymers. Hollo (45) prepared the sodium salt of 2-
hydroxyethoxy acetic acid obtained from chloroacetic acid and
the monosodium derivative of ethylene glycol. The salt was
barely acidified and the hydroxy-acid distilled. The lactone

was obtained through the elimination of water from the hydroxy-acid. Its polymerization upon standing was studied and it was found that traces of acid catalyzed the polymerization. The polymerization was also studied by Carothers, Dorough and Van Natta (13). Salmi, Leimu and Kallio (96) prepared the lactone of 2-hydroxyethoxyacetic acid by dry distillation of the sodium salt of 2-chloroethoxyacetic acid. His study of the polymerization of the lactone confirmed the conclusion of the other investigators. The lactone polymerized rapidly in the presence of acid and very slowly when acid was absent.

2-Carboxymethoxy-3-acetoxybutane was prepared by the acid hydrolysis of the nitrile group of 2-cyanomethoxy-3-acetoxy-butane with the calculated amount of water; the lactone (5,6-dimethyl-2-p-dioxenone) was formed by intramolecular elimination of acetic acid. The following equations illustrate the synthesis:

(1) $CH_3CH(OCH_2CN)CH(OAc)CH_3 + 2H_2O + H_2SO_4 \xrightarrow{H_2SO_4}$

$CH_3CH(OCH_2COOH)CH(OAc)CH_3 + NH_4HSO_4$
(I)

(2) (I) $\xrightarrow{H_2SO_4}$ $CH_3CH-CHCH_3 + CH_3COOH$
$\quad\quad\quad\quad\quad\quad O\diagdown\,CH_2-C=O$
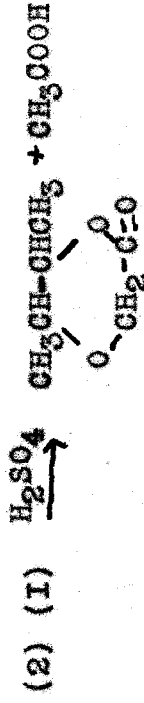
The reaction (2) was carried out in the presence of a large volume of benzene which served as a diluent and favored the intramolecular condensation.

5,6-dimethyl-2-p-dioxenone. Fifty grams of 2-cyanomethoxy-3-acetoxybutane was heated to 70° on a water bath. A solution

containing 30.0 g. of concentrated sulfuric acid and 15.8 g.
of water was added dropwise over a period of 15 minutes while
the reaction mixture was stirred. The reaction was exothermic
but was controlled at 70-75°. The temperature was maintained
for one hour and the reaction was completed at 90-95° in $2\frac{1}{2}$
hours. Two hundred and fifty milliliters of benzene was added
and the reaction mixture distilled. The benzene-acetic acid
azeotrope was collected and analyzed for free acid. Period-
ically fresh benzene was added to the reaction flask to main-
tain the original volume. A total of 15.6 g. of acetic acid
was removed in this manner. The NH_4HSO_4 was filtered off and
washed with benzene. The washings were combined with the fil-
trate and treated with 2 g. of sodium acetate to neutralize
the sulfuric acid catalyst. The benzene and any residual
acetic acid was distilled and the product was fractionated in
vacuo. The 5,6-dimethyl-2-p-dioxanone was collected over the
range 54-56° (4 mm.). The yield was 31.7 g. (83.7%). The
product was a colorless oil of pleasant odor which was heavier
than water and, although insoluble in the latter, it slowly
dissolved with the formation of acid. The hydrolysis by water
to the free acid did not require a catalyst. The physical
constants were: b.p. 54-56° (4 mm.), n_D^{25} 1.4438, d_4^{25} 1.1130.

Analysis. Calculated for $C_6H_{10}O_3$: Saponification equiv-
alent, 130; MR_D, 31.00. Found: Saponification equivalent,
127; MR_D, 30.91.

The molecular weight was not determined when the product was freshly prepared, but it was investigated after the sample had stood at room temperature for four months. At this time the molecular weight (Rast) was 149. The calculated molecular weight of the monomeric lactone is 130.

The structure of the 5,6-dimethyl-2-p-dioxanone was established by converting it to the amide, 1-methyl-2-hydroxypropoxy acetamide.

1-Methyl-2-hydroxypropoxy acetamide. Two and one-half grams of the lactone, 5,6-dimethyl-2-p-dioxanone, was added to 3.2 ml. of cold concentrated aqueous ammonia. (Cf. Fittig (29)). After standing ten minutes at room temperature, the mixture was placed in a vacuum desiccator over sulfuric acid and the excess ammonia and water removed in vacuo. The syrup thus obtained crystallized after two days. The crude crystals were washed with cold, anhydrous ether and dried. The crude yield was 2.53 g. (89.5%) and the product melted over the range 55-60°. A sample for analysis was recrystallized twice from hot, anhydrous ether. The white, crystalline 1-methyl-2-hydroxy propoxy acetamide was obtained (m.p. 63-64°). It was extremely soluble in water and ethanol, quite soluble in chloroform and difficulty soluble in xylene and ether.

Analysis. Calculated for $C_6H_{13}O_3N$: N, 9.52%. Found: N, 9.45%.

4. Reaction of sodium alkoxides and phenoxides with 2-chloro-methoxy-3-acetoxybutane.

It was apparent from preliminary experiments that solutions of sodium alkoxides in the corresponding alcohols could not be used to prepare the 2-alkoxymethoxy-3-acetoxybutanes from the 2-chloromethoxy-3-acetoxybutane. The excess alcohol in the solution reacted with the acetoxy group by alcoholysis; furthermore, if the alkoxide solution was added to the chloro-ether, the reaction mixture became acidic and the alkoxy-methoxy group also underwent alcoholysis. The following reactions illustrate the difficulties encountered.

(1) $CH_3CH(OCH_2OR)CH(OAc)CH_3 + ROH \xrightarrow[OH^-]{H^+}$

$ROAc + CH_3CH(OCH_2OR)CH(OH)CH_3;$

(2) $CH_3CH(OCH_2OR)CH(OH)CH_3 + ROH \xrightarrow{H^+}$

$CH_3CH(OH)CH(OH)CH_3 + (RO)_2CH_2.$
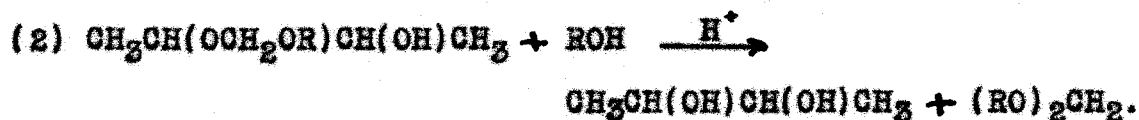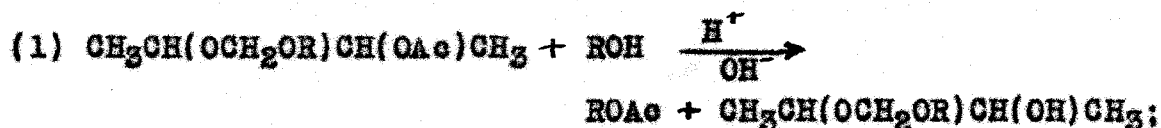
The sodium alkoxides and phenoxides were prepared by dissolving a calculated amount of appropriate alcohol or phenol in anhydrous ether and refluxing this solution with a small excess of metallic sodium until the reaction ceased. The suspension and solution of the sodium derivative was screened from the excess sodium metal and added dropwise to the 2-chloromethoxy-3-acetoxybutane which was maintained at 0° in an ice bath. The reaction was instantaneous and sodium chloride precipitated. The salts were filtered off, washed with ether, and discarded. The washings and the main filtrate were distilled

to remove the ether and then fractionally distilled in vacuo. The products obtained in poor yield by this method, were all liquids.

5-Acetoxy-4-methyl-1,3-dioxahexyl ethane. The reaction product of 30 g. of anhydrous ethanol in 200 ml. of ether with 15 g. of metallic sodium according to the general procedure above, was added to 70 g. of 2-chloroethoxy-3-acetoxybutane over a one hour period and the reaction was continued three hours. Fractional distillation yielded, besides about 8 g. of ethyl acetate, 28 g. of crude product (38%) distilling over the range 43-48° (1.5 mm.). Other physical constants were: n_D^{25} 1.4150, d_4^{25} 0.9700. The saponification equivalent was 261 (calculated for 5-acetoxy-4-methyl-1,3-dioxahexyl ethane; 190). This value indicated that the product prepared by this procedure was contaminated with a by-product distilling in the same range. The pure product was later prepared by an alternate procedure.

1-(4-methyl-5-acetoxy-1,3-dioxahexyl)butane. Forty-eight grams of butanol dissolved in 200 ml. of anhydrous ether was treated with 15 g. of sodium metal according to the general procedure. The resulting suspension was added to 70 g. of 2-chloromethoxy-3-acetoxybutane during 45 minutes and the reaction continued two hours at 0°. Fractional distillation of the reaction mixture yielded 14 g. of n-butyl acetate which distilled at 42-45° (28 mm.) and 5 g. of an unidentified pro-

duct distilling at 44-50° (4 mm.). The main product 1-(4-

methyl-5-acetoxy-1,3-dioxahexyl)butane, distilled over the

range 81-89° (4 mm.). The yield was 32 g. (34%). The phys-

ical constants of the purified product were: b.p. 87-89°

(4 mm.), n_D^{28} 1.4185, d_4^{25} 0.9502.

Analysis. Calculated for $C_{11}H_{22}O_4$: Saponification

equivalent, 218.0; MR_D, 57.98. Found: Saponification equiv-

alent, 223.5; MR_D, 57.52.

There was also a high boiling fraction of 18 g. which

distilled over the range 105-115° (1.5 mm.).

4-Methyl-5-acetoxy-1,3-dioxahexylbenzene. Sixty-one grams

of phenol was dissolved in 100 ml. of anhydrous ether and

treated with 15 g. of sodium suspended in 200 ml. of ether.

The suspension of sodium phenoxide was added to 70 g. of 2-

chloromethoxy-5-acetoxybutane at 0°. The reaction mixture

was stirred for two hours and then treated as in the general

procedure. When fractionally distilled, a forerun of approxi-

mately 6 g. was obtained. The product, 4-methyl-5-acetoxy-1,

3-dioxahexylbenzene, distilled at 126-130° (25 mm.). The

yield was 46.2 g. or 50%. The residue in the distillation

flask had set to a waxy polymer insoluble in water, acids and

ether. The physical constants of the product were: b.p. 126-

130° (2.5 mm.), n_D^{25} 1.4828, d_4^{25} 1.0652.

Analysis. Calculated for $C_{13}H_{18}O_4$: Saponification

equivalent, 238; MR_D, 63.55 Found: Saponification equiv-

alent, Saponification equivalent.

230; MR_D, 63.89.

The compound was a somewhat viscous, odorless oil. Its polymerization by acid was studied and the results are reported in a later section describing the preparation of this compound by a modified method.

1,3-bis(4-methyl-5-acetoxy-1,3-dioxahexyl)benzene. The method of preparing the disodium derivative of resorcinol was different from that described in the general procedure. It was more rapid and more easily carried out. Fifteen grams of sodium metal was suspended in 100 ml. of anhydrous ether and a solution of 35 g. of resorcinol and 60 ml. of absolute ethanol in 200 ml. of anhydrous ether was added slowly. When the reaction had ceased, 250 ml. of xylene was added and the mixture distilled to remove the ether and ethanol. The resulting suspension of disodium resorcinate in xylene was added to 70 g. of 2-chloromethoxy-3-acetoxybutane at 0°. After two hours the product was worked up in the usual manner. The xylene was distilled off at 70 mm. and the reaction mixture was fractionated. At 1 mm. 8 g. of an unidentified oil distilled over the range 101-104°. The main product was a heavy, viscous oil which distilled over the range 185-188° (1 mm.). After 16 g. (21% yield) had distilled, it was necessary to discontinue the distillation because the residue in the flask had polymerized to a red, glass-like polymer. Because the temperature required to distil the oil induced polymerization, it was not further purified. The physical constants of the

crude product, 1,3-bis(4-methyl-5-acetoxy-1,3-dioxahexyl)
benzene were: b.p. 183-188° (1mm.) n_D^{25} 1.4710, d_4^{25} 1.0961.

Analysis. Calculated for $C_{20}H_{30}O_8$: Saponification equiv-
alent, 199; MR_D, 100.82. Found: Saponification equivalent,
195; MR_D, 100.80.

When treated with concentrated sulfuric acid, the oil
instantaneously polymerized to a brilliant red, amorphous
solid. The polymerization could be moderated and a cast resin
produced by heating the oil in a test tube at 100° with several
drops of 2-chloromethoxy-3-acetoxybutane and water; the latter
reagents liberated hydrogen chloride uniformly through the
solution. After several hours, a bright red, glass-like ther-
mosetting resin and formed. The polymer was brittle and on
exposure to air, darkened and became harder.

Since the reaction of 2-chloromethoxy-3-acetoxy butane with
the sodium alkoxides and phenoxides gave unsatisfactory yields
of products it seemed advisable to develop an alternate method
for preparing the same products. The strongly alkaline sodium
derivatives apparently induced a side reaction with the acetoxy
group of the chloroether. The appearance of the alkyl ace-
tates among the products of the reaction was significant of
this. The use of the free alcohol would obviate this diffi-
culty; however, as was mentioned earlier, the by-product hydro-
gen chloride would induce the alcoholysis of the desired mixed
acetal. Therefore the feasibility of conducting the reaction

with the alcohols and phenols in the presence of pyridine as

a condensing agent was investigated.

5. Reaction of 2-chloromethoxy-3-acetoxybutane with alcohols and phenols in the presence of pyridine

The esterification of alcohols was acyl halides in the

presence of pyridine is a common and satisfactory procedure.

The use of pyridine as a condensing agent in the reaction of

α-chloroethers and alcohols, however, is complicated by the

affinity of the pyridine for the chloroether. The condensa-

tion was attempted using a large excess of alcohol so that

the competing reaction of the chloroether with pyridine would

be suppressed. This reaction was conducted at two tempera-

tures. The addition of the chloroether to equivalent amounts

of pyridine and alcohol in the presence of an inert diluent

was investigated. This suggested the addition of the chloro-

ether to the alcohol dissolved in an inert diluent and the

addition of the pyridine only as needed to neutralize the

hydrogen chloride produced.

a. The addition of 2-chloromethoxy-3-acetoxybutane to a solution of pyridine in a large excess of alcohol.

2-Chloromethoxy-3-acetoxybutane was added dropwise over a

period of 45 minutes to a 10% excess of pyridine dissolved in

a ten-fold excess of the appropriate alcohol while the latter

was stirred rapidly. A definite temperature was maintained

during the reaction and for an additional ten minutes. The

excess alcohol was removed by distillation and the residue was cooled and poured on ice to dissolve out the pyridinium salts and excess pyridine. The aqueous layer was saturated with sodium chloride and extracted with ether. The ether layer was dried over night over Drierite and distilled. After removal of the ether, the residue was fractionated in vacuo through a Vigreux column and the yield of the desired acetal was estimated.

5-Acetoxy-4-methyl-1,3-dioxahexylethane. Seventy grams of 2-chloromethoxy-3-acetoxybutane when added to 33.6 g. of anhydrous pyridine dissolved in 180 g. of absolute ethanol at 70° according to the general procedure yielded 44 g. (59.7%) of 5-acetoxy-4-methyl-1,3-dioxahexylethane which distilled over the range 46-49° (1.5 mm.). There was almost no forerun or residue. The refractive index, n_D^{25}, was 1.4218.

1-(5-Acetoxy-4-methyl-1,3-dioxahexyl)butane. Seventy grams of 2-chlormethoxy-3-acetoxybutane was added to 33.6 g. of anhydrous pyridine dissolved in 287 g. of n-butyl alcohol at 70° according to procedure a. The excess butanol, however was distilled off at 40-45° (20-25 mm.) to prevent alcoholysis during distillation. There were 17 g. of by-products which distilled at 3 mm. below the distillation temperature for the main product. Thirty-four grams (30.5%) of 1-(5-acetoxy-4-methyl-1,3-dioxahexyl)butane was obtained over the range 82-85° (3 mm.). The refractive index, n_D^{25} 1.4189, checked with the preparation from sodium butoxide.

The reaction was repeated at 0°. Although the product was not worked up, the syrupy residue of the pyridinium salt of the chloroether which remained after the evaporation of the butanol from a small test sample indicated the chloroether had again reacted with the pyridine in preference to the butanol.

b. The addition of 2-chloromethoxy-3-acetoxybutane to a solution of pyridine and an equivalent amount of alcohol dissolved in an inert diluent (ethyl ether).

Sixty grams of 2-chloromethoxy-3-acetoxy butane was added to a solution of 26.3 g. of anhydrous pyridine (5.0% excess) and 25.9 g. of n-butanol dissolved in 370 ml. of anhydrous ether. The reaction temperature was 0° and the time required to complete the reaction was two hours. Crystalline pyridine hydrochloride which is insoluble in ethyl ether did not precipitate but a heavy syrup, probably the pyridinium salt of the chloroether, settled out. The reaction mixture was washed with brine and dried as usual. After the ether had been removed, only 37 g. of residue remained and a major portion of this was n-butanol which had not reacted.

c. The addition of 2-chloromethoxy-3-acetoxybutane to a solution of the alcohol in an inert solvent; addition of a pyridine solution as required to remove hydrogen chloride produced.

(1) _Ether as the solvent._ The alcohol was dissolved in
ether and a few crystals of methyl red were added. The equiv-
alent amount of 2-chloromethoxy-3-acetoxybutane was added
dropwise while stirring vigorously and refluxing on a water
bath. The color change of methyl red in the ether solution
was orange to red as acid was formed. A solution of pyridine
in ether was prepared and was added as necessary to prevent
the color of the indicator from becoming red. Pyridine hydro-
chloride precipitated. The reaction mixture was washed with
brine and dried over Drierite. The ether was evaporated and
the product obtained by distillation _in vacuo._

5-Acetoxy-4-methyl-1,3-dioxahexylethane. Sixty grams of
2-chloromethoxy-3-acetoxybutane was added to 16.2 g. of abso-
lute ethanol dissolved in 250 ml. of anhydrous ether and
treated with 27.5 g. of anhydrous pyridine dissolved in 150
ml. of anhydrous ether in the manner described above. The
liberation of hydrogen chloride appeared to be very slow and
when all the chloroether had been added, only half of the
pyridine had been used. The remainder was added slowly over
a period of several hours. Crystalline pyridine hydrochloride
precipitated throughout the addition of pyridine. The yield
of 5-acetoxy-4-methyl-1,3-dioxahexylethane was 46.4 g. (65%).
The product was not contaminated by products distilling in
the same range as was that prepared by the action of the sodium
ethoxide upon the chloroether. The physical constants were as

follows: b.p. 46-49° (1.5 mm.), n_D^{25} 1.4122, d_4^{25} 0.9737.

Analysis. Calculated for $C_9H_{18}O_4$: Saponification equivalent, 190; MR_D, 48.70. Found: Saponification equivalent, 187; MR_D 48.81.

1-(5-Acetoxy-4-methyl-1,3-dioxahexyl)butane. Sixty grams of 2-chloro-methoxy-3-acetoxybutane and 25.9 g. of n-butanol when treated with 27.5 g. of pyridine in 150 ml. of ether according to the procedure described above yielded 46.4 (64%) of 1-(5-acetoxy-4-methyl-1,3-dioxahexyl)butane. The product distilled over the range 77-80° (2 mm.). The index of refraction, n_D^{25}, was 1.4183. There was a small forerun of about 2 g. and very little residue. Again the methyl red indicator indicated that the liberation of hydrogen chloride was very slow.

2-(5-Acetoxy-4-methyl-1,3-dioxahexyl)propane. Sixty grams of 2-chloromethoxy-3-acetoxybutane was added to 21 g. of 2-propanol dissolved in 250 ml. of anhydrous ether and treated with 27.5 g. of pyridine dissolved in 150 ml. of ether as indicated in the general procedure. Crystalline pyridine hydrochloride did not immediately precipitate in this preparation but a heavy syrup or oil separated. The hydrogen chloride produced in this reaction seemed to concentrate in the syrup phase as the methyl red indicator became deep red in the syrup; furthermore it was difficult to neutralize the acid with pyridine because the latter dissolved first in the upper

ether layer. The syrup phase may have been a pyridine hydro-
chloride alcoholate or it may have contained water from some
side reaction such as the reaction of hydrogen chloride with
2-propanol. As the reaction progressed the syrup thickened
and crystallized partially. Upon fractional distillation of
the reaction mixture 23 g. of a product distilled over the
range $64.5-66.5^\circ$ (2 mm.) and possessed a refractive index,
n_D^{25}, of 1.4145. This product, later prepared by a modified
procedure and analyzed, was 2-(5-acetoxy-4-methyl-1,3-dioxa-
hexyl)propane and the yield corresponded to 33% of the theo-
retical.

5-Acetoxy-4-methyl-1,3-dioxahexyl benzene. When sixty
grams of 2-chloromethoxy-3-acetoxybutane was added to a
solution of 33 g. of phenol in 250 ml. of anhydrous ethyl
ether and treated with 23.5 g. pyridine dissolved in 150 ml.
of ether according to the general procedure, crystalline
pyridine hydrochloride did not appear, but again, a syrupy
phase settled out. The reaction appeared to occur, for the
most part, in this syrup phase since the indicator which had
dissolved in it remained red throughout the reaction while
the hydrogen chloride liberated in the ether layer was easily
removed by the addition of the pyridine solution. When the
ether was volatilized from a sample of the ether layer the
small residue indicated the yield of product would be very
poor. This preparation was not pursued further, but the pro-

cedure was modified.

From the observations of the last two reactions it was apparent that the distribution of the concentrations of reagents between two phases was introducing complications in the reaction. Since chloroform is a solvent for pyridine hydrochloride as well as the various reagents used in the reaction, it was substituted for ethyl ether as the inert diluent so that a homogeneous reaction media might be obtained.

(2) Chloroform as the solvent. The appropriate alcohol or phenol was dissolved in chloroform and an equivalent amount of 2-chloromethoxy-3-acetoxybutane was added dropwise over a period of 2½ hours while stirring rapidly. The reaction mixture which was controlled at 25-30° contained a few crystals of methyl red to indicate the presence of free hydrogen chloride. A solution of pyridine (5% excess) in chloroform was added to remove the free hydrogen chloride as indicated by the methyl red. The reaction mixture was finally heated to 50° for fifteen minutes and then washed three.times with water and dried over Drierite. The chloroform was removed by distillation using a steam bath, and the product fractionated in vacuo. In almost all instances tested, the yields were good and there was little formation of by-products.

1-(5-Acetoxy-4-methyl-1,3-dioxahexyl)butane. Sixty grams of 2-chloromethoxy-3-acetoxybutane was added to 25.9 g. of n-butanol, according to the general procedure, and 27.5 g. of n-butanol,

pyridine dissolved in chloroform was added as required. Fractional distillation of the treated reaction mixture yielded 56.8 g. (78.4%) of crude 1-(5-acetoxy-4-methyl-1,3-dioxahexyl)-butane collected over the range 65-71° (1mm.). The physical constants of the purified product were: b.p. 69-71° (1mm.), n_D^{25} 1.4184, d_4^{25} 0.9520.

Analysis. Calculated for $C_{11}H_{22}O_4$: Saponification equivalent, 218; MR_D, 57.98. Found: Saponification equivalent, 219; MR_D, 57.74.

2-(5-Acetoxy-4-methyl-1,3-dioxahexyl)propane. In accordance with the general procedure, 60 g. of 2-chloromethoxy-3-acetoxybutane, when added to 21 g. of isopropyl alcohol dissolved in 250 ml. of chloroform and treated with 27.5 g. of pyridine in 150 ml. of chloroform, yielded 51 g. (75%) of 2-(5-acetoxy-4-methyl-1,3-dioxahexyl)propane. The distillation range was 53-58° (1mm.). The pure compound had the following constants: b.p. 55-57.5° (1mm.), n_D^{25} 1.4132, d_4^{25} 0.9599.

Analysis. Calculated for $C_{10}H_{20}O_4$: Saponification equivalent, 204; MR_D 53.31. Found: Saponification equivalent, 201; MR_D 53.31.

3-(5-Acetoxy-4-methyl-1,3-dioxahexyl)propene. The addition in the usual manner, of 60 g. of 2-chloromethoxy-3-acetoxybutane to 20.3 g. of allyl alcohol and treated with 27.5 g. of pyridine dissolved in 150 ml. of chloroform yielded 57.9 g. (86%) of crude 3-(5-acetoxy-4-methyl-1,3-dioxahexyl)propene, a

colorless oil of grape-like aroma which distilled at 81-85°
(5 mm.). The refractionated product had the following char-
acteristics: b.p. 83.5-85° (5 mm.), n_D^{25} 1.4258, d_4^{25} 0.9836.

Analysis. Calculated for $C_{10}H_{18}O_4$: Saponification equiv-
alent, 202; MR_D, 52.84. Found: Saponification equivalent,
200; MR_D, 52.94.

5-Acetoxy-4-methyl-1,3-dioxahexylcyclohexane. Cyclo-
hexanol (34.8 g.) was dissolved in 250 ml. of chloroform and
60 g. of 2-chlormethoxy-3-acetoxy butane and 27.5 g. of pyri-
dine dissolved in 150 ml. of chloroform were introduced
according to the general procedure. The yield of 5-acetoxy-
4-methyl-1,3-dioxahexyl cyclohexane was 54 g. (66.8%). The
product, a colorless oil of mild odor, had the following
physical constants: b.p. 86-88° (0.5 mm.), n_D^{25} 1.4443, d_4^{25}
1.0007.

Analysis. Calculated for $C_{13}H_{24}O_4$: Saponification equiv-
alent, 244; MR_D, 64.97. Found: Saponification equivalent,
241; MR_D, 65.07.

Approximately 10 g. of unreacted cyclohexanol was recovered
in this synthesis which indicated that some chloroether and
pyridine had combined.

1,2-bis(5-Acetoxy-4-methyl-1,3-dioxahexyl)ethane and 1-
hydroxy-2-(5-acetoxy-4-methyl-1,3-dioxahexyl)ethane. Ethylene
glycol (10.3 g.) was added to 250 ml. of chloroform. Solu-
bility was not complete. Fifteen grams of acetamide acted as

a mutual solvent and produced a homogeneous solution. A solution of 29 g. of pyridine and 5 g. of acetamide in 150 ml. of pyridine was used to remove the hydrogen chloride produced when 60 g. of 2-chloromethoyoxy-3-acetoxybutane was added to the glycol solution according to the general procedure. The reaction mixture was treated in the usual way, and fractional distillation yielded two products in addition to about 7 g. of unreacted ethylene glycol. The mono-condensation product, 1-hydroxy-2-(5-acetoxy-4-methyl-1,3-dioxahexyl)ethane distilled over the range 94-95° (0.5 mm.) and 14.5 g. (30.5%) was collected. It was a somewhat viscous, odorless, colorless oil which was soluble in water. The physical constants of the redistilled product were: b.p. 94-95° (0.5 mm.), n_D^{25} 1.4348, d_4^{25} 1.0706.

Analysis. Calculated for $C_9H_{18}O_5$: Saponification equivalent, 206; MR_D, 49.82. Found: Saponification equivalent, 205; MR_D, 50.13.

The di-substituted condensation product of the glycol, 1,2-bis(5-acetoxy-4-methyl-1,3-dioxahexyl)ethane was collected over the range 148-152° (0.5 mm). It, also was a somewhat viscous, colorless, odorless oil but it was insoluble in water. The physical constants were: b.p. 148-152° (0.5 mm), n_D^{25} 1.4360, d_4^{25} 1.0657. The yield was 23.4 g. (40.3%).

Analysis. Calculated for $C_{16}H_{30}O_8$: Saponification equivalent, 175; MR_D, 85.96. Found: Saponification equivalent, 173;

MR_D, 85.77.

4-Acetoxy-3-methyl-1,3-dioxahexylbenzene. Thirty-three grams of phenol was dissolved in 250 ml. of chloroform. Since the solution was acid to methyl red several indicators were tested which when dissolved in the phenol-chloroform solution would give a color change in the presence of free hydrogen chloride. A few crystals of the most successful, methyl violet-B, were used. The color change in the presence of excess hydrogen chloride was violet to light blue. Sixty grams of 2-chloromethoxy-3-acetoxybutane was added in accordance with the general procedure, and 27.5 g. of pyridine dissolved in 150 ml. of chloroform was added as required to maintain an intermediate blue violet color in the reaction mixture. After treating it in the customary manner, fractional distillation of the reaction mixture _in vacuo_ yielded, in addition to 20 g. of an unidentified oil distilling over the range 56-66° (1mm.), 39 g. (49.3%) of 4-acetoxy-3-methyl-1,3-dioxahexylbenzene. The distillation range was 111-117°. The physical constants which follow agreed well with those of the product prepared from sodium phenoxide: b.p. 114-116° (1 mm.), n_D^{25} 1.4820, d_4^{25} 1.0652.

Analysis. Calculated for $C_{13}H_{18}O_4$: Saponification equivalent 238; MR_D, 63.55. Found: Saponification equivalent, 236; MR_D, 63.90.

The product, a colorless, almost odorless oil, was poly-

TABLE V

PHYSICAL CONSTANTS OF SOME 5-ACETOXY-4-METHYL-1,3-DIOXAHEXANE DERIVATIVES.
(PREPARED FROM 2-CHLOROMETHOXY-3-ACETOXYBUTANE AND ALCOHOLS OR PHENOLS USING PYRIDINE AS A CONDENSING AGENT.)

$$CH_3CH(OAc)CH(CH_3)OCH_2OR$$

R	Yield %	b.p. °C.	mm.	n_D^{25}	d_4^{25}	Sapn. Equiv. Calc'd.	Sapn. Equiv. Obs.	MR_D Calc'd.	MR_D Obs.
CH_3CH_2-	65.0	46-9	1.5	1.4122	0.9737	190	187	48.70	48.81
$CH_3(CH_2)_3-$	78.4	69-71	1.0	1.4184	0.9520	218	219	57.98	57.74
$(CH_3)_2CH-$	75.0	55-7.5	1.0	1.4132	0.9599	204	201	53.31	53.31
CH_2CHCH_2-	86.0	83.5-5	5.0	1.4258	0.9836	202	200	52.84	52.94
Cyclohexyl	66.8	86-8	0.5	1.4443	1.0007	244	241	64.97	65.07
$-(CH_2)_2-$	40.3	148-52	0.5	1.4360	1.0657	175	173	85.96	85.77
$CH_2(OH)CH_2-$	30.5	94-5	0.5	1.4348	1.0706	206	205	49.82	50.13
C_6H_5-	49.3	114-6	1.0	1.4820	1.0652	238	236	63.55	63.90
meta-phenylene*	21.0	183-8	1.0	1.4710	1.0961	199	195	100.82	100.80

* Prepared from disodium resorcinate and 2-chloromethoxy-3-acetoxybutane.

merized with concentrated sulfuric acid. The reaction was instaneous and extremely exothermic, and a pink plastic mass was formed. The polymerization was moderated by heating, at 100°, several milliliters of 4-acetoxy-3-methyl-1,3-dioxahexylbenzene with several drops of water and 2-chloromethoxy-3-acetoxybutane as a source of hydrogen chloride. After one day the reaction mixture had set to a pliable, colorless gel which, when exposed to air became bright red and on further heating set to a hard, brittle red resin.

6. Reaction of Grignard reagents with 2-chloromethoxy-3-acetoxybutane.

Grignard reagents were prepared from bromobenzene and butyl bromide in the usual manner (34) and these were coupled with 2-chloromethoxy-3-acetoxy butane. The Grignard reagent was added to the chloroether rather than the more common reverse manner so that the chloroether would not encounter a high concentration of Grignard reagent. In this manner the reaction of the Grignard reagent with the acetoxy-group might be minimized.

2-Benzyloxy-3-acetoxybutane. Sixty grams of bromobenzene was dissolved in 150 ml. of anhydrous ethyl ether and this solution added slowly with stirring to 8.9 g. (10% excess) of magnesium ribbon in a 500 ml. 3-neck flask. The resulting solution of phenylmagnesium bromide was added dropwise while stirring to 60 g. of 2-chloromethoxy-3-acetoxybutane dissolved

in 150 ml. of ether. The rate of addition of Grignard reagent
solution was maintained so that the reaction mixture refluxed
gently. The reaction was instantaneous and two liquid phases
formed. After standing fifteen minutes, the mixture was
poured into 500 g. of ice and then acidified with 1:1 hydro-
chloric acid. The layers were separated and the aqueous phase
was extracted with ether and the ether layers combined. The
ether solution was then washed with water and dried over
Drierite. The ether was removed on a steam bath and the
benzene from excess Grignard reagent was distilled out. The
residual oil was fractionated by distillation in vacuo.
Approximately 5 g. distilled at 46-50° (1.5 mm.). The main
product then was collected over the range 90-93.5° (0.5 mm.).
The yield of crude 2-benzyloxy-3-acetoxybutane was 55.1 g.
(74.5%). The product, a colorless oil with a faint pleasant
odor, was redistilled and the physical data for the pure com-
pound follow: b.p. 94-96° (0.5 mm.), n_D^{25} 1.4858, d_4^{25} 1.0224.

Analysis. Calculated for $C_{13}H_{18}O_3$: Saponification equiv-
alent, 222; MR_D, 61.93. Found: Saponification equivalent,
220; MR_D, 62.23.

2-Amyloxy-3-acetoxybutane. Eight and nine-tenths grams
of magnesium ribbon was dissolved in a solution of 52.7 g. of
n-butyl bromide in 150 ml. of anhydrous ether. The solution
of butylmagnesium bromide was added slowly, with stirring, to
60.2 g. of 2-chloromethoxy-3-acetoxybutane. The reaction mix-

ture was stirred in an ice bath during the addition of the Grignard reagent and held an additional hour at 0°. It was poured into 500 g. of ice and acidified with 1:1 hydrochloric acid. The evolution of formaldehyde was noted which would indicate some of the chloromethoxy-group was unreacted. The ether was separated and the aqueous layer washed with fresh ether. The ether layer and washings were washed with water and then dried over Drierite. After removal of the ether by distillation from a steam bath, the residue was distilled through the Vigreux column in vacuo. No definite fractions could be obtained and the 53 g. of material was collected over the range 44-48° (0.5 mm.). The distillate was, however, resolved into four portions. Each portion was then fraction-ally distilled at atmospheric pressure. Again the fractiona-tion was very difficult. Approximately 15 g. was collected at 177-182° which might have been 2,3-butanediol monoacetate. Ten grams distilled over the range 196-210° and then 22 g. (31%) of a colorless, pleasant smelling oil, 2-amyloxy-3-acetoxy-butane, distilled over the range 210-213°. The physical data were: b.p. 210-213° (740 mm.), n_D^{25} 1.4170, d_4^{25} 0.8971.

<u>Analysis.</u> Calculated for $C_{11}H_{22}O_3$: Saponification equiv-alent, 202; MR_D 56.29. Found: Saponification equivalent, 203; MR_D 56.68.

VI. DISCUSSION

The excellent yields obtained in the conversion of 2,3-butanediol to 2-chloromethoxy-3-acetoxybutane by way of 4,5-dimethyl dioxolane is further highlighted by the difficulties encountered when the same chloroether is prepared by the more conventional route through the glycol monoacetate and its chloromethylation. The difficulty in separating mono-and di-acetates of glycols which was encountered in the monoester-ification of 2,3-butanediol with acetic acid is not peculiar to the latter, but is common to all glycols. This, of course, is due to the fact that the boiling point of an acetate ester and the corresponding alcohol do not differ markedly. The preparation of pure ethylene glycol monoacetate has attained industrial importance; the method of preparation however, is the reaction of acetic acid and ethylene oxide. A correspond-ing preparation of pure 2,3-butanediol monoacetate from 2,3-butylene oxide has been reported (131), but would be impract-ical if 2,3-butanediol is to be the starting material. The necessity of having a pure glycol monoacetate free of the diacetates as a starting material for the chloromethylation reaction is further emphasized by the proximity in boiling points of the chloromethyl ether and the acetate ester of the corresponding alcohols.

Although the difficulty was not observed when 2,3-butane-

diol monoacetate was converted to 2-chloro methoxy-3-acetoxy butane in carbon tetrachloride solution, one might anticipate the cleavage of the acetoxy group of the monoacetate by the hydrogen chloride. Lucas and Gould (70) reported the preparation of 2-chloro-3-butanol by the reaction of 2,3-butanediol diacetate in saturated aqueous hydrochloric acid. The presence of the nonaqueous carbon tetrachloride may have depressed this side reaction.

The reaction of 2-chloromethoxy-3-acetoxybutane with carboxylic acid anhydrides is a new reaction. The products are the 4-acetoxy-3-methyl-2-oxapentyl esters and the acyl halides derived from the acid anhydrides. The reaction is only applicable when the acyl halide is the lowest distilling component. Further investigation should indicate the possible extension of this reaction to other chloromethyl ethers and to α-chloroethers in general. The acyl halide is also obtained in excellent yield and the reaction might be applied in some special instance for preparation of the acyl halide from the anhydride.

The failure of bis(4-acetoxy-3-methyl-2-oxapentyl) phthalate to distil without decomposition is in agreement with the observation of Walker (127) who found that the simplest ester of this type, bis(2-oxapropyl)phthalate could not be distilled at 15 mm. without decomposition. It was noted in the experimental section that the decomposition occurred when the still

temperature reached 190-200°. The products of decomposition
were formaldehyde and phthalic anhydride. It may be noted that
this decomposition temperature corresponds to the temperature
at which phthalic acid loses water and forms phthalic anhydride.
The presence of a small amount of phthalic acid in the reaction
mixture is most likely and its decomposition may be supposed
to initiate the following chain reaction during distillation:

(1)
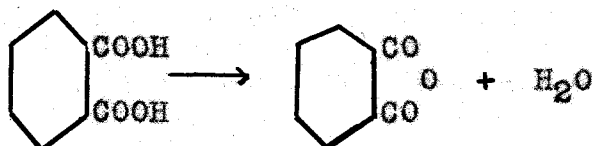
(2)
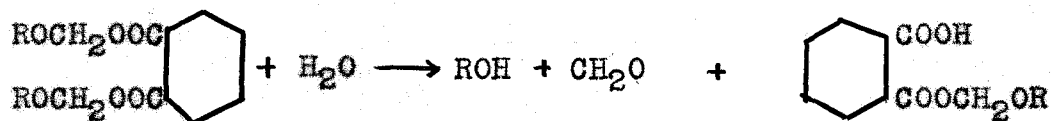
(3)
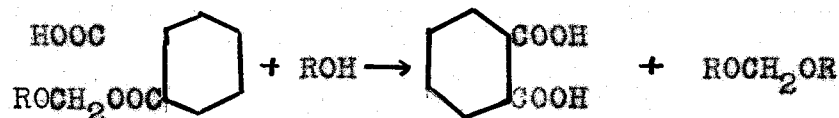
Should this hypothesis prove correct it might be possible to
avoid the decomposition by conducting the reaction in the
presence of anhydrous sodium acetate. The phthalic acid would
be converted to the stable sodium salt and acetic acid vola-
tilized from the still.

The method devised for the preparation of the lactone,
5,6-dimethyl-2-p-dioxanone is unique for lactones of this type.
As was described in the experimental section, Hollo(45) and
later Carothers and co-workers (13) prepared the similar unsub-
stituted lactone 2-p-dioxanone by distillation of the hydroxy

acid; water was eliminated during the distillation. Salmi,

Leimu and Kallio (96) prepared 2-p-dioxanone by dry distilla-

tion of the sodium salt of 2-chloroethoxy acetic acid. It was

most difficult to obtain a product free of traces of water by

the first method and the product of the latter preparation was

contaminated with traces of hydrogen chloride from pyrolysis.

The azeotropic distillation procedure described herein elim-

inated the last traces of water from the reaction mixture and

the ring closure, to form the lactone, proceeded through the

elimination of acetic acid from 2-carboxymethoxy-3-acetoxy-

butane. The acetic acid was also removed azeotropically prior

to the distillation of the product. Thus, the observation

that 5,6-dimethyl-2-p-dioxanone failed to suffer a high degree

of polymerization upon long standing might be due to the

absence of catalytic impurities in the product. Another pos-

sibility in this regard is the fact that the lactone described

in this work is one derived from a β-hydroxy acid in which the

hydroxyl is secondary and therefore less susceptible to ester-

ification.

Although the reaction of an α-chloroether with a sodium

alkoxide or phenoxide is a standard procedure for the prepara-

tion of mixed acetals, the acetoxy-group of the α-chloroether,

2-chloromethoxy-3-acetoxybutane introduced complications in the

reaction. Because an acetal is stable to alkalies, the general

method of preparation has been to add the chloroether to the
suspension or solution of the alkoxide. The susceptibility
of esters to condensation in the presence of sodium alkoxides
necessitated the reversal of the manner of addition. Never-
theless the yields of the desired products were poor. Although
the chloromethyl ether was not intentionally exposed to high
concentrations of alkali, low yields may be accounted for by
the local concentrations of sodium alkoxide produced because
it was necessary to introduce the latter as a concentrated
suspension rather than as a dilute solution.

The method finally devised for the preparation of mixed
acetals by the reaction of the alcohol or phenol with the
chloromethyl ether in chloroform solution, removing the hydro-
gen chloride with pyridine, gave excellent yields. The fact
that in most cases there was an absence of by-products, might
indicate the reaction could be carried out to obtain almost
quantitative yields. Interference by the acetoxy-group was
not observed. It must be pointed out that there are several
competing reactions in this process and only the proper rate
of addition of the reagents will give maximum yields. The
chloromethyl ether may react with either the alcohol or with
pyridine; also the latter may form salts with either hydrogen
chloride or the chloromethyl ether. It has been shown that
the affinity of the chloromethyl ether for pyridine is greater
than for alcohols in a competing reaction. Also the reaction

of pyridine with hydrogen chloride should proceed in preference to its reaction with the chloroether. From this it is apparent that a large concentration of unreacted 2-chloromethoxy-3-acetoxybutane must not be present in the reaction mixture. Furthermore, a sensitive method of determining when free hydrogen chloride is present in the reaction mixture would facilitate obtaining good yields of the desired mixed acetals. The use of methyl red for this purpose was not entirely satisfactory, especially in the later stages of the reaction when a color change was difficult to discern.

An extension of this procedure for producing mixed acetals to other more common α-chloroethers would indicate the relative value of this method when compared with the standard procedure of reacting the sodium alkoxide with the chloroether. The mixed phenyl formals can probably be best prepared by the first method discussed, i.e. from the chloromethyl ether and the sodium phenoxide. The phenyl formals have been shown to be very susceptible to polymerization in the presence of traces of mineral acids. It would be most difficult to avoid this acid condition when a free phenol is condensed with a chloromethyl ether.

A competitive reaction was expected when Grignard reagents were coupled with 2-chloromethoxy-3-acetoxybutane. Both the chloromethoxy and acetoxy-groups are capable of reacting with Grignard reagents. The good yield obtained when phenylmagnesium

bromide was coupled indicated that this reaction was favored over tertiary alcohol formation. Although the products were not studied in detail, the presence of unreacted chloromethoxy-groups after an equivalent amount of butylmagnesium bromide had been added indicated apparent consumption of the Grignard reagent in the competitive reaction. Further study might reveal more optimum conditions for coupling Grignard reagents with chloromethyl ethers in the presence of an ester group.

The steric configuration of the 2-chloromethoxy-3-acetoxy-butane and its derivatives was not considered in this investigation. According to the report of Neish and MacDonald (82), the 4,5-dimethyldioxolane prepared from meso-2,3-butanediol was the meso-isomer. If no inversion of configuration occurred when the dioxolane ring was opened, the 2-chloromethoxy-3-acetoxybutane used was the erythro isomer.

VII. SUMMARY

(1) 2-Chloromethoxy-3-acetoxybutane was prepared by the reaction of acetyl chloride and 4,5-dimethyl dioxolane. It was found that the reaction required a catalyst. Ortho-phosphoric acid was satisfactory.

(2) 2-Chloromethoxy-3-acetoxybutane was prepared from 2,3-butanediol monoacetate, formaldehyde and hydrogen chloride. An inert reaction medium, immiscible with water was required. Carbon tetrachloride was satisfactory.

(3) The conclusion was reached that 2-chloromethoxy-3-acetoxybutane could be prepared more satisfactorily from acetyl chloride and 4,5-dimethyl dioxolane than from 2,3-butanediol monoacetate, formaldehyde and hydrogen chloride.

(4) 2-Chloromethoxy-3-acetoxybutane reacted with the sodium salts of carboxylic acids and yielded a series of 4-acetoxy-3-methyl-2-oxapentyl esters. The products ranged in properties from a colorless, fluid oil to a white, low melting wax.

(5) The reaction of 2-chloromethoxy-3-acetoxybutane with carboxylic acid anhydrides has been investigated. The corresponding 4-acetoxy-3-methyl-2-oxapentyl esters and acyl chlorides were obtained in very good yields.

(6) 2-Chloromethoxy-3-acetoxybutane and cuprous cyanide yielded 2-cyanomethoxy-3-acetoxybutane. The latter was con-

verted to the lactone, 5,6-dimethyl-2-p-dioxanone in good yield. The lactone, which was unusually stable toward spontaneous polymerization, was converted by aqueous ammonia to the amide, 1-methyl-2-hydroxypropoxyacetamide.

(7) The sodium derivatives of several alcohols and phenols were condensed with 2-chloromethoxy-3-acetoxybutane. The mixed formals were obtained in relatively poor yields.

(8) A method has been devised for condensing alcohols with 2-chloromethoxy-3-acetoxy butane. Pyridine was added to remove the hydrogen chloride as it was formed. A chloroform solution provided a homogeneous reaction mixture which was essential for the attainment of good yields.

(9) A preliminary investigation of the coupling of Grignard reagents with 2-chloromethoxy-3-acetoxybutane has been made. 2-Benzyloxy-3-acetoxybutane and 2-amyloxy-3-acetoxy-butane were prepared.

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