

NEW ADDITION REACTIONS
OF ETHYLENE OXIDE

By

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INTRODUCTION

Since its discovery by Wurtz (105) in 1859, ethylene oxide has come to be a large-tonnage chemical with an annual production in the United States of about 700 million pounds (1). Of this amount about 615 million pounds is converted into ethylene glycol (1), much of which is used in permanent antifreeze preparations. The remaining 85 million pounds find uses in the manufacture of nonionic detergents and other materials which serve as chemical intermediates for other processes (1). In addition, a small amount is used as a sterilizing agent and fumigant (1).

The low cost, relative abundance, and reactivity of ethylene oxide make it a very attractive material for use in processes where the introduction of a $-\text{CH}_2\text{CH}_2\text{O}-$ group can be used to advantage. It is therefore not surprising that a great deal of work has been done to study reactions of ethylene oxide in the hopes of finding commercially useful products.

The purpose of the research covered by this thesis was to conduct exploratory studies of possible new syntheses involving ethylene oxide. To that end, two broad areas of study were chosen. The first of these involved the study of the addition of compounds containing no active hydrogen groups to ethylene oxide under conditions of acid catalysis, and the second consisted of the interaction of ethylene oxide with compounds thought capable of forming sodium enolates.

HISTORICAL

Preparation of Ethylene Oxide

The classical preparation of ethylene oxide as described by Wurtz (105) is the dehydrohalogenation of ethylene chlorohydrin. This remains as one of the principal industrial processes for the manufacture of the oxide.

The second major process for producing ethylene oxide is the air oxidation of ethylene over a silver catalyst. This process was discovered by Lefort (47,88,89) in 1931.

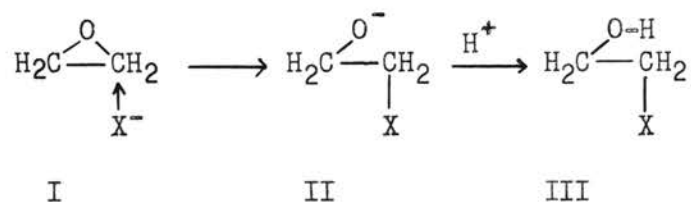
Both processes have been reviewed by Curme and Johnston (18) and by Goldstein (31).

Physical Properties

Ethylene oxide is a mobile liquid boiling at 10.7°C. As a liquid it is miscible in all proportions with water and forms azeotropic mixtures with hydrocarbons boiling in the range from -7 to +36° (34,35). Liquid ethylene oxide cannot be detonated, but the pure vapor is flammable and explosive, as are air-ethylene oxide mixtures. A comprehensive discussion of the physical properties of ethylene oxide can be found in the American Chemical Society Monograph Number 114, Glycols (18).

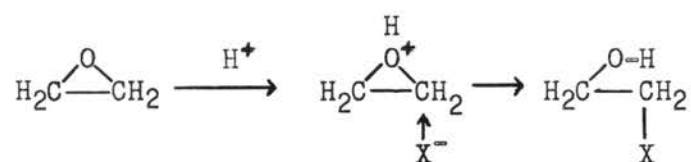
Mechanism of Reaction of Ethylene Oxide

The reaction of ethylene oxide invariably involves the opening of the oxide ring. The mechanism by which this occurs is a nucleophilic displacement on carbon, with the ring oxygen atom as the displaced group (25). Such a displacement is illustrated below.



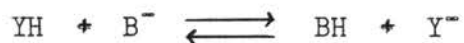
Displacement on the oxide itself gives II as the intermediate, which upon acquiring a proton gives III as the final product.

The displacement may also take place on the much more reactive conjugate acid of the oxide as illustrated by the following equation.



As a consequence of the ready attack on the conjugate acid of the oxide, acid catalysis of reactions of the oxide is very common.

If the attacking nucleophilic agent, as symbolized by YH, is capable of reacting with a base B⁻ so as to convert at least part of YH to a more strongly nucleophilic agent Y⁻, then the attack on ethylene oxide will be carried out by Y⁻. An equation for the formation of Y⁻ by the reaction of YH with base B⁻ is shown below.



It is in this manner that the observed base-catalyzed reactions of ethylene oxide can be explained.

Reactions of Ethylene Oxide

The reactions of ethylene oxide can be divided into two classes. The first of these encompasses the active-hydrogen compounds, in which reaction takes place in the manner shown by the following equation.



The other class involves the reactions of compounds not containing

active hydrogen with ethylene oxide. This is illustrated below for a general case.



Both of these classes are illustrated below by a brief review of the literature dealing with reactions of ethylene oxide. A comprehensive survey and bibliography of a large section of the ethylene oxide literature up to 1951 has been made by Durr (24). A general discussion of these and additional references follows.

Reactions with Compounds Containing Active Hydrogen

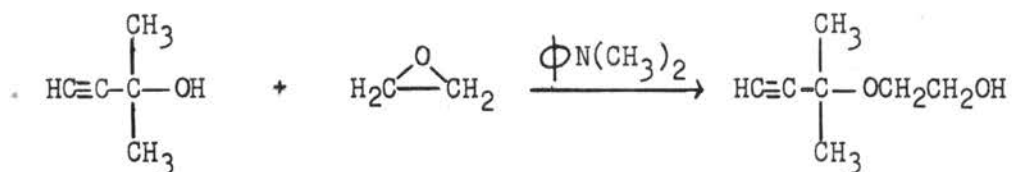
Water. Ethylene oxide reacts with water to yield ethylene glycol, which in turn can yield some diethylene glycol, triethylene glycol, and higher polyethylene glycols by consecutive reactions. The hydrolysis may be carried out in the liquid phase in the presence of trace amounts of sulfuric, hydrochloric, or oxalic acids. Alternatively, a catalytic vapor-phase process using catalysts such as the oxides of aluminum, titanium, zirconium, thorium, tungsten, molybdenum, or vanadium may be used.

Alcohols and Phenols. The reaction of alcohols and phenols with ethylene oxide is exemplified by the following general equation in which R may be aliphatic or aromatic.

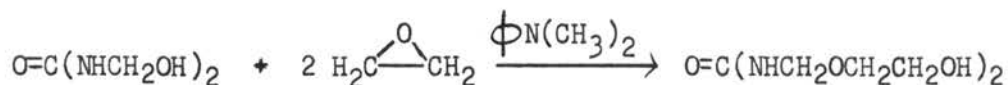


At temperatures of 200-220° and pressures up to 45 atmospheres, the reaction proceeds non-catalytically at a relatively low rate. However, reactions involving catalysis by acids, such as boron trifluoride, sulfuric acid, stannic chloride, and aluminum hydrosilicate, or bases, such as sodium or potassium hydroxide, are much more practical.

Recent work includes further studies on the conversion of ethylene glycol to diethylene glycol (68), which can then be converted to triethylene glycol in 98% yield by treatment with more ethylene oxide (39). Lange and Wahl (46) have prepared the N-acyl derivatives of 5-amino-3-oxa-1-pentanol and 8-amino-3,6-dioxa-1-octanol by treatment of the N-acyl derivative of ethanolamine with ethylene oxide. Petrov and Lagucheva (76) report the dimethylaniline-catalyzed reaction of ethylene oxide with dimethylethynylcarbinol to yield the mono-dimethylethynylcarbinyl ether of ethylene glycol. This reaction is illustrated below.



Another dimethylaniline-catalyzed reaction described by Petrov (75) is the reaction of 1,3-bis-(hydroxymethyl)urea as shown below.

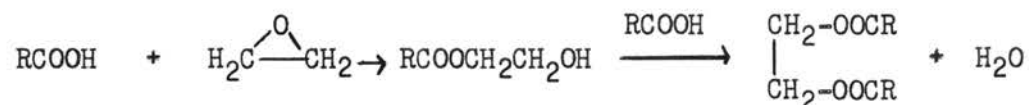


The preparation of the alpha-methylbenzyl ether of ethylene glycol by the sodium cyanide-catalyzed reaction of alpha-methylbenzyl alcohol with ethylene oxide is reported by Britton and Sexton (8). Aqueous alkali-catalyzed reactions are reported by Senju (83) for the hydroxyethylation of cellulose and by Kosmin (41) for the reaction of a hydroxymethylmelamine with ethylene oxide. Other studies with alcohols have been reported by Cohen (16) and with phenols by Miller, Bann and Thrower (60).

The reaction of tert-butyl hydroperoxide with ethylene oxide produces beta-hydroxyethyl-tert-butyl peroxide in a 30% yield (4).

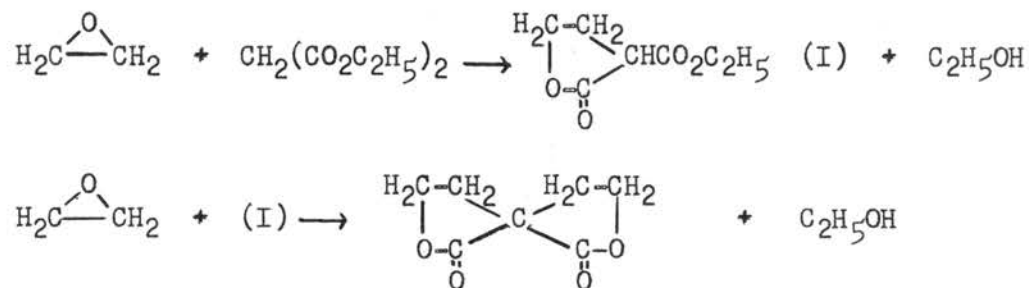
Carboxylic Acids. Carboxylic acids, both monobasic and dibasic,

react with ethylene oxide to form ethylene glycol mono- or diesters of the acids as shown below.



Where R is large (of the order of C₁₇) and a large excess of ethylene oxide is present it is possible to form high-molecular-weight carboxylic acid esters of polyethylene glycol which can be used as surface-active agents. Acid catalysis is generally used, although a non-catalyzed high-temperature process has been reported. Two recent patents (42,43) serve to supplement Durr's (24) review of these reactions.

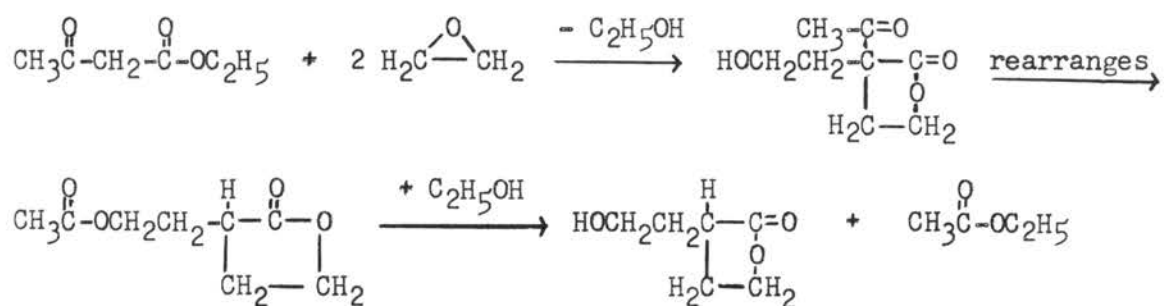
Carboxylic Esters Containing Active Methylene Groups. Reaction of the sodium enolate of diethyl malonate with ethylene oxide to yield the ethyl ester of butyrolactone-alpha-carboxylic acid was first reported by Traube and Lehmann (95,96). Pakendorf (69) reported yields up to 86% of the dilactone of 1,5-dihydroxypentane-3,3-dicarboxylic acid prepared by the interaction of ethylene oxide and diethyl malonate in the presence of piperidine, diethylamine or triethanolamine. The reaction can be represented by the following equation.



In addition to the main product described above, Pakendorf (70) also claimed to have obtained some alpha-(2-hydroxyethyl)butyrolactone from the ethylene oxide-malonic ester reaction. The condensation of ethylene oxide with substituted malonic esters (such as the ethyl- and

isoamylmalonic esters) has been carried out by Pakendorf and Machus (71). Other similar studies on the opening of the ethylene oxide ring by sodium malonic esters have been made by Rothstein (80) and McRae (59).

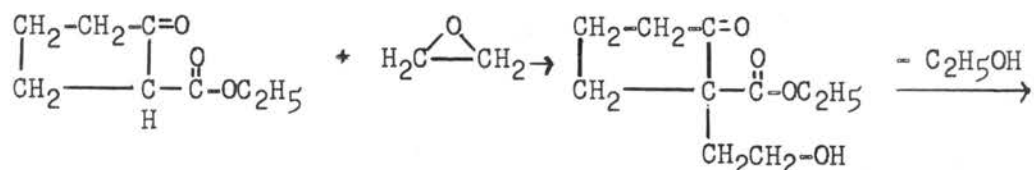
Pakendorf and Machus (72) report the piperidine-catalyzed reaction of ethylene oxide and ethyl acetoacetate to yield alpha-(2-hydroxyethyl)-butyrolactone and offer the following sequence of reactions to explain it.

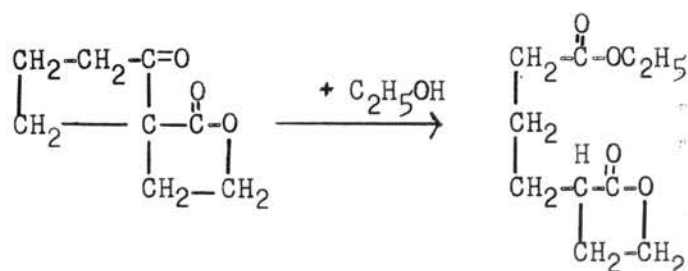


The rearrangement is said to be a rare example of an acetyl migration from a carbon to an oxygen atom.

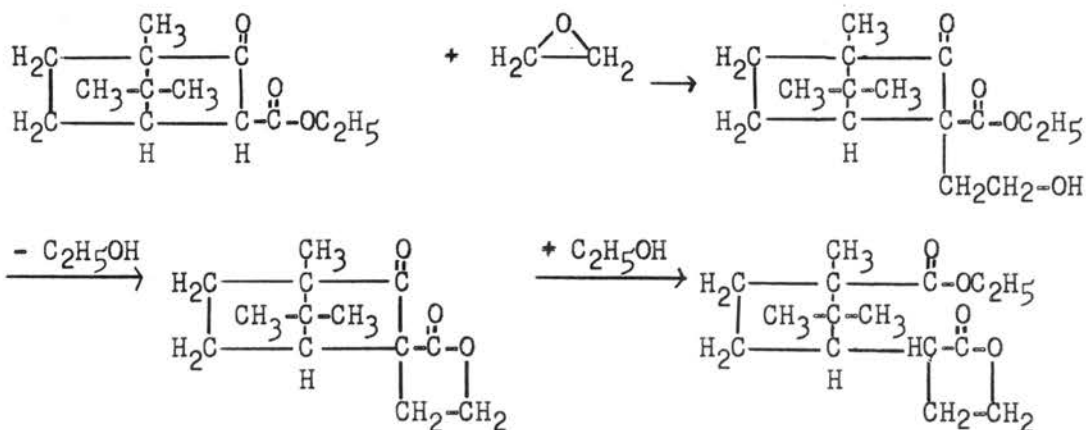
A good yield (60%) of alpha-acetylbutyrolactone of high purity has been obtained by Johnson (40) from ethylene oxide and ethyl acetoacetate in an aqueous solution of an alkali metal hydroxide catalyst.

The reaction of ethylene oxide with cyclic beta-keto esters such as 2-carbomethoxycyclopentanone and 2-carbomethoxy-6-methylcyclohexanone has been described by Pakendorf and Machus (73) to proceed as shown below.





Gandini and Sparatore (29) report the reaction of ethyl campho-carboxylate with ethylene oxide to yield alpha-(3-carbethoxy-2,2,3-trimethylcyclopentyl)butyrolactone. As can be seen below, the postulated series of reactions is similar to those described by Pakendorf and Machus for 2-carbethoxycyclopentanone.



Hudson and Hauser (36) report the reaction of ethylene oxide with the sodium enolate of ethyl isobutyrate to give a 55% yield of alpha, alpha-dimethylbutyrolactone. The enolate was formed by the action of triphenylmethylsodium on the ethyl isobutyrate.

Sulphydryl Compounds. Hydrogen sulfide reacts with ethylene oxide to form 2-mercaptoethanol. Catalysts for this reaction reported in the literature include mineral acids, chlorides of aluminum and heavy metals, and glass beads moistened with the reaction product. A recent patent (104) describes the passage of ethylene oxide and a large excess of hydrogen sulfide into preformed thiodiglycol or preformed 2-mercaptoethanol at 30-60° to give good yields of 2-mercaptoethanol. Passage of

ethylene oxide into an aqueous solution of sodium sulfide followed by treatment with sulfuric acid is reported to yield dithiodiglycol (6). Vapor-phase reactions in the temperature range of 200 to 450° over ferric or aluminum sulfide catalysts yield 2-mercaptoethanol. However, when aluminum oxide is used as the catalyst, mixtures containing such compounds as thiophene, ethanethiol, acetaldehyde, 1,4-dioxan, 1,4-thioxan, and 1,4-dithian are obtained. Recent work in this area of study is reported by Yurev and Novitskii (107).

Mercaptans react with ethylene oxide to form 2-hydroxyethyl thioethers. Catalysis by bases such as sodium methoxide has been described for these reactions. A recent patent (3) describes the removal of mercaptans from light hydrocarbons by treatment with ethylene oxide to form condensation products with the mercaptans. The condensation products are higher-boiling than the charge and may be separated by distillation.

Treatment of 2-mercaptobenzothiazole with ethylene oxide in the presence or absence of catalysts such as activated carbon or alkali yields 2-(2-hydroxyethylmercapto)benzothiazole (23). Passage of ethylene oxide into an aqueous sodium bicarbonate solution of 2,4-dinitrothiophenol yields 2-(2,4-dinitrophenylthio)ethanol, which when dissolved in alcohol and treated with potassium hydroxide at room temperature yields ethylene sulfide and the potassium salt of 2,4-dinitrophenol (17).

Reactions of ethylene oxide with carbothiolic acids to yield 2-hydroxyethyl esters, and with alkali acid sulfites to give beta-hydroxyethanesulfonates have been noted in the literature.

Ammonia and Amines. Ammonia and amines constitute one of the

largest classes of compounds which react with ethylene oxide. Treatment of dilute or concentrated ammonia solutions with ethylene oxide yields mono-, di- and triethanolamines, the proportions of the products obtained depending on the proportion of the reactants used. Durr (24) lists more than twenty references dealing with the preparation of ethanolamines and their further reaction with ethylene oxide to yield mono-, bis-, and tris(2-hydroxyethyl)ethers of triethanolamine. Recent patents in this field have been issued to Moren (62) and Huscher (37).

Vapor-phase reactions of ethylene oxide with ammonia over aluminum oxide, as catalyst, at 300-450° are reported to yield pyridine, picolines and ethanolamines as well as acetaldehyde, carbon monoxide, carbon dioxide, and hydrogen (54,55,106). Use of a mixture of chromic oxide and aluminum oxide at 400-450° with various ratios of ethylene oxide and ammonia yield a mixture consisting of pyrrole and pyridine derivatives and some ethanol (52). Malinovskii and Baranov (49) report that when magnesium oxide is used as catalyst in the processes described above a mixture of 2-methyl-1,3-dioxolane, pyrrole, and picolines is obtained, whereas when zinc oxide is used, acetaldehyde, ethanol, ethanolamine, ethylene, carbon monoxide, and carbon dioxide (but no heterocyclic compounds) are obtained.

Primary and secondary amines can be condensed with ethylene oxide to yield the corresponding alkyl- and arylamino alcohols. The course of the reaction is invariably the same, with the hydrogen of the amine going to the oxygen and the nitrogen uniting with the beta carbon of the ethylene oxide unit. Publications since 1951 dealing with primary aromatic amines (77,108) and secondary aliphatic amines (10,56) have been noted. Malinovskii and Morgum (53) have reported that the vapor-phase reaction of aniline and ethylene oxide over a chromic oxide-

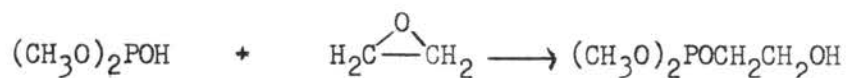
aluminum oxide catalyst at 400-450° gives a mixture containing quinaldine, quinoline, 3- and 4-methylquinoline, 2-phenylpyrrole, 2-hydroxyethylaniline, and traces of indole.

Other types of compounds having an active hydrogen bonded to nitrogen which react with ethylene oxide include imines, amino esters, hydrazines, amides, imides, and guanidines. A bibliography of published work covering these classes is available (24).

Hydrogen Halides and Other Acids. Ethylene oxide reacts rapidly with hydrogen halides in aqueous solution to yield the corresponding halohydrins. Perchloric and periodic acids react with the oxide to yield the hydroxyethyl perhalogenates, which yield the halohydrin upon reduction. Reaction of the halides of aluminum, chromium, iron, thorium, and zinc in dilute solution with ethylene oxide yields the colloidal hydrous metal oxide and ethylene halohydrins. Other metal halides which have been similarly studied include those of magnesium, tin, manganese, and copper.

Heating ethylene oxide with anhydrous hydrogen cyanide yields ethylene cyanohydrin. Aqueous solutions of alkylamines (11) and aqueous suspensions of the oxide, hydroxide, or cyanide of magnesium have been used as catalysts for this reaction. The vapor-phase reaction of hydrogen cyanide and ethylene oxide over aluminum oxide at 200° yields acrylonitrile whereas if silicon dioxide is used as the catalyst, appreciable amounts of succinonitrile are produced as well.

Sulfonic acids react with ethylene oxide to produce 2-hydroxyethyl sulfonates. Dimethyl or diethyl phosphites (79) react in a similar manner in the presence of boron trifluoride etherate as catalyst.



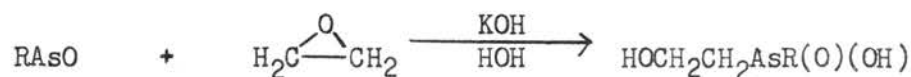
Nichols, Magnusson and Ingham (65) report that the reaction of ethylene oxide and nitric acid in the presence of aqueous solutions of nitrate ion yields 2-hydroxyethyl nitrate. The yield of nitrated products was promoted by the high concentration of nitrate ion. Other epoxides are reported to react in a similar manner. A Japanese patent (94) reports the reaction of ethylene oxide and nitric acid to give good yields of glyoxal and 1,2-dinitroethane, but such a result appears to be rather unlikely.

Hydrocarbons. Aromatic hydrocarbons react with ethylene oxide under Friedel-Crafts conditions to yield beta-arylethanols. The consecutive reactions leading to sym-diarylethanes usually associated with the severe conditions of this reaction are greatly repressed by maintaining temperatures of the order of 5-10°. Recent publications dealing with the beta-hydroxyethylation of benzene, toluene, and ortho- and para-xylenes have been noted (33,85).

Miscellaneous. Phosphine reacts with ethylene oxide to yield the expected mono-, bis-, and tris-(2-hydroxyethyl)phosphines. Diphenylarsine, however, gives only small amounts of 2-(hydroxyethyl)diphenylarsine.

Diborane and ethylene oxide react at -80° to form diethoxyborine and a polymer of the type $H(CH_2CH_2O)_nBH_2$ (92).

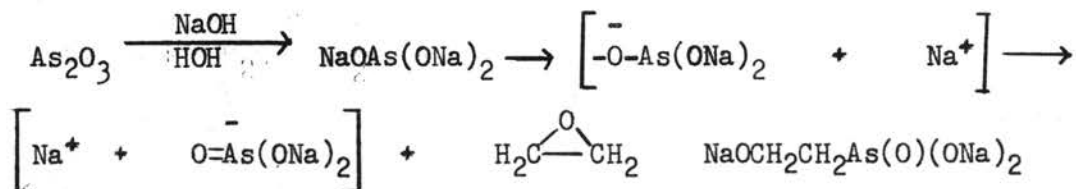
Ethylene oxide is reported to react with arsenous acid (12) to yield 2-hydroxyethanearsonic acid and with the salts of alkyl- and aryl- arsonous acids (44) to give the reaction illustrated below where R is methyl, ethyl, or phenyl.



A mechanism suggested by Chelintsev and Kuskov (12) explains the

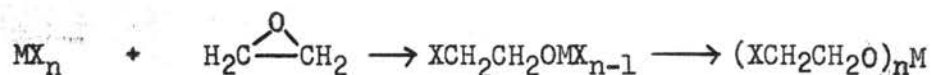
alkylation on the basis of a tautomeric change of the acid ions involved.

Their mechanism is illustrated below.



Reactions with Compounds Containing No Active Hydrogen

Halogens and Active Halides. Non-metallic halides react with ethylene oxide according to the following general equation.

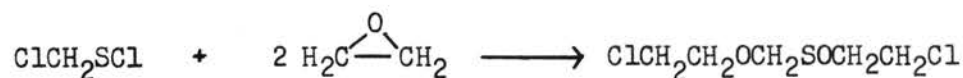


The ratio of ethylene oxide to the halide controls the extent of 2-haloethylation. The literature records reactions of this type for PCl_3 , PCl_5 , PBr_3 , POCl_3 , S_2Cl_2 , AsCl_3 , $\text{C}_6\text{H}_5\text{AsCl}_2$, SiCl_4 and a number of chlorosilanes (24,86). The phosphites produced are readily isomerized by heat to phosphonic esters of the type $\text{XCH}_2\text{CH}_2\text{PO}(\text{OCH}_2\text{CH}_2\text{X})_2$.

The reaction of ethylene oxide with diethyl chlorophosphate to form diethyl 2-chloroethyl phosphate followed by dehydrohalogenation to yield diethyl vinyl phosphate has been described by Upson (97).

Malinovskii (48) reports the reaction of ethylene oxide with sulfur chloride to give the 2-chloroethyl ester of chlorosulfonic acid. The bis-(2-chloroethyl)sulfate was not obtained. Similarly, the reaction of ethylene oxide with phosgene (51) is reported to yield* only the 2-chloroethyl chloroformate with no bis-(2-chloroethyl)carbonate detected among the reaction products. However, the preparation of bis-(2-dichloroethyl)sulfite in 83% yield from ethylene oxide and thionyl chloride has been described by Pechukas (74). The acid chloride of diethyl phosphite reacts as expected with ethylene oxide to yield 2-chloroethyl diethyl phosphite (79). Ethylene oxide reacts with chloromethane-

sulfenyl chloride to yield 2-chloroethyl 2-chloroethoxymethanesulfenate as shown below (7).

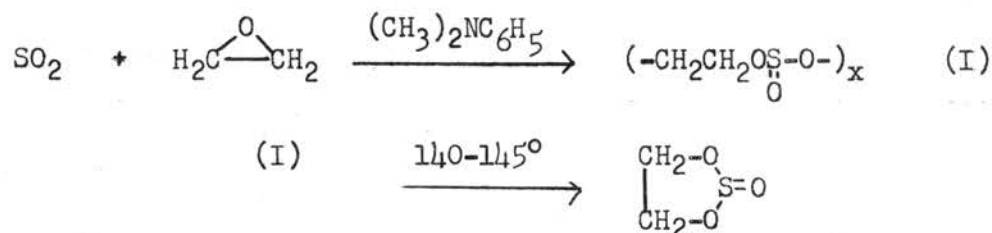


Nitrosyl chloride is reported to yield 2-chloroethyl nitrite when treated with ethylene oxide (50).

Acyl halides react as expected with ethylene oxide to yield the 2-haloethyl esters. Methyl 2-chloroethyl formal results from the reaction of ethylene oxide with the active halogen of chloromethyl ether.

Acid Anhydrides. Acid anhydrides, such as acetic anhydride, react with ethylene oxide to form diesters of ethylene glycol, such as ethylene glycol diacetate. The glycol diacetate can be combined further with ethylene oxide at elevated temperature and pressure and in the presence of the chlorides of zinc, tin or nickel as catalysts to give the diacetates of di-, tri- and polyethylene glycols (63). Reactions between ethylene oxide and phthalic and succinic anhydrides are also noted in the literature.

Sulfur dioxide (the anhydride of sulfurous acid) reacts with ethylene oxide in the presence of a tertiary amine to give a polymer, which upon being heated at 140-150° gives the monomer, glycol sulfite (87).



Woodstock (103) reports the reaction of ethylene oxide with phosphorus pentoxide and phosphorus pentasulfide in chloroform to yield polymeric materials of uncertain structure.

Aldehydes, Ketones, and Acetals. Aldehydes and ketones react with

ethylene oxide in the presence of Lewis acids to yield 1,3-dioxolanes. Dermer and Durr (21) have shown that acetals add to ethylene oxide in the presence of boron trifluoride. Thus methylal and ethylene oxide yield $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{OCH}_3$ and $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{OCH}_3$. Similarly the ethylene oxide-ethylal pair yields $\text{C}_2\text{H}_5\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OC}_2\text{H}_5$ and dimethyl acetal-ethylene oxide yields $\text{CH}_3\text{OCH}(\text{CH}_3)\text{OCH}_2\text{CH}_2\text{OCH}_3$.

Organometallic Compounds. In general, ethylene oxide reacts with alkyl or aryl Grignard reagents to form primary alcohols containing two more carbon atoms than the reagents. A recent patent (67) describes the reaction of ethylene oxide with benzylmagnesium chloride to yield 3-phenylpropyl alcohol. However, Huston and D'Arcy (38) report that the reaction of ethylene oxide with methylmagnesium iodide results in explosion and the reaction with other alkylmagnesium iodides yields the alcohol and ethylene iodohydrin. Gaylord and Becker (30) have prepared an extensive review, including 235 references, of the reaction between Grignard reagents and compounds containing the oxirane ring.

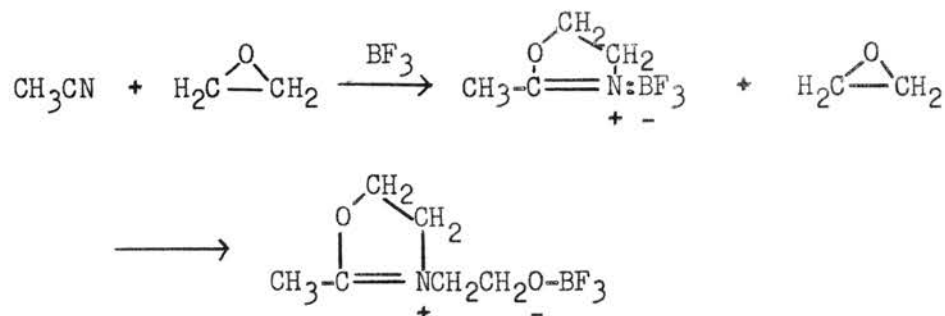
Other organometallic compounds which have been caused to react with ethylene oxide include phenylsodium and para-tolylsodium which yield the corresponding 2-arylethanol. Ethylene oxide and alpha-picolyl-lithium react in a similar manner. Schick and Hartough (81) have extended this reaction to include thienyl- and substituted thienylsodium compounds.

The reaction of ethylene oxide with the stilbene-disodium adduct in 1,2-dimethoxyethane yields up to 35% 3,4-diphenyl-1,6-hexanediol (9).

Miscellaneous Compounds

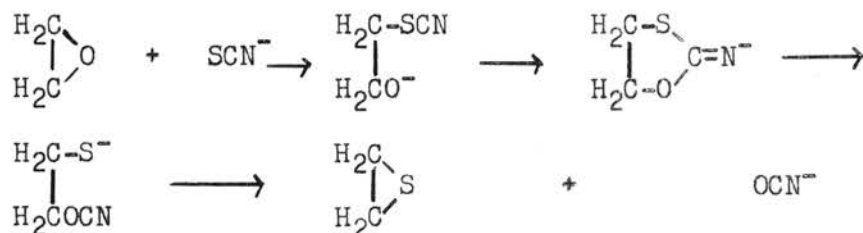
The boron trifluoride-catalyzed reaction of ethylene oxide with acetonitrile gives 2-methyl-1,3-oxazoline in yields up to 10% on occasion (86). The reaction is not reproducible in that the oxazoline

apparently undergoes a consecutive reaction with ethylene oxide to yield a choline-like salt which was not identified.



Miura (61) reports that the treatment of a sodium nitrite solution with ethylene oxide and carbon dioxide at 25-30° gives an 85% yield of 2-nitroethanol. The treatment of ethylene oxide simultaneously with a stream of ethylene and bromine to give BrCH₂CH₂OCH₂CH₂Br and BrCH₂CH₂OCH₂CH₂OCH₂CH₂Br has been described by Nesmeyanov, Sazonova, and Vasil'eva (64). A similar reaction is said to occur when propylene, isobutylene or cyclohexene is used in place of ethylene.

Several recent publications deal with the formation of ethylene sulfides by the interaction of an epoxide with an alkali thiocyanate. Recent studies of this reaction by van Tamelen (98) and Price and Kirk (78) support the mechanism which was proposed by Ettliger (26) and which is illustrated below.



Other related recent work deals with the interaction of ethylene oxide and thiourea to yield ethylene sulfide (28).

Polymerization of ethylene oxide to such materials as 1,4-dioxan and polyethylene glycols is an important reaction commercially. Good

reviews of ethylene oxide polymerization products and processes are available (18,31). A relatively recent patent deals with the copolymerization of ethylene oxide with ethylene in the presence of catalysts such as benzalazine to yield polymers, suitable for use as lubricating oil additives, containing 3-50 moles of ethylene per mole of ethylene oxide (15).

Ethylene oxide also undergoes thermal isomerization to acetaldehyde at 300-400°. Under the influence of dehydrating catalysts such as activated alumina, phosphoric acid or metallic phosphates the isomerization takes place at lower temperatures (150-300°). Goldstein (31) presents some discussion of possible mechanisms involved in such an isomerization.

EXPERIMENTAL - PART A

Preparation of Methoxymethyl Acetate and Methylene Diacetate

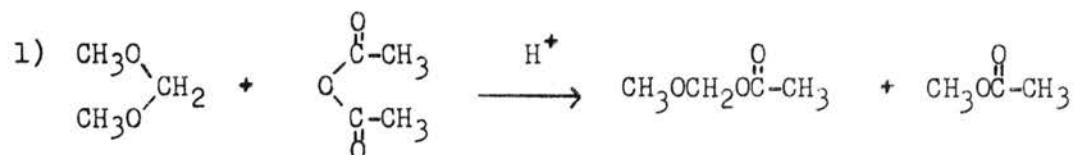
Introduction

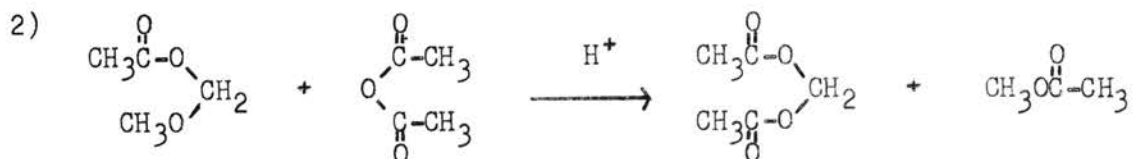
The work discussed in this section arose from the need to prepare a supply of methoxymethyl acetate and methylene diacetate for use in the study of acid-catalyzed reactions of ethylene oxide with esters. Although both of these compounds are known, their classical preparation is open to some criticism.

The interaction of chloromethyl methyl ether with sodium acetate, as reported by Friedel (27) and others (14,101,102), to yield methoxymethyl acetate has its disadvantage in the relatively high cost of chloromethyl methyl ether. The preparation of methylene diacetate as set forth by Descude (22) and confirmed by others (90,91) involves the heating of an equimolar mixture of acetic anhydride and formaldehyde (as paraformaldehyde) in the presence of an acid catalyst such as zinc chloride. In this case the reagents are cheap and readily available but the method suffers from the disadvantage of producing di- and other polymethylene diacetates in addition to the desired methylene diacetate.

It was thought that both of these compounds could be prepared from methylal and acetic anhydride under the influence of acid catalysts.

Equations for the expected reactions are:





A survey of the literature showed no examples of methylal-acid anhydride reactions to give the products discussed above. However, Senkus (84) did obtain reactions of this general type when he carried out the sulfuric acid-catalyzed condensation of acetic anhydride with 1,3-dioxolane and 1,3-dioxan to obtain respectively 2-oxa-1,4-butane-diol diacetate and 2-oxa-1,5-pentane-diol diacetate. Baum and Hennion (5) treated ketals with acetic anhydride but not under conditions of acid catalysis and did not obtain products of the type under consideration.

Procedure and Results

Methoxymethyl Acetate

Preliminary experiments indicated that refluxing an equimolar mixture of acetic anhydride and methylal with a trace of acid catalyst followed by destruction of the catalyst with a base and distillation of the mixture would give satisfactory yields of methoxymethyl acetate. Methanol-free methylal and reagent grade acetic anhydride gave the best results but the use of the methylal-methanol azeotrope and technical grade acetic anhydride gave almost as satisfactory yields. The cheaper reagents were used except where noted otherwise for all the work described in this section. The detailed procedure given below can be considered typical.

Methylal-methanol azeotrope (83 g., equivalent to one mole of methylal) and acetic anhydride (103 g., 1 mole) were added to a 500-ml. round-bottom flask equipped with a reflux condenser. Two drops of concentrated sulfuric acid were added as catalyst. The mixture warmed up and maintained itself at a gentle reflux for about 30 minutes and then refluxing was continued on a steam bath for an additional 30 minutes. After the solution had cooled to room temperature it was treated with a slurry of about 10 g. of sodium bicarbonate in 20 ml. of water to neutralize the acid catalyst. After about 30 minutes, 20 g. of anhydrous sodium carbonate were added to dehydrate the solution and the mixture was allowed to stand overnight. The solids were filtered off and washed with about 20 ml. of methylal-methanol azeotrope. The combined filtrates were distilled at atmospheric pressure through a Todd column. In addition to methylal-methanol azeotrope and methyl acetate, 80 g. (80% of theory) of methoxymethyl acetate were obtained, boiling from 116 to 118°.

Physical constant determinations on a redistilled portion of methoxymethyl acetate gave the following results.

Boiling range	117-118°/740 mm.
Refractive index	n_D^{20} 1.3830
Density	d_{20} 1.0227
Calculated molecular weight	104.1
Experimental molecular weight	114 (Avg.)
Calculated molar refraction	23.76
Experimental molar refraction	23.75

The molecular weight was determined by the standard Beckmann freezing-point-depression method using cyclohexane as the solvent (20). The calculated molar refraction was obtained by using the atomic refraction values published by Vogel (99) in conjunction with the Lorenz-Lorentz equation. It was found that the use of the value of an acetal oxygen rather than an ether oxygen gave a molar refraction value which was in better agreement with the experimental molar refraction.

A study of other acid catalysts showed that 1 drop of anhydrous stannic chloride, 2 drops of commercial boron trifluoride etherate or 0.5 ml. of 85% phosphoric acid could be used in place of the specified amount of sulfuric acid without affecting the yield of product. On the other hand, use of up to 2 ml. of 12N hydrochloric acid did not catalyze the reaction. Concentrations of catalyst greater than those indicated may be used but such a practice is not suggested since it causes the reaction to proceed with extreme vigor and makes it difficult to control.

After the reaction is complete, the acid catalyst can be destroyed with a variety of bases such as sodium or potassium carbonate or sodium bicarbonate. The bases can be used either as the solids, in the form of slurries, or as concentrated solutions.

Methylene Diacetate

It was thought that the preparation of methylene diacetate could be accomplished by the acid-catalyzed reaction of an equimolar mixture of acetic anhydride and methoxymethyl acetate or of a mixture consisting of 2 moles of acetic anhydride and 1 mole of methylal. Both of these proved feasible.

A much higher concentration of acid catalyst was required for the conversion of either methylal or methoxymethyl acetate to methylene diacetate than was required for the formation of methoxymethyl acetate from methylal. Treatment of a mixture of 2 moles of acetic anhydride and 1 mole of methylal with a few drops of sulfuric acid as catalyst resulted only in the formation of methoxymethyl acetate. Addition of 5 ml. of sulfuric acid to this mixture served to complete the reaction with the formation of methylene diacetate. Similarly the treatment of 1 mole of acetic anhydride and 1 mole of methoxymethyl acetate with 5 ml. of sulfuric acid resulted in the formation of methylene diacetate. Detailed procedures, which can be considered typical, for both of these methods follow.

Method I

Methoxymethyl acetate (104 g., 1 mole) and acetic anhydride (100 ml., 1 mole) were added to a 500-ml. round-bottom flask equipped with a reflux condenser. Concentrated sulfuric acid (5 ml., 0.1 mole) was added as catalyst. After the initial reaction had subsided, the mixture was heated on a steam bath for an hour.

After the mixture had cooled to room temperature, it was poured into 100 ml. of water and treated with small portions of solid sodium bicarbonate until effervescence ceased. The mixture was then extracted with three 50 ml. portions of ethyl ether.

The ether extracts were combined, dried over anhydrous sodium sulfate and distilled. After the ether and methyl acetate had been removed, 94 g. (70% of theory) of methylene diacetate, boiling at 166-169°, were received.

Method II

Methylal-methanol azeotrope (90 ml., 1 mole) and acetic anhydride (200 ml., 2 moles) were added to a 500-ml. round-bottom flask equipped with a reflux condenser. Concentrated sulfuric acid (3 drops) was added as catalyst. After the initial reflux had subsided and the mixture allowed to stand an additional 30 minutes, 5 ml. (0.1 mole) of concentrated sulfuric acid were added to aid in the second conversion. After the vigor of the reaction had again subsided, the mixture was refluxed on a steam bath for an hour and then allowed to cool to room temperature.

The mixture was poured into 100 ml. of water and treated with small portions of solid sodium bicarbonate until effervescence ceased. The mixture was then extracted with three 50-ml. portions of ethyl ether, and the extracts were combined, dried over anhydrous sodium sulfate, and distilled.

After the ether and methyl acetate had been removed, 66 g. (50% of theory) of methylene diacetate, boiling range 166-169°, were obtained.

Determination of physical constants on a redistilled portion of methylene diacetate gave the following results.

Boiling range	168-168.5°/741 mm.
Refractive index	n_D^{20} 1.4030
Density	d_{20} 1.126
Calculated molecular weight	132.1

Experimental molecular weight	141
Calculated molar refraction	28.35
Experimental molar refraction	28.63

The molecular weight was determined by the Beckmann freezing-point-depression method using glacial acetic acid as the solvent (20) and the calculated molar refraction was obtained from the atomic refraction values reported by Vogel (99).

Reaction of Methylal with Phthalic Anhydride

Because of the success of the methylal-acetic anhydride reaction, a preliminary investigation of the methylal-phthalic anhydride reaction was undertaken.

Phthalic anhydride (150 g., 1 mole) and methylal-methanol azeotrope (200 ml., 2 moles) were added to a 500-ml. round-bottom flask equipped with a reflux condenser. Concentrated sulfuric acid (5 ml., 0.1 mole) was added as catalyst. Because no apparent reaction took place, the mixture was refluxed on a steam bath for 23 hours, at the end of which time all the solid had dissolved in the black solution. Some paraformaldehyde was noted in the condenser. The mixture was neutralized with a slurry of 20 g. of anhydrous potassium carbonate in 25 ml. of water. An additional 20 g. of potassium carbonate were added later. During the neutralization the color of the mixture changed from black to a light brown and upon standing, the mixture separated into a small yellow bottom layer and a large oily brown upper layer. Distillation of the upper layer yielded about 30 ml. of a water-white liquid boiling at 120-127°/2 mm. After about 12 hours, long white needles formed in the distillate. This resulted in the as yet unproved idea that the reaction did indeed yield some methyl methoxymethyl phthalate, some of which then decomposed to yield methylal and phthalic anhydride.

Reaction of Methylal with Maleic Anhydride

A preliminary trial involved refluxing for three hours a mixture consisting of one mole of maleic anhydride and one mole of methylal-methanol azeotrope in the presence of 1 ml. of sulfuric acid. Neutralization of the acid followed by distillation of the organic filtrate did not yield any material boiling over 100°.

Discussion

The procedures described on the preceding pages have proven themselves novel, yet relatively simple, ways of preparing methoxymethyl acetate and methylene diacetate in good yield.

Extensive studies of the generality of the reaction were not made because the reaction of acetals and acid anhydrides was not the objective of the work covered in this thesis. However, the inconclusive preliminary trial with phthalic anhydride did indicate that the reaction is probably general as far as the acid anhydrides are concerned. Also, it is almost certain that experimental work would show the reaction to be general for acetals and possibly ketals as well.

The simplicity of apparatus and procedure as well as the choice of acid catalysts and bases for the subsequent destruction of the catalyst have been pointed out in the experimental section. Some refinement of procedure is probably possible which might improve the yield of the products to the point of being almost quantitative in the case of methoxymethyl acetate and methylene diacetate.

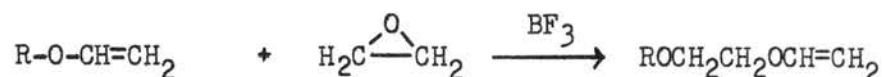
EXPERIMENTAL - PART B

Acid-Catalyzed Reactions of Ethylene Oxide with Esters and Acetal Analogs

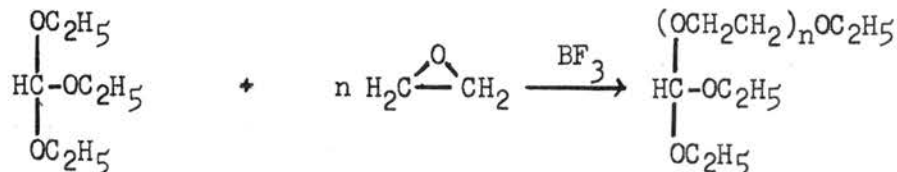
Introduction

A previous attempt to effect an acid-catalyzed reaction of ethylene oxide with the ester linkage of a carboxylic ester did not give any indication of the desired reaction (86).

Orthoesters, of both carboxylic and inorganic acids, were chosen for this study because of their greater degree of hydrolyzability and their similarity (in many respects) to acetals, which do react with olefin oxides in the presence of acids (21). Methoxymethyl acetate, methylene diacetate, and *n*-butyl vinyl ether were also chosen for the study because of their resemblance to acetals. For the vinyl ether the hoped-for reaction may be expressed as



The expected reaction between an orthoester and ethylene oxide in the presence of an acid catalyst is shown below, with ethyl orthoformate as an example.



Procedure and Results

Exploratory Work

Ethyl orthoformate was chosen for the initial work and a series of studies was made to find a catalyst and an efficient procedure to cause the desired reaction.

Sulfuric Acid-Catalyzed Reactions

Ethyl orthoformate (30 g., 0.2 mole) was mixed with 9 g. (0.2 mole) of ethylene oxide at 0-5°. Varying amounts of concentrated sulfuric acid (see table below) were added dropwise as catalyst and the resulting mixture was allowed to warm to room temperature and allowed to remain so for varying periods of time. Vigorous sputtering was observed as the acid was added. The catalyst was neutralized with either solid or aqueous bases, the organic layer dried over anhydrous sodium sulfate, and the mixture distilled.

Table I

Sulfuric Acid-Catalyzed Reaction of Ethyl Orthoformate and

Ethylene Oxide

Trial	Amt. Conc. H ₂ SO ₄ Added	Hours at Room Temperature	Base for Neutralization	Distillation Products
1	2 drops	24	Solid Na ₂ CO ₃	Unchanged ortho- ester and hydroly- sis products
2	4 drops	48	Solid Na ₂ CO ₃	As above
3	8 drops	48	Solid Na ₂ CO ₃	As above
4	16 drops	48	Solid Na ₂ CO ₃	As above
5	10 grams	2	Aqueous Na ₂ CO ₃	Only orthoester hydrolysis prod- ucts
6	10 grams	5	a. Aqueous NH ₃ b. Solid Na ₂ CO ₃	As above As above

Stannic Chloride-Catalyzed Reactions

The procedure used was the same as described above except that anhydrous stannic chloride was used in place of sulfuric acid.

Table II

Stannic Chloride-Catalyzed Reaction of Ethyl Orthoformate and

Ethylene Oxide

Trial	Amt. of SnCl ₄ Added	Hours at Room Temperature	Base for Neutralization	Distillation Products
1	2 drops	24	Solid Na ₂ CO ₃	Unchanged ortho-ester and hydrolysis products
2	4 drops	72	None. White solid in reaction mixture	As above
3	8 drops	72	filtered off	As above
4	16 drops	72	before distillation	As above
5	1 gram	48	Solid Na ₂ CO ₃	Orthoester hydrolysis products

Hydrated Calcium Silicate (Silene)-Catalyzed Reaction

Hydrated calcium silicate (Silene) (10 g.) was added to ethyl orthoformate (60 g., 0.4 mole) in a 500-ml. three-neck flask equipped with a power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The reaction flask was placed in an ice-bath. Ethylene oxide (18 g., 0.4 mole) was slowly added, with stirring to the catalyst suspension. The mixture was allowed to warm to room temperature and stirring continued for 24 hours. After standing an additional 24 hours, the Silene was filtered off and the filtrate distilled. About 7 ml. of distillate were received up to 114^o, 42 ml. of ethyl orthoformate were obtained boiling at 110-114^o, and less than 1 ml. of yellow liquid residue remained.

Uncatalyzed Reactions

Ethyl orthoformate (60 g., 0.4 mole) was mixed with 18 g. (0.4 mole) of ethylene oxide at 0-5°. The resulting mixture was divided among three Carius tubes which were sealed off and placed in a Carius furnace. The tubes were brought up to a temperature of 145-147°, maintained there for 24 hours, and then cooled down to room temperature. Two tubes failed before the end of the 24-hour period and the third exploded while being opened.

The procedure outlined above was repeated except that the tubes were maintained at 110-135° for a 12-hour period. After opening, the contents of the tubes were combined and distilled. Before any distillate was received, some gas (presumed to be ethylene oxide) was evolved. Distillation yielded 5 ml. of liquid boiling up to 144°, 50 ml. of recovered ethyl orthoformate boiling at 144-145°, and 2 ml. of a pale yellow liquid residue.

Boron Trifluoride Etherate-Catalyzed Reaction

Boron trifluoride (46 g., 0.68 mole) was dissolved in about 100 ml. of ethyl ether and this solution was transferred to a 500-ml. three-neck flask equipped with a power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The reaction flask was placed in an ice bath.

A mixture of ethyl orthoformate (75 g., 0.5 mole) and ethylene oxide (20 g., 0.5 mole) at 0° was added to the catalyst solution at such a rate as to maintain the reaction temperature between 5 and 10°. The reaction mixture started out colorless but gradually became brown. As the addition of the orthoester-ethylene oxide solution was continued the solution became orange in color and somewhat viscous. The addition required 1.5 hours, after which the reaction mixture was allowed to

warm to room temperature.

Solid sodium carbonate was added to the reaction mixture with stirring, until gas evolution ceased. The mixture was filtered with suction and the residue washed twice with 50-60 ml. portions of ethyl ether. After the ether had been removed the combined filtrates distilled to yield 61 ml. of orthoester decomposition products boiling up to 112° and a small amount of tar as residue.

Trace Amounts of Boron Trifluoride as Catalyst

Ethyl orthoformate (75 g., 0.5 mole) was weighed into a flask and cooled to 0° . Boron trifluoride was passed into the chilled orthoester at a very low rate for about ten minutes. A small lower layer was observed in the flask. The mixture was transferred to a 500-ml. three-neck flask equipped and situated as described above.

Ethyl orthoformate (75 g., 0.5 mole) was mixed with ethylene oxide (44 g., 1 mole) at $0-5^{\circ}$. This solution was added down the reflux condenser at such a rate as to maintain the reaction temperature at 5° or lower. A total of 3.5 hours was required for the addition. Stirring was continued for 1.5 hours at $0-5^{\circ}$ and then about 30 g. of sodium carbonate were stirred in over a 15-minute period to neutralize the boron trifluoride. Some gas evolution was noted. The mixture was filtered and the filtrate allowed to stand overnight before distillation. Distillation of the mixture through a three-bulb Snyder column gave the results tabulated on page 32.

Two more trials like that described above were made. The liquid residues boiling higher than ethyl orthoformate were combined and subjected to precise fractional distillation at reduced pressure. Such a distillation established the presence of one condensation product boiling at about $110^{\circ}/37$ mm. and another boiling at $145-149^{\circ}/35$ mm.

Cut	Vol.,ml.	Temperature	Comments
1	30	54-143°	Degradation products
2	75	143-145°	Ethyl orthoformate
3	15	137-170°	Water-white liquid
4	15	170-201°	Pale yellow liquid
5	15	201-219°	Pale yellow liquid
6	15	219-229°	Pale yellow liquid
7			Charred residue

These experiments served to show the feasibility of an acid-catalyzed ethylene oxide-ethyl orthoformate reaction and also gave some indication of the type of general procedure to be used in making larger-scale trials.

Preparatory and Analytical Work

Each of the esters studied will be discussed in a separate section below. While this causes some repetition of general procedure, it also serves to eliminate ambiguity where the specific procedures vary. The procedures given can be considered to be typical of the reaction discussed within the section.

Ethyl Orthoformate-Ethylene Oxide

Boron trifluoride (1.5 g., 0.02 mole) was dissolved in ethyl orthoformate (300 g., 2 moles) at 0° contained in a one-liter, three-neck flask equipped with an ice-water-cooled reflux condenser, a power stirrer, and a thermometer. The reaction flask was immersed in an ice bath.

Ethylene oxide (22 g., 0.5 mole) was dissolved in chilled ethyl orthoformate (150 g., 1 mole) and the resulting solution was added with stirring to the catalyst solution at such a rate as to maintain the reaction temperature between 3 and 6°. Forty-five minutes were required

for the addition. The reaction mixture was then stirred at $0-5^{\circ}$ for an additional five hours.

Anhydrous potassium carbonate (25 g.) in about 30 ml. of water was added to neutralize the boron trifluoride. After the mixture had been stirred for 30 minutes, 50 g. of anhydrous sodium sulfate were added. After an additional 15 minutes, the stirrer was shut off and the mixture allowed to warm to room temperature overnight.

The solids were filtered off, washed with ethyl ether and the ether washings combined with the filtrate. The mixture was distilled at atmospheric pressure to remove the ethyl ether, ethyl orthoformate decomposition products, and finally the excess ethyl orthoformate. The residue was distilled at reduced pressure through a Todd column to separate the products which were obtained in three principal fractions.

Forty-five grams (47% yield) of material corresponding to the 1 oxide : 1 orthoester adduct were obtained boiling at $112-117^{\circ}/35$ mm.

A second fraction of 10 g. (17% yield) corresponding to the 2 oxide : 1 orthoester adduct isomers was obtained boiling at $156-158^{\circ}/35$ mm. and a third fraction of 7 g. (15% yield) corresponding to the 3 oxide : 1 orthoester adduct isomers was obtained boiling at $184-187^{\circ}/35$ mm. or $149-158^{\circ}/1$ mm.

The physical properties of the above adducts are summarized in Table III.

The molecular weight was obtained by the standard Beckmann freezing-point-depression method using cyclohexane as the solvent (20). The theoretical molar refraction was calculated from the group constants of Vogel (99), the values of acetal oxygen being used for the three oxygen atoms attached to a single carbon and ether oxygen values used for other oxygen atoms in the molecule. The standard microanalytical pro-

cedure was used to determine the experimental percentages of carbon and hydrogen content of the adducts (66).

Table III

Physical Properties of Ethyl Orthoformate-Ethylene Oxide Adduct Isomers

Property	$C_9H_{20}O_4$ 1 $C_2H_4O:$ 1 $(EtO)_3CH$	$C_{11}H_{24}O_5$ 2 $C_2H_4O:$ 1 $(EtO)_3CH$	$C_{13}H_{28}O_6$ 3 $C_2H_4O:$ 1 $(EtO)_3CH$
Boiling Range	112-117°/35 mm.	156-158°/35 mm.	184-187°/35 mm.
n_D^{20}	1.4060	1.4190	1.4208
d_{20}	0.9254	0.9824	0.9887
Calculated Mol. Wt.	192.3	236.3	280.3
Avg. Exp. Mol. Wt.	185	224	259
Calc. Molar Refraction	50.40	61.46	72.51
Exp. Molar Refraction	51.02	60.62	71.85
% C Calc.	56.22	55.90	55.69
Exp.	56.40	55.70	55.84
% H Calc.	10.49	10.23	10.06
Exp.	10.51	10.36	10.36

Proof of structure was accomplished by hydrolysis of the ethylene oxide-ethyl orthoformate adduct isomers and identification of the fragments.

The general procedure used was to reflux 15-20 ml. of the material to be hydrolyzed for about two hours with 30-50 ml. of 6N hydrochloric acid. After cooling, the solution was neutralized with anhydrous potassium carbonate, and a large excess of the carbonate was used to salt out the organic material. The organic layer was removed and the solids

extracted with ethyl ether. The ether washings were combined with the organic layer for distillation through a Todd column.

Distillation of the hydrolysis products of the 1 ethylene oxide : 1 ethyl orthoformate adduct yielded ethanol and 2-ethoxyethanol. The latter was identified by the formation of the 3,5-dinitrobenzoate (13) which melted at 67-69°. A mixture of the above derivative with the 3,5-dinitrobenzoate of a known sample of 2-ethoxyethanol melted at 68-70°. The fact that no products other than ethanol and 2-ethoxyethanol were found as alcohols shows that the 1:1 adduct corresponds to I in the nomenclature section, to follow.

Distillation of the hydrolysis products from the 2 ethylene oxide : 1 ethyl orthoformate adduct isomer mixture yielded ethanol, 2-ethoxyethanol, and some material boiling in the range 185-195° and believed to be 2-(2-ethoxyethoxy)ethanol (literature b.p., 196°). The 2-ethoxyethanol was again identified by the formation of the 3,5-dinitrobenzoate. No satisfactory derivative of the higher-boiling material could be obtained. The only other material which might be present and which would have a boiling range in the region observed for the higher-boiling material would be ethylene glycol. The product obtained was found to be miscible with petroleum ether whereas ethylene glycol was found to be insoluble. Thus the high-boiling material is in all probability 2-(2-ethoxyethoxy)ethanol. From the nature of the hydrolysis fragments, it follows that the 2:1 product is an isomeric mixture of II and III.

Distillation of the hydrolysis products from the 3 ethylene oxide : 1 ethyl orthoformate adduct isomers yielded ethanol, 2-ethoxyethanol, 2-(2-ethoxyethoxy)ethanol and some still higher-boiling material believed to be 2-(2-(2-ethoxyethoxy)ethoxy)ethanol. The 2-ethoxyethanol was again identified as the 3,5-dinitrobenzoate. Again no derivative of the

2-(2-ethoxyethoxy)ethanol could be obtained. It was assumed to be the material stated on the basis of boiling range (194-197°), solubility in water and petroleum ether, and refractive index (n_D^{20} 1.4237 as compared to a literature n_D^{26} 1.4244 (45)). Since only a small amount (1-2 ml.) of material boiling above 197° was obtained, no direct identification of the material could be made. However, from its mode of formation and its high boiling point, it is likely to have been 2-(2-(2-ethoxyethoxy)ethoxy)ethanol. On the basis of the hydrolysis fragments obtained, it follows that the 3:1 adduct is an isomeric mixture of IV, V, and VI.

The nomenclature of these adducts is rather complicated. The isomers whose existence can be reasonably well justified by the experimental evidence presented above are listed in Table IV.

Table IV

Nomenclature of Ethyl Orthoformate-Ethylene Oxide Adduct Isomers

The 1 oxide : 1 orthoester adduct



1-diethoxymethoxy-2-ethoxyethane or
diethyl 2-ethoxyethyl orthoformate

The 2 oxide : 1 orthoester adducts

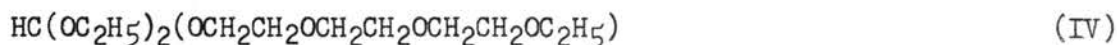


1-diethoxymethoxy-2-(2-ethoxyethoxy)ethane or
diethyl 2-(2-ethoxyethoxy)ethyl orthoformate

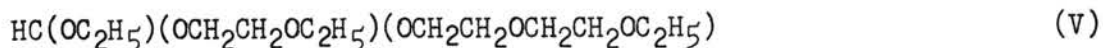


ethoxy-bis-(2-ethoxyethoxy)methane or
ethyl bis-2-ethoxyethyl orthoformate

The 3 oxide : 1 orthoester adducts



1-diethoxymethoxy-2-(2-(2-ethoxyethoxy)ethoxy)ethane or
diethyl 2-(2-(2-ethoxyethoxy)ethoxy)ethyl orthoformate



1-ethoxy(2-ethoxyethoxy)methoxy)-2-(2-ethoxyethoxy)ethane or
ethyl 2-ethoxyethyl 2-(2-ethoxyethoxy)ethyl orthoformate



tris-(2-ethoxyethoxy)methane or
tris-2-ethoxyethyl orthoformate

Ethyl Orthoformate-Propylene Oxide

Boron trifluoride (1.5 g., 0.02 mole) was dissolved in ethyl orthoformate (300 g., 2 moles), at 0°, contained in a one-liter round-bottom flask equipped with an ice-water-cooled reflux condenser, a power stirrer and a thermometer. The reaction flask was immersed in an ice bath.

Propylene oxide (30 g., 0.5 mole) was dissolved in chilled ethyl orthoformate (150 g., 1 mole) and the resulting mixture was added to the catalyst solution, with stirring, at such a rate as to maintain the reaction temperature between 3 and 8°. One hour was required for the addition and then the reaction mixture was stirred at 0-5° for an additional seven hours.

Anhydrous potassium carbonate (30 g.) in about 30 ml. of water was added to neutralize the boron trifluoride. After the mixture had been stirred for twenty minutes, 50 g. of anhydrous sodium sulfate were added. After an additional 30 minutes the stirrer was shut off and the mixture allowed to warm to room temperature overnight. The solids were filtered off and washed with ethyl ether. The ether washings were combined with the filtrate and the mixture distilled at atmospheric pressure to remove the ether, ethyl orthoformate decomposition products, and finally the excess ethyl orthoformate. The residue was distilled at reduced pressure through a Todd column to separate the products, which were obtained in three principal fractions.

Thirty-nine grams (37% yield based on propylene oxide) of material corresponding to the 1 oxide : 1 orthoester adduct isomers were obtained boiling at 113-119°/36 mm.

A second fraction of 26 g. (20% yield) corresponding to the 2 oxide : 1 orthoester adduct isomers was received boiling at 151-153°/36 mm.

A third fraction of 18 g. (11% yield) corresponding to the 3 oxide : 1 orthoester adduct isomers was obtained boiling at 172-179°/36 mm.

The physical properties of the above adducts are summarized in Table V.

Table V

Physical Properties of Ethyl Orthoformate-Propylene Oxide Adduct Isomers

Property	$C_{10}H_{22}O_4$ 1 Propylene Oxide : 1 (EtO) ₃ CH	$C_{13}H_{28}O_5$ 2 Propylene Oxide : 1 (EtO) ₃ CH	$C_{16}H_{34}O_6$ 3 Propylene Oxide : 1 (EtO) ₃ CH
Boiling Range	113-119°/36 mm.	151-153°/36 mm.	172-174°/36 mm.
n_D^{20}	1.4040	1.4169	1.4211
d_{20}	0.9123	0.9411	0.9572
Calc. Mol. Wt.	206.3	264.4	322.4
Avg. Exp. Mol. Wt.	188	206	252
Calc. Molar Refraction	55.02	70.71	86.39
Exp. Molar Refraction	55.28	70.62	85.43
% C	Calc. 58.22 Exp. 57.99	Calc. 59.05 Exp. 58.40	Calc. 59.59 Exp. 59.71
% H	Calc. 10.75 Exp. 11.12	Calc. 10.67 Exp. 10.71	Calc. 10.62 Exp. 10.94

The same procedures were used to determine the data tabulated above

as were used in the case of the ethyl orthoformate-ethylene oxide adduct isomers previously described.

It is believed that propylene oxide and ethyl orthoformate give the same type of isomers as noted in Table IV for the ethylene oxide-ethyl orthoformate adduct isomers. However, they introduce new possibilities of isomerism because of the fact that the propylene oxide ring can open in either of two ways. It can be shown that there can be two isomers corresponding to I, four to II, three to III, eight to IV, six to V, and four to VI of Table IV. No attempt was made to prove the structure of these compounds on account of the large variety of isomers that would undoubtedly result from the hydrolysis of the adducts. The structure of these compounds must follow by analogy to the ethylene oxide-ethyl orthoformate adducts.

Methyl Orthoformate-Ethylene Oxide

Trial I

Boron trifluoride (1.5 g., 0.02 mole) was passed into methyl orthoformate (106 g., 1 mole) at 0°. The resulting solution was transferred to a one-liter three-neck flask equipped with an efficient power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The reaction flask was immersed in an ice bath. An additional 106 g. (1 mole) of chilled methyl orthoformate were used to rinse the catalyst solution into the reaction flask.

Ethylene oxide (50 ml., 1 mole) and methyl orthoformate (106 g., 1 mole) at 0° were mixed and the resulting solution added to the catalyst solution, with stirring, over a 1.5-hour period. The temperature of the reaction mixture was maintained between 3 and 5°.

After all the ethylene oxide solution had been added, the mixture was stirred at 0-5° an additional three hours and then was treated with

30 g. of anhydrous potassium carbonate in about 30 ml. of water. Over a 30-45-minute period of stirring, the mixture changed in color from a deep brown-red, through a wine color, to a yellow orange solution. Anhydrous sodium sulfate (30-40 g.) was then added to the reaction mixture and stirring was continued an additional 30 minutes.

The solids were filtered off and washed with two 25-ml. portions of ethyl ether. The ether washings were combined with the organic filtrate and the mixture was distilled. After the ethyl ether, methyl orthoformate decomposition products, and excess methyl orthoformate were removed, 30 g. (20% yield) of dimethyl 2-methoxyethyl orthoformate were obtained boiling at 172-174°/743 mm. The residue distilled with decomposition even at reduced pressure (20 mm.).

Trial II

The second trial was carried out in the same general manner as described above except that a higher ratio of ethylene oxide was used in the hope of getting more of the 2 and 3 ethylene oxide to 1 methyl orthoformate adduct isomers. A total of 245 g. (2.3 moles) of methyl orthoformate and 100 ml. (2 moles) of ethylene oxide was used in conjunction with 1.5 g. (0.02 mole) of boron trifluoride as catalyst.

Distillation of the neutralized reaction mixture gave a great deal of orthoester degradation products but no unreacted methyl orthoformate.

Only 10 ml. of what was probably impure 1:1 adduct was obtained; it boiled at 104-105°/20 mm. The remainder to the distillate boiled over a wide range, without definite plateaus and with considerable decomposition in the stillpot.

The physical properties were determined by the methods described in the section dealing with the ethylene oxide-ethyl orthoformate adducts. The carbon and hydrogen analyses were performed by Geller Laboratories.

Table VI

Physical Properties of Methyl Orthoformate-Ethylene Oxide Adduct

Property	$1 \text{ C}_6\text{H}_{14}\text{O}_4$ $1 (\text{CH}_3\text{O})_3\text{CH} : 1 \text{ C}_2\text{H}_4\text{O}$
Boiling Range	172-174°/743 mm.
n_D^{20}	1.4012
d_{20}	1.001
Calc. Mol. Wt.	150.2
Avg. Exp. Mol. Wt.	152
Calc. Molar Refraction	36.36
Exp. Molar Refraction	36.47
% C Calc.	47.99
Exp.	48.09
% H Calc.	9.39
Exp.	9.41

A sample of dimethyl 2-methoxyethyl orthoformate was hydrolyzed with 6N hydrochloric acid by the same procedure used for ethylene oxide-ethyl orthoformate adducts. Distillation of the extracted hydrolysis products yielded methanol and 2-methoxyethanol. The alcohols were identified by the formation of their alpha-naphthylurethans (13).

The alpha-naphthylurethan of methanol obtained by this hydrolysis melted at 118.5-119.5°. A mixture of the above derivative with the alpha-naphthylurethan of a known sample of pure methanol melted at 119.5-120.5°. Similarly the alpha-naphthylurethan of 2-methoxyethanol obtained by hydrolysis melted at 112-113° while its mixture with the alpha-naphthylurethan of a known sample of 2-methoxyethanol melted at 112-112.5°.

The above data prove that the alcohols obtained by the hydrolysis

were methanol and 2-methoxyethanol, and therefore that the parent compound must have been dimethyl 2-methoxyethyl orthoformate as postulated.

Ethyl Orthoacetate-Ethylene Oxide

Trial I

Boron trifluoride (0.5 g., 0.007 mole) was dissolved in 175 g. (1 mole) of chilled ethyl orthoacetate and the resulting solution transferred to a 500-ml. three-neck flask equipped with a power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The reaction flask was immersed in an ice bath.

A cold solution of ethylene oxide (17 g., 0.4 moles) in ethyl orthoacetate (104 g., 0.64 mole) was added, slowly and with stirring, to the catalyst solution. The reaction temperature was kept below 10° during the 20 minutes required for the addition. Very little evidence of reaction was noted during the addition. Stirring was continued for an additional hour.

Anhydrous potassium carbonate (30 g.) in 25 ml. of water was added to the reaction mixture, which was stirred for about an hour to neutralize the boron trifluoride. Anhydrous sodium carbonate was then added to remove the water.

The organic liquid was decanted off and the solid residue washed several times with ethyl ether. The ether washings were combined with the decanted material for distillation. After the ether, orthoester cleavage products, and 182 g. of ethyl orthoacetate (boiling range 142-148°) had been removed, less than 10 ml. of a brown liquid residue remained.

Trial II

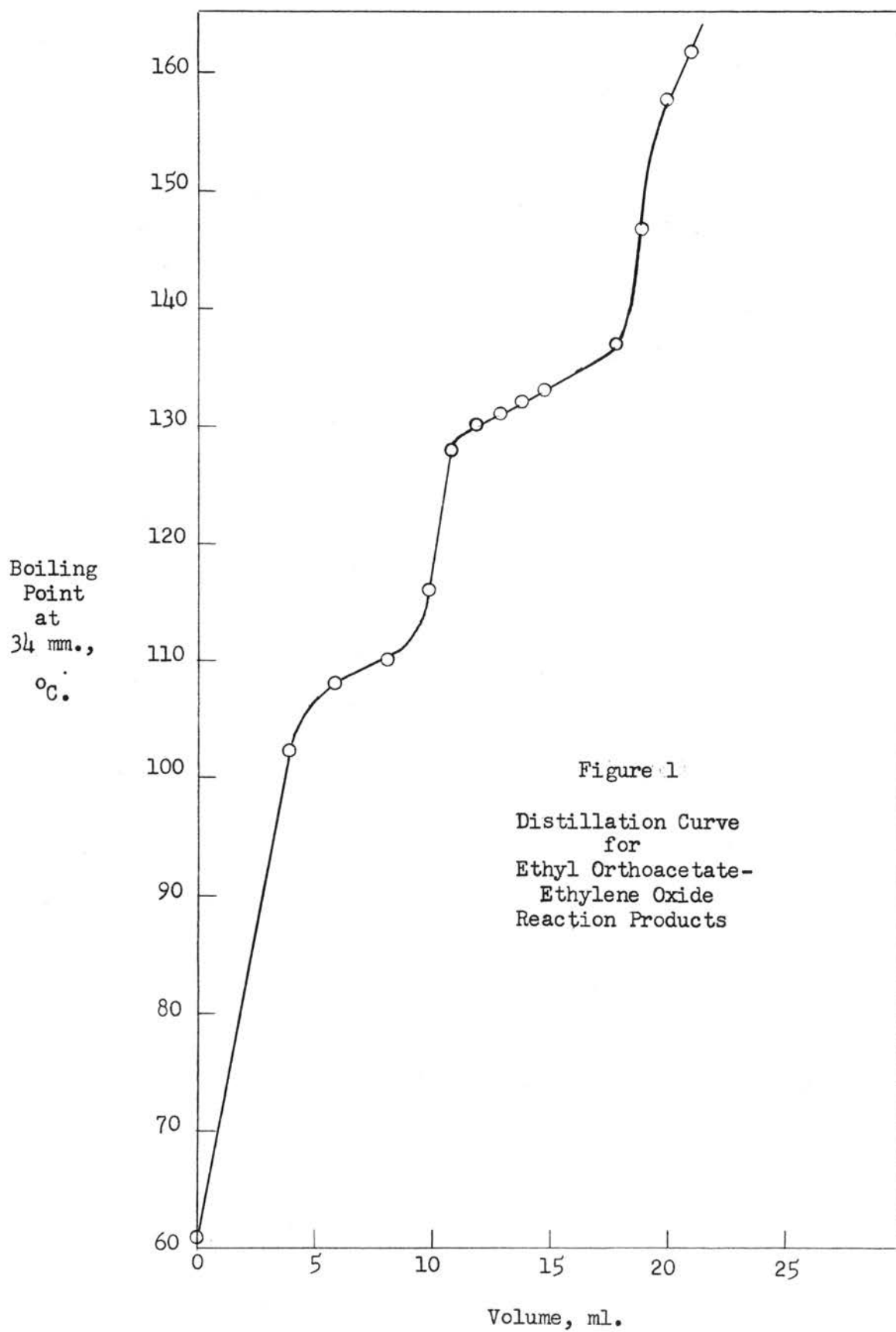
The experiment described above was repeated by adding ethylene oxide (22 g., 0.5 mole) in chilled ethyl orthoacetate (88 g., 0.54 mole)

to a chilled solution of boron trifluoride (0.5 g., 0.007 mole) in ethyl orthoacetate (94 g., 0.58 mole).

Half of the ethylene oxide-ethyl orthoacetate solution was added to the chilled catalyst solution without any evidence of reaction being noted. The mixture was allowed to warm to 10° and the remaining ethylene oxide solution was added. No evidence of reaction was noted over the two-hour period during which the mixture was allowed to warm to 20°. The reaction mixture was cooled to 10° and 1 g. (0.014 mole) of boron trifluoride was added, followed by 15 g. (0.34 mole) of ethylene oxide. There was still no evidence of reaction. Hence, the reaction flask was removed from the ice bath and allowed to warm up. Over a period of three hours the temperature of the reaction mixture rose to 34° and then slowly dropped to room temperature (23°). The reaction mixture was treated with 50 g. of anhydrous potassium carbonate in 50 ml. of water to neutralize the boron trifluoride. Some gas evolution was noted. After 30 minutes of stirring, solid anhydrous potassium carbonate was added to remove the water and the mixture was allowed to stand overnight.

The organic layer was decanted off and the solids were washed with several portions of ethyl ether. The ether washings were combined with the organic layer for distillation. All but about 25 ml. of the mixture boiled below 142°. No ethyl orthoacetate was recovered, it apparently having undergone acid cleavage at the higher temperature employed.

The 25-ml. brown residue was combined with the residue from Trial I for a reduced-pressure analytical distillation through a Todd column. The results are plotted as a distillation curve in Figure 1, which shows two incipient plateaus approximately in the regions expected for the 1 oxide : 1 orthoester and 2 oxide : 1 orthoester products. The curve suggests that the desired products are formed but in extremely



small and unprofitable yields. No further work with this reaction was carried out.

Methyl Orthobenzoate-Ethylene Oxide

The methyl orthobenzoate used in the following trials was prepared from benzotrichloride according to the procedure of McElvain and Venerable (57).

Trial I

A 250-ml. erlenmeyer flask was fitted with a calcium chloride drying tube and a gas-dispersion tube. Methyl orthobenzoate (100 g., approximately 0.5 mole) was added to the flask which was then chilled in an ice bath. Boron trifluoride (1.5 g., 0.02 mole) was passed into the chilled orthoester through the gas dispersion tube, whereupon the formation of a brown oil was observed. Some of the brown oil solidified and became dispersed in the excess orthoester. The resulting solution was transferred to a chilled 500-ml. three-neck flask equipped with a power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The flask was immersed in an ice bath.

A solution of ethylene oxide (25 ml., 0.5 mole) in chilled methyl orthobenzoate (100 g., approximately 0.5 mole) was added to the catalyst solution over a 1.5-hour period. During the addition of the ethylene oxide solution the dark oil disappeared leaving some white solids suspended in the otherwise clear solution. After all the ethylene oxide had been added the mixture was stirred at 0-5° for an additional three hours.

A solution of potassium carbonate (30 g.) in 25 ml. of water was added to the reaction mixture. A cloudiness was noted but no reaction beyond that. After 20 minutes, about 20 g. of anhydrous sodium carbonate were added to aid in the removal of water. After an additional

20 minutes the clear organic liquid was decanted into a 500-ml. round-bottom flask and the residue was washed twice with 25-ml. portions of ethyl ether. The ether washings were added to the organic liquid and the mixture was distilled.

Unreacted ethylene oxide, ethyl ether, and methanol were removed at atmospheric pressure. Distillation was then continued at reduced pressure. Except for a 17-ml. residue, all the organic material distilled at or below the boiling point of methyl orthobenzoate. Because the quantity of the brown, partially water-soluble residue was relatively small, no further attempts at purification or identification of products were made.

Trial II

The apparatus and procedure were the same as in Trial I except as noted below.

When boron trifluoride (3 g., 0.04 mole) was passed into the chilled orthoester a vigorous exothermic reaction took place, during the course of which the solution became bright red and a considerable quantity of white solid separated out. It was believed that the red color and the white solid were due to a boron trifluoride-methyl orthobenzoate complex. The solution was transferred to the 500-ml. reaction flask.

During the addition of the ethylene oxide solution to the catalyst solution, only a very slow rise in temperature was noted even when 10-20-ml. portions of the ethylene oxide solution were added. At one point the temperature rose to 7° but the rest of the time it was kept between 3 and 5°. Two hours were required for the addition of the ethylene oxide solution. At the end of the addition the mixture still had the red color and still contained some of the white solid. Stirring at 0-5° was

continued for an additional 5.5 hours. At the end of this time the mixture was neutralized as before.

As the boron trifluoride was neutralized, the mixture lost its red color and became light yellow instead. After an additional 25 g. of anhydrous sodium carbonate had been added to help remove the water, the mixture was allowed to warm to room temperature while standing overnight.

The solids were filtered off and the organic filtrate was distilled at reduced pressure through a Todd column. All but a 20-25-ml. residue distilled off below the boiling point of methyl orthobenzoate. The bulk of the distillate consisted of methyl orthobenzoate. As the amount of the residue was small, no further work was done with it.

Methyl Orthoborate-Ethylene Oxide

The methyl orthoborate was prepared according to the procedure of Schlesinger, Brown, Maysfield, and Gilbreath (82).

A one-liter three-neck flask was equipped with a power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The flask was immersed in an ice bath.

Methyl orthoborate (420 g., 4 moles) was placed in the flask, cooled to 2°, and treated with boron trifluoride (3 g., 0.44 mole) as catalyst. A mixture of ethylene oxide (45 g., 1 mole) and methyl orthoborate (105 g., 1 mole) was made and cooled to 2°. This solution was added with stirring to the catalyst solution over a period of one hour during which a rise in temperature (to 5°) was observed.

Stirring was continued at 0-5° for an additional 9 hours. The solution was then allowed to warm to 20° and 12 ml. of dimethylaniline were added to destroy the boron trifluoride catalyst. Stirring was continued at room temperature for 36 hours.

The reaction mixture was decanted out of the reaction flask, leaving an oily residue of dimethylaniline containing some crystals of $C_6H_5N(CH_3)_2 \cdot BF_3$. The excess methyl orthoborate was distilled off at $20^\circ/77$ mm. Ice water was circulated in the condenser and two ice traps were used in series between the receiver and vacuum line to insure condensation of the methyl orthoborate. Approximately 180 ml. of residue remained.

The residue was then subjected to fractional distillation through a Todd Column. About 100 ml. of methyl orthoborate, b.p. $68-69^\circ$, were received. Raising the temperature yielded 4-5 ml. of dimethylaniline boiling from 178 to 196° . Approximately 50-60 ml. of liquid residue remained.

The residue was readily soluble in water and the solution gave no boric acid upon acidification with dilute sulfuric acid. These results were taken to indicate that the amount of boric acid present, free or esterified, was small and that the high-boiling material was essentially polymerized ethylene oxide. It was not investigated further.

Ethyl Orthosilicate-Ethylene Oxide

The ethyl orthosilicate used was the Eastman practical grade which boiled at $60-62^\circ/10$ mm.

Trial I

The apparatus used was the same as that used for the methyl orthobenzoate-ethylene oxide work.

Boron trifluoride (1.5 g., 0.02 mole) was passed into chilled ethyl orthosilicate (105 g., 0.5 mole). The solution became pale yellow and upon further standing and cooling it became clear brown in color. The solution was transferred to the reaction flask.

Ethylene oxide (25 ml., 0.5 mole) was added to chilled ethyl ortho-

silicate (105 g., 0.5 mole) and the resulting solution was added to the catalyst solution, in small portions, at such a rate as to keep the temperature of the reaction mixture between 2 and 4°. After about 10 ml. of the ethylene oxide solution had been added, the brown color disappeared and a fluffy white solid formed in the now clear solution. After another 20-30 ml. of the ethylene oxide solution had been added, the fluffy solid changed to a yellow paste and remained that way during the rest of the reaction. All the ethylene oxide was added over a one-hour period. After the ethylene oxide addition was complete, the mixture was stirred at 0-5° for an additional ten hours.

The boron trifluoride was neutralized by the addition of 3 ml. (0.03 mole) of pyridine. A white milky solution resulted immediately upon the addition of the pyridine. After the mixture had been stirred an additional two hours, the ice bath was removed and the mixture allowed to warm to room temperature. The reaction mixture was filtered through glass wool into a 500-ml. round-bottom flask for distillation at reduced pressure.

Most of the ethyl orthosilicate was recovered between 56 and 61° at a pressure of 10 mm. Only 5-10 ml. of residue remained.

Trial II

The procedure and apparatus were the same as used in Trial I with the following differences.

The amount of boron trifluoride was doubled so that 3 g. (0.04 mole) were used. A total of two hours was required for the addition of the ethylene oxide solution. The oily paste noted in Trial I was again observed. After all the ethylene oxide had been added, the mixture was stirred an additional seven hours. Pyridine (6 ml., 0.06 mole) was added to neutralize the boron trifluoride. The resulting cloudy solution

was allowed to warm to room temperature and stirred overnight and then allowed to stand 15 hours beyond that. After the clear liquid had been decanted off for distillation a partially water-soluble wax-like white residue remained in the reaction flask.

Distillation at reduced pressure again yielded a considerable quantity of recovered ethyl orthosilicate and about 30 ml. of a brown water-insoluble residue. The residue hydrolyzed to a gel in water faster than pure ethyl orthosilicate.

Trial III

The procedure was essentially the same as in Trials I and II except that 6 g. (0.08 mole) of boron trifluoride were used and after the addition of ethylene oxide solution was complete, 10 ml. (0.1 mole) of pyridine were added to remove the catalyst. After distillation to remove unreacted ethyl orthosilicate, a 30-40-ml. residue remained. The properties of the residue were similar to those of the residues obtained in the previous trials. No further work in this series was carried out.

Methoxymethyl Acetate-Ethylene Oxide

Boron trifluoride (7 g., 0.1 mole) was dissolved in chilled methoxymethyl acetate (210 g., 2 moles) contained in a 500-ml. three-neck flask equipped with a power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The reaction flask was cooled in an ice bath.

A chilled solution of ethylene oxide (44 g., 1 mole) in methoxymethyl acetate (105 g., 1 mole) was added with stirring to the catalyst solution at such a rate as to maintain the reaction temperature between 3 and 8°. Five hours were required for the addition and the mixture was stirred at 0-5° for an additional hour.

A solution of 28 g. of anhydrous potassium carbonate in 25 ml. of water was added in small portions and with stirring to the reaction

mixture to neutralize the acid catalyst. After an hour of stirring, the mixture was transferred to a separatory funnel and the lower aqueous layer was withdrawn and extracted twice with 25-ml. portions of ethyl ether. The ether washings were combined with the organic layer and the mixture dried over 30-40 g. of anhydrous potassium carbonate. Considerable effervescence took place as the potassium carbonate was added, probably due to incomplete neutralization of the catalyst or the presence of acetic acid from the breakdown of methoxymethyl acetate.

The mixture was filtered to remove the solids and the filtrate was distilled through a 2 x 20 cm. column packed with 4 mm. glass beads and equipped with a total-reflux partial take-off head. The residue remaining after the removal of the ethyl ether, some methyl acetate, and excess methoxymethyl acetate yielded fractions whose physical properties corresponded to ethylene glycol monoacetate, ethylene glycol diacetate, ethylene glycol, and some high-boiling water-insoluble residue. A considerable quantity of paraformaldehyde was also formed during the course of the distillation. There was not enough residue or other indication of the desired product to warrant further work.

Methylene Diacetate-Ethylene Oxide

Three trials were made, the procedure being essentially the same in each case except for the concentration of boron trifluoride catalyst. For the sake of convenience, only the procedure for Trial III will be given since it is representative of the procedure used. The concentration of catalyst per mole of ethylene oxide used is noted below.

Trial	Moles BF_3
I	0.04
II	0.12
III	0.25

Methylene diacetate (132 g., 1 mole) was placed in a 250-ml.

erlenmeyer flask equipped with a calcium chloride drying tube and a gas-dispersion tube. The flask and its contents were chilled in an ice bath and then boron trifluoride (17 g., 0.25 mole) was passed in slowly through the gas-dispersion tube. The resulting pale yellow solution was transferred to a 500-ml. three-neck flask equipped with a power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The flask was immersed in an ice bath. The erlenmeyer flask was rinsed with chilled methylene diacetate (66 g., 0.5 mole) and this was also transferred to the reaction flask.

Methylene diacetate (198 g., 1.5 moles) was chilled, ethylene oxide (50 ml., 1 mole) added to it, and the resulting solution added to the catalyst solution at such a rate as to keep the temperature of the reaction mixture between 3 and 6°. A total of about 7.5 hours was required for the addition. After an additional three hours' stirring at 0-5° the acid catalyst was neutralized by the addition of 50 g. of anhydrous potassium carbonate in 50 ml. of water and the mixture was allowed to stand overnight. The solids were filtered off and the organic liquid dried over Drierite.

Distillation of the organic filtrate yielded about 100 ml. of distillate boiling below methylene diacetate and about 250 ml. of methylene diacetate. A considerable quantity of paraformaldehyde was formed during the course of the distillation. About 15 ml. of material boiling above 180° were also obtained as well as a 10 ml. black tarry residue.

Acid-Catalyzed Reaction of Vinyl Ethers with Ethylene Oxide

The reaction apparatus consisted of a one-liter three-neck flask equipped with a power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The reaction flask was immersed in an ice bath.

Trial I

Ethyl ether (200-250 ml.) was poured into the reaction flask and allowed to cool. To this was added 3 ml. of boron trifluoride etherate equivalent to 1.5 g. (0.02 mole) of boron trifluoride. The following solution was made up in a separate chilled 500-ml. erlenmeyer flask: ethyl ether (50 ml.), *n*-butyl vinyl ether (100 g., 1 mole), and ethylene oxide (45 g., 1 mole). This solution was added to the catalyst solution over a 30-minute period with a 1° rise in temperature observed. Stirring was continued at ice-bath temperature. An additional rise of 1° was observed over the next 30 minutes. During the following hour the temperature dropped to 2° where it remained for the next five hours. At this time 2 g. of monoethanolamine were added to neutralize the boron trifluoride. Stirring was continued for 20 minutes; then the stirrer was shut off and the solution allowed to warm to room temperature overnight.

The solution was slightly cloudy before the addition of the ethanolamine and became even cloudier after the addition. The solution was weakly acidic to Hydrion paper before the addition of the base, and neutral afterward. After the 20 minutes of stirring following the addition of the base, the solution had cleared up and left a white film on the walls of the flask.

On standing overnight the white film turned orange and the solution a pale yellow. The odor of *n*-butyl vinyl ether was still evident.

Upon distillation, a highly volatile material came off with the ethyl ether. The material was not trapped and identified but it may have been either acetaldehyde or ethylene oxide. After the ethyl ether was taken off, 8 g. of *n*-butyl vinyl ether were recovered boiling at 90-96°/748 mm. The residue, which had changed from a pale yellow to a

deep orange, was saved for distillation at reduced pressure through a small glass-packed Todd column.

Cut	Temp.°C.	Vol.ml.	Pressure	Comments
1	45-58	5	8 mm.	<u>n</u> -butyl vinyl ether
2	58-73	4	8 mm.	
3	73-76	5	8 mm.	water-white liquid
4	76-118	10	7 mm.	very pale yellow
5	118-132	5	7 mm.	yellow liquid
6	132-148	5	7 mm.	yellow liquid
7	148-158	10	7 mm.	yellow liquid
8	temp. drop		7 mm.	black tar

Trial II

The apparatus and general procedure were the same as in Trial I. After all the ethylene oxide solution had been added the temperature of the reaction vessel was kept at 15-20° during a six-hour period of stirring.

The ethyl ether and excess n-butyl vinyl ether were removed by distillation through a 3-bulb Snyder column. The residue was distilled at reduced pressure through a Todd column.

Cut	Temp.°C.	Vol.ml.	Pressure	Comments
1	39-60	17	2 mm.	<u>n</u> -butyl vinyl ether
2	60-68	4	2 mm.	
3	68-75	15	2 mm.	water-white liquid
4	88-105	5	4 mm.	
5	105-122	12	4 mm.	
6		10		brown liquid residue

In both trials, the material obtained in cut 3 decolorized bromine

in carbon tetrachloride very readily and decolorized 1% aqueous potassium permanganate slowly. Cuts numbered 3 from the two trials were combined, and a 10-ml. portion was placed in a small distillation flask along with 30 ml. of 2N hydrochloric acid. The flask was heated on a steam bath. Acetaldehyde was condensed at a cold-finger condenser and identified by odor, positive iodoform test, and formation of the 2,4-dinitrophenylhydrazone..

The hydrolysis mixture residue was neutralized with anhydrous potassium carbonate and an excess of the carbonate was used to salt out the organic layer. Upon separation of the organic layer and distillation, only n-butyl alcohol was obtained. This would indicate that no condensation of the vinyl ether with ethylene oxide was obtained.

Discussion

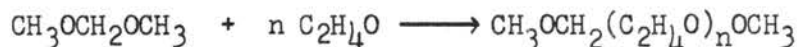
The reaction of ethylene or propylene oxide with ethyl orthoformate in the presence of boron trifluoride catalyst gives good yields of the orthoester-olefin oxide adducts. The 1 oxide : 1 orthoester adducts are obtained in the best yield but substantial amounts of the 2 oxide : 1 orthoester and 3 oxide : 1 orthoester adduct isomers are also produced. Methyl orthoformate reacts with ethylene oxide in a similar manner to give a satisfactory yield of dimethyl 2-methoxyethyl orthoformate. There is good evidence that the higher adduct isomers are also formed but they appear to be unstable and decompose upon distillation. It is almost certain that the reaction is a general one for alkyl orthoformates and olefin oxides.

The reaction proceeds smoothly at temperatures in the neighborhood of 10° or below, in the presence of 0.5% or less of boron trifluoride. Even at room temperature the catalyst degrades and destroys the orthoformate quite rapidly, so that it is essential to maintain cooling during the reaction. Catalyst concentrations higher than 0.5% are unsatisfactory since they also lead to decomposition of the orthoformate to ethyl formate and ethyl ether with a consequent lowering of the yield.

It is probable that the failure of such other catalysts as concentrated sulfuric acid, stannic chloride, hydrated calcium silicate, and boron trifluoride etherate merely means they are not strong enough acids compared to boron trifluoride. The uncatalyzed thermal reaction does not succeed, at least up to 135°.

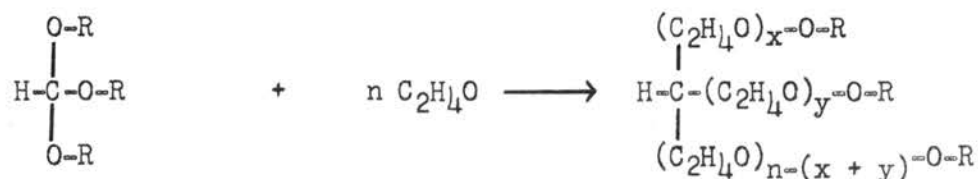
It should be noted that the ethyl orthoformate-ethylene oxide reaction differs in two important respects from the acetal-olefin oxide reaction on which its study was based. The first difference is the fact that the orthoester-olefin oxide reaction will not tolerate the

relatively high boron trifluoride concentration used in the acetal work. The second big difference is in the number of acetal or orthoester carbon-oxygen linkages attacked. The reaction of methylal with ethylene oxide proceeds as shown below.



No products of the type $\text{CH}_3\text{O}(\text{C}_2\text{H}_4\text{O})_x\text{CH}_2(\text{C}_2\text{H}_4\text{O})_{n-x}\text{OCH}_3$ were reported by Dermer and Durr (21).

In other words, in the case of the methylal-ethylene oxide condensation, reaction takes place at one or the other of the susceptible linkages but never at both. In the orthoformate-ethylene oxide reaction, on the other hand, reaction can and does take place at all three susceptible linkages so as to give a reaction of the type shown below.



where x and y can be any integers including zero and n is one or any larger integer.

This difference in behavior is probably the result of the OR groups of the orthoesters being more labile than in the case of acetals. That this is the case is indicated by the fact that acetals will tolerate a higher concentration of boron trifluoride than the orthoesters can stand without decomposition.

The poor results with ethyl orthoacetate and apparent failure of methyl orthobenzoate require some explanation. If the orthoester is required to form a carbonium ion as a transitory reaction intermediate, then the presence of the central methyl group in ethyl orthoacetate should facilitate the formation of the ion. Similarly, if the phenyl group is considered as an electron source, then the formation of a carbonium ion

from methyl orthobenzoate should also be facilitated. The fact that, once formed, these ions apparently do not react with ethylene oxide to any appreciable extent indicates that the carbonium ions formed may be relatively stable and therefore less reactive.

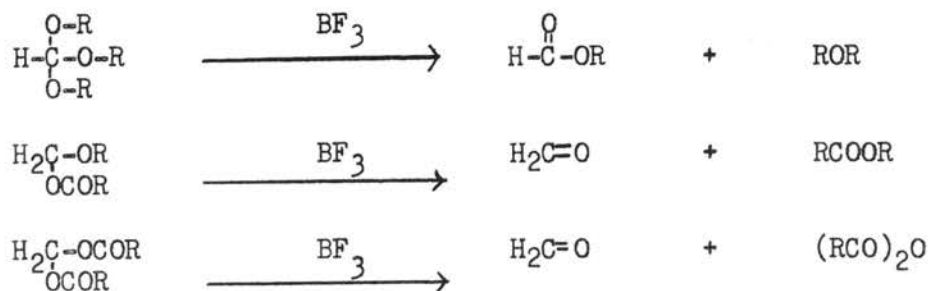
Another possible explanation is that the relatively bulky phenyl or methyl groups create sufficient steric hindrance to prevent reaction between the carbonium ion and ethylene oxide. If this is the case then the carbonium ion has the choice of reforming the orthoester or rearranging to a carboxylic ester and an alkyl carbonium ion which could react with the anion from the orthoester so as to yield an ether. Thus the overall effect would be the breakdown of the orthoester into a carboxylic ester and an ether and either non-reaction or polymerization of ethylene oxide, with little detectable reaction taking place between the orthoester and the ethylene oxide.

A further test of the role played by steric hindrance in a reaction of this type might be demonstrated by the reaction of ethyl orthoformate with sym-tetramethylethylene oxide, sym-tetraphenylethylene oxide or other similarly highly substituted and presumably sterically hindered ethylene oxide.

It is possible that a combination of factors such as unfavorable steric relationships and inability to form sufficiently reactive ions are responsible for the apparent lack of reaction of methyl orthoborate and ethyl orthosilicate with ethylene oxide. It is of interest to remember that silicon tetrachloride adds ethylene oxide readily to yield the corresponding tetrakis-2-chloroethyl silicate; but to be sure, acid chlorides usually react faster than esters.

The fact that paraformaldehyde was formed in the case of the reactions involving methoxymethyl acetate and methylene diacetate indicates

that some breakdown of these compounds occurred. From the nature of the fragments obtained it would seem that the degradation of these esters follows a path similar to that of the breakdown of orthoesters. This similarity is illustrated below.



The last equation illustrates a commercial method of manufacturing acetic anhydride from ethylidene diacetate.

Treatment of methoxymethyl acetate with boron trifluoride apparently causes a breakdown of the ester to formaldehyde and methyl acetate without allowing any of the intermediate complex to react with ethylene oxide. Upon treatment of the reaction mixture with aqueous base, further breakdown of the methoxymethyl acetate to methanol, formaldehyde and acetic acid can take place. Any ethylene oxide present at this stage would tend to react with the water to form ethylene glycol or with the acetic acid to form ethylene glycol monoacetate. The presence of the small amount of ethylene glycol diacetate can probably be accounted for by an ester exchange between methoxymethyl acetate and ethylene glycol monoacetate to give glycol diacetate, methanol and formaldehyde.

A similar acid-induced breakdown into formaldehyde and acetic anhydride can take place with methylene diacetate. Reaction of the acetic anhydride with ethylene oxide to form ethylene glycol diacetate would then account for some of the high-boiling residues obtained.

An alternate explanation of the apparent failure of the reaction with ethylene oxide would be that the hoped-for products are formed

but break down upon treatment with aqueous base. If this is true, such a breakdown might be prevented by the use of a tertiary amine to destroy the boron trifluoride catalyst.

In either case, it is evident that methoxymethyl acetate and methylene diacetate are not very similar to acetals as far as the stability and reactivity of their boron trifluoride complexes are concerned.

The experiments with n-butyl vinyl ether have shown that boron trifluoride etherate apparently will not catalyze a reaction between the vinyl ether and ethylene oxide. It is evident that the vinyl ether was partly polymerized by the acid - hence the higher-boiling fractions - but there was no sign that any ethylene oxide units were present in the products. If boron trifluoride could be added directly to the vinyl ether at a very low temperature, without polymerizing or decomposing the ether, the hoped-for addition of ethylene oxide might subsequently be obtained. This possibility was not followed up because of the pressure of other scheduled experimental work.

EXPERIMENTAL - PART C

Reaction of Ethylene Oxide with Compounds Capable of Forming Sodium Enolates

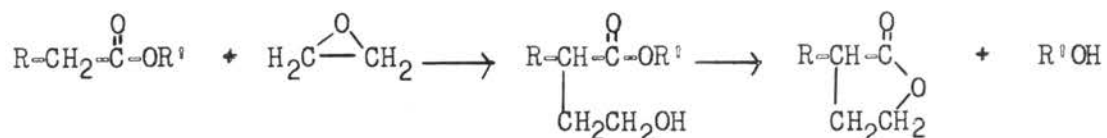
Introduction

The addition of the enolates of several active methylene compounds to ethylene oxide has been discussed in the historical section. The most thoroughly studied reactions of this type are the diethyl malonate-ethylene oxide reaction and the ethyl acetoacetate-ethylene oxide reaction. Zuidema, Cook, and Van Zyl (109) have also studied the addition of the sodium enolate of ethyl cyanoacetate to styrene oxide and butadiene monoxide.

Reaction media reported for these reactions include aqueous solutions of alkali metal hydroxides, alcoholic sodium ethoxide, and mixtures of the reagents in the presence of piperidine or diethylamine as catalyst. The reaction mixtures were maintained at temperatures ranging from 0° to the reflux temperature of the reagents although almost all the work involving ethylene oxide was carried out at or below room temperature, probably to avoid the use of pressure vessels.

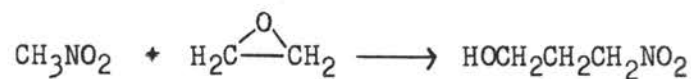
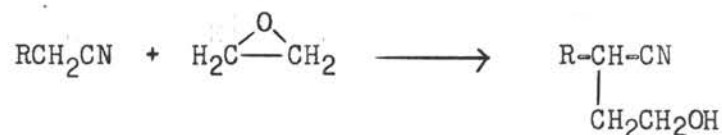
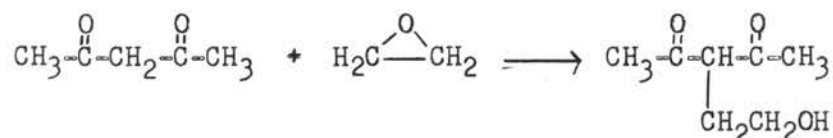
The purpose of the work covered by this section was to extend the reaction with ethylene oxide to nucleophilic agents other than those known to react. In pursuit of this objective, a variety of possible enolate-forming compounds were chosen for study under a variety of conditions.

Using ethyl acetate, methyl acetate, or ethyl phenylacetate, the hoped-for reaction is illustrated by the equation:



where R can be methyl or phenyl and R', methyl or ethyl.

Other enolate-forming compounds used in the study include acetylacetone, acetonitrile, phenylacetonitrile, and nitromethane. The hoped-for reactions between these materials and ethylene oxide are illustrated below.



The general reaction conditions cited above were used for part of the work because of their demonstrated success in causing the formation of an enolate anion or other reactive intermediates from active methylene compounds similar to several of those used in this study. Other bases thought favorable for the formation of similar reactive species from active methylene compounds included sodium sand, colloidal sodium adsorbed on inert solids (2) and tertiary amines such as triethylamine.

Procedure and Results

The various experiments will be grouped according to the procedure used for the formation of the enolate anion. All the experiments carried out in conjunction with a given section will not be described; only those which can be considered typical of the procedure will be reported.

Use of Sodium Sand for the Preparation of Sodium Enolates

Apparatus

A one-liter three-neck flask heated by a one-liter Glas-Col mantle was fitted up in the following manner. The center neck was fitted with a 2-inch monel metal stirring paddle connected to a cone-drive stirring motor. One of the side necks was furnished with an ice-water-cooled reflux condenser which was connected to a 500-ml. gas-measuring burette. A 500-ml. erlenmeyer flask was inserted in the path between the condenser and the gas-measuring burette to act as a trap for volatile materials. The flask was kept in an ice bath.

The gas-measuring burette was furnished with a three-way stopcock so that the gas stream from the reaction flask could be directed into the burette or else vented out the window. The water in the gas-measuring burette was displaced into a large leveling bulb.

The third neck could be fitted in three ways, depending on the operation being carried out. During the sodium sand preparation, a rubber stopper holding a thermometer was used. For the preparation of the enolate, a separatory funnel was fitted into the opening, a pressure-equalizer tube being connected from the flask to the top of the separatory funnel. For the reaction of the enolate with ethylene oxide, the third neck was furnished with a gas-inlet tube which dipped below the level of the liquid in the reaction flask.

Preparation of Sodium Sand

Sodium metal (23 g., 1 mole) was added to 200 ml. of xylene in the reaction flask. About 1 ml. of oleic acid was added as a dispersion aid. The mixture was heated to 105° and the stirrer started at the highest speed of a cone-driven stirrer (1200 R.P.M.). The high-speed stirring was continued for about 30 minutes, by the end of which time the sodium had been dispersed to the size of small grains of sand. Heating and stirring were discontinued.

After the mixture had cooled to room temperature, the xylene was decanted off and the residual sodium sand washed with about 100 ml. of anhydrous ethyl ether, which was also decanted. A fresh portion of 200-300 ml. of anhydrous ethyl ether was then added as a medium for the formation of the enolate.

Preparation of the Sodium Enolates of Carboxylic Esters and their

Reaction with Ethylene Oxide

Trial I

After the sodium sand had been prepared as described above, the third neck of the reaction flask was fitted with the separatory funnel and ethyl acetate (100 ml., 1 mole) was placed in it. The sodium sand-ether slurry was stirred at low speed and heated until the ether was at a gentle reflux. With this rate of heating continued, the dropwise addition of ethyl acetate was started and completed in three hours. During this time, 25% of the theoretical hydrogen evolution was observed. At the end of the addition, the reaction mixture was an orange-yellow slurry.

Ethylene oxide (50 ml., 1 mole) was condensed and slowly bubbled through the reaction mixture on a stream of dry nitrogen. Two hours were required for this addition. No indication of reaction was noted. The mixture was allowed to stir an additional four hours and during

this time the mixture darkened until it had become deep red-brown in color.

Acetic acid (60 ml., 1 mole) was added dropwise over a 45-minute period to decompose any sodium enolates or alkoxides present. The material was transferred to a one-liter erlenmeyer flask and the reaction flask rinsed with a total of 250 ml. of water in several small portions. The aqueous rinses were combined with the organic material and the mixture was allowed to stand in the ice chest overnight.

The mixture was poured into a separatory funnel and after the phases had separated, the lower aqueous layer was drawn off and discarded. The upper ether layer was washed twice with 50-ml. portions of cold saturated sodium bicarbonate solution. The ether layer was then dried over anhydrous calcium chloride and the material distilled to remove the ether. The residue was subjected to fractional distillation on a Todd column.

On the basis of physical properties observed, the following products were obtained: ethanol-ethyl acetate azeotrope, ethylene glycol diethyl ether, ethylene glycol monoethyl ether, and possibly some ethylene glycol monoacetate and ethylene glycol diacetate.

Trial II

The same general procedure used in Trial I was used with the same general results except that only 15% of the theoretical amount of hydrogen was evolved during the enolate formation stage.

Trial III

The same general procedure used in Trial I was used except that one mole of methyl acetate was used in place of ethyl acetate. The observed hydrogen evolution was 31% of theory. After the addition of ethylene oxide had been completed, the reaction mixture was not as dark as in the case of the reaction using ethyl acetate. No material boiling in the

desired range was found after the reaction had been worked up and distilled as in Trial I.

Trial IV

Sodium metal (5 g., 0.2 mole) was converted to a suspension of sodium sand in anhydrous ethyl ether as described above and then was treated with 34 g. (0.2 mole) of ethyl phenylacetate. A total of three hours was required for the addition of the ester but no accurate measure of gas evolution was obtained because of leaks which were discovered in the system.

Ethylene oxide (15 ml., 0.3 mole) was condensed and bubbled through the mixture on a stream of dry nitrogen over a 2-hour period. The mixture was then allowed to stand at room temperature for 15 hours before being treated with glacial acetic acid (15 ml., 0.25 mole) to convert the salts into the free hydroxylic materials. The reaction mixture was then treated with 300 ml. of water, saturated with sodium chloride and allowed to stand in the ice chest over the week end.

The ether phase was separated and washed with two 50-ml. portions of saturated sodium bicarbonate solution. The ether phase was then dried over anhydrous sodium sulfate and the ether distilled off. Fractional distillation of the residue at 4 mm. yielded about 4 ml. of ethyl phenylacetate and about 10-15 ml. of a yellow-brown gum as residue.

Preparation of the Sodium Enolate of Nitromethane

One mole (23 g.) of sodium sand was prepared as described previously, slurried with 300 ml. of anhydrous ethyl ether and brought to a gentle reflux. The dropwise addition of nitromethane (53 g., 1 mole) was started from the separatory funnel. At first a great deal of hydrogen was rapidly evolved but this stopped and it then came off very slowly for about 3.5 hours. During the period of rapid hydrogen evolution,

each addition of nitromethane resulted in an extremely vigorous reaction whereas later additions caused almost no reaction.

After all but about 3 ml. of the nitromethane had been added and 50% of the theoretical hydrogen had been evolved, a rapid evolution of hydrogen set in. The system was not capable of handling the volume of gas being evolved and so various stoppers were blown out. The gas and ether spray became ignited (probably by the arcing of the centrifugal pump motor). As the worst of the fire was put out, the contents of the flask detonated, completely demolishing the apparatus.

It is thought that the explosion was due to the detonation of the sodium enolate of nitromethane, which was probably formed in almost quantitative yield.

Preparation of High-Surface Sodium (2) and its use to Prepare Sodium Enolates of Carboxylic Esters

The apparatus used in the sodium enolate reaction described above was modified as follows. The cone-drive stirrer was replaced with a gear-driven Mixmaster motor, and the two-inch monel metal stirring paddle was replaced with a three-inch one of the same type.

One pound (454 g.) of Alcoa Activated Alumina, grade F-1, 8-14 mesh was charged into the one-liter reaction flask and under slow stirring was heated to 150°. Sodium metal (24 g., 1 mole), in the form of small pieces, was then added. The sodium metal melted and spread upon the surface of the alumina which changed from white to light grey during the process. The mixture was then allowed to cool to room temperature.

Sufficient anhydrous ethyl ether was then added to cover the solids and 100 ml. (1 mole) of ethyl acetate was added dropwise over a 1.5-hour period. Over a seven-hour period, only 25% of the theoretical amount of hydrogen was evolved. An additional 100-200 ml. of anhydrous ethyl

ether was added to the thick white slurry at this point.

Ethylene oxide (50 ml., 1 mole) was bubbled through the reaction mixture on a stream of dry nitrogen over a 1.5-hour period. No evidence of reaction was observed. The reaction mixture was allowed to stand at room temperature (35-40°) overnight.

The mixture was then treated with 60 ml. (1 mole) of glacial acetic acid over a 45-minute period. The mixture was then treated with about ten 100-ml. portions of water to wash the material free of the alumina although much of the fine alumina powder came with the washings. The aqueous washings were combined and steam distilled and the 300-ml. steam distillate was saturated with sodium chloride and then extracted with ethyl ether.

The ether extract was dried and distilled. After the ether was removed, further distillation did not give any material boiling in the desired range.

Reactions in an Aqueous Sodium Hydroxide Medium

The general procedure used is described below and is followed by Table VII, which summarizes the results obtained by the use of several different compounds.

Sodium hydroxide (10 g., 0.25 mole) was dissolved in water (70 ml.) in a 500-ml. round-bottom flask, ethanol (75 ml.) was added and the solution cooled to 0°. Ethylene oxide (13 ml., 0.25 mole) and the reagent to be used (0.25 mole) were cooled to 0°, mixed and added with swirling to the basic solution.

After standing at 0° for 24-41 hours, the mixture was treated with glacial acetic acid (15 ml.) and extracted with three 50-ml. portions of benzene. The benzene extracts were combined, dried over anhydrous sodium sulfate, and then distilled to remove the benzene and to separate any

products.

Table VII

Reaction of Ethylene Oxide (0.25 mole) with Various Reagents
(0.25 mole) in Aqueous Sodium Hydroxide

Reagent	Hours at 0°	Products of Distillation	Residue
Acetonitrile	24	Acetonitrile and 2-ethoxy-ethanol	less than 2 ml. liquid
Phenylacetonitrile	24	Phenylacetonitrile	less than 1 ml. liquid
Ethyl phenylacetate	24	Ethyl phenylacetate	Phenylacetic acid
Acetylacetone	41	Acetylacetone	2 ml. orange liquid

A reaction involving ethylene oxide and nitromethane was carried out in aqueous sodium hydroxide as follows.

Sodium hydroxide (40 g., 1 mole) was dissolved in 200 ml. of water contained in a three-neck flask equipped with a power stirrer, a thermometer, and an ice-water-cooled reflux condenser. The reaction flask was cooled in an ice bath.

After the above solution had cooled to ice temperature, nitromethane (53 g., 1 mole) was added in small portions at such a rate as to keep the temperature of the reaction mixture below 30°. When the addition was complete (30 minutes), the mixture was cooled to below 5° and ethylene oxide (50 ml., 1 mole) was added in portions over a 30-minute period so as to keep the temperature of the reaction mixture below 10°. The mixture was stirred at ice-bath temperature for an additional 6 hours after which it was allowed to warm to room temperature. At the end of this time, the mixture was black.

After standing at room temperature for 36 hours the reaction mixture

was cooled in an ice bath and treated with 60 ml. (1 mole) of glacial acetic acid to destroy the sodium hydroxide or alkoxide present. The mixture was then stirred at ice temperature for 2.5 hours before being allowed to warm to room temperature.

The resulting red-black viscous oil was extracted with two 100-ml. portions of ethyl ether and the ether extracts were combined, dried, and distilled. After the ether had been removed, only a small residue remained.

The acidic aqueous phase was steam-distilled and the distillate saturated with sodium chloride and extracted with ethyl ether. The ether extracts were combined, dried, and distilled but left almost no residue after the ether had been removed.

Reactions in Alcoholic Sodium Ethoxide

The general procedure used is described below, followed by Table VIII, which summarizes the results obtained by the use of several different compounds.

Sodium metal (6 g., 0.25 mole) was dissolved in 150 ml. of absolute ethanol in a 500-ml. round-bottom flask and the solution was cooled to 0°. Ethylene oxide (13 ml., 0.25 mole) and the reagent to be used (0.25 mole) were cooled to 0°, mixed and added with swirling to the basic solution. After standing at 0° for 27-40 hours, the mixture was distilled to remove the ethanol.

The residue was treated with 50 ml. of benzene, 150 ml. of ice and water, and finally with 25 ml. of 12N hydrochloric acid. The benzene layer was separated and the aqueous phase extracted twice more with 50-ml. portions of benzene. The three benzene extracts were combined and dried over anhydrous sodium sulfate, and the mixture was distilled to remove the benzene and to separate any products.

Table VIII

Reaction of Ethylene Oxide (0.25 mole) with Various Reagents
(0.25 mole) in Alcoholic Sodium Ethoxide

Reagent	Hours at 0°	Products of Distillation	Residue
Acetonitrile	27	Acetonitrile	5 ml. residue
Phenylaceto- nitrile	27	Phenylacetonitrile	Phenylacetic acid
Ethyl phenyl- acetate	40	Very small amount of ethyl phenylacetate	Phenylacetic acid
Acetylacetone*	27	Acetylacetone	Essentially none

* A total of 250 ml. of ethanol was required in this experiment in order to keep the sodium salt of acetylacetone in solution.

Use of Anhydrous Sodium Methoxide as an Enolate-forming Reagent

Anhydrous sodium methoxide (16 g., 0.3 mole) was added, over a 30-minute period, to acetonitrile (106 ml., 2 moles) in a 250-ml. round-bottom flask. The mixture was allowed to stand at room temperature for an hour and then was distilled to remove methanol-acetonitrile azeotrope. Very little material came over at the azeotrope boiling point (63.5°) but 70 ml. of distillate were collected up to 81°.

The residue was cooled to ice temperature and ethylene oxide (20 ml., 0.4 mole) in acetonitrile (25 ml., 0.5 mole) was added in small portions over a 30-minute period. No evidence of reaction was noted. The mixture was allowed to warm to room temperature and stand for 5 hours. It was then cooled to ice temperature again and slowly acidified with 25 ml. of 12N hydrochloric acid. Anhydrous sodium sulfate was then added and the mixture allowed to stand for 30-40 minutes, before the organic material was decanted off and arranged for distillation.

After the excess acetonitrile had been removed, only a small amount

of red liquid remained as residue.

Triethylamine-Catalyzed Reactions of Ethylene Oxide

Twelve reaction mixtures were set up in the following manner. The amount indicated below of the reagent being tested was placed in a 500-ml. round-bottom flask and 5 ml. (0.036 mole) of triethylamine were added. The mixture was chilled and ethylene oxide (25 ml., 0.5 mole) was added, the mixture swirled to mix the reagents, and then the flask was stoppered with an aluminum foil-covered cork. The mixture was allowed to stand at room temperature for some days.

The compounds and amounts used were: diethyl malonate (16 g., 0.1 mole), ethyl acetoacetate (13 g., 0.1 mole), ethyl cyanoacetate (12 g., 0.1 mole), ethyl chloroacetate (12 g., 0.1 mole), ethyl phenylacetate (17 g., 0.1 mole), ethyl acetate (18 g., 0.2 mole), acetonitrile (12 g., 0.3 mole), phenylacetonitrile (12 g., 0.1 mole), benzonitrile (11 g., 0.1 mole), alpha-picoline (19 g., 0.2 mole), gamma-picoline (19 g., 0.2 mole), and nitromethane (12 g., 0.2 mole).

At the end of eleven days it was noted that there was no pressure in the flasks, giving rise to the possibility that some of the ethylene oxide had escaped. Distillation of the mixtures yielded a variety of results. In many cases the starting materials were recovered, in other cases water-soluble residues remained, and in still other cases, insoluble tars remained. The results of the experiments are summarized in Table IX. The residues would not distill at reduced pressure.

Diethylamine-Catalyzed Reactions

Trial I

Ethyl phenylacetate (41 ml., 0.25 mole) was cooled to 0° in a 500-ml. round-bottom flask. Diethylamine (5 ml., 0.07 mole) and ethylene oxide (25 ml., 0.5 mole) were added, the solution swirled to mix the

Table IX

Triethylamine-Catalyzed Reactions of Ethylene Oxide

Reagent	Days at Room Temperature	Nature of Distillate	Nature of Residue
Diethyl malonate	11	Some recovered reagents	4 ml. black tar
Ethyl acetoacetate	13	Some recovered reagents	4 ml. red viscous liquid
Ethyl cyanoacetate	14	Triethylamine and some ethanol	Black tarry solid
Ethyl chloroacetate	27	Some recovered reagents	Black viscous oil
Ethyl phenylacetate	30	Recovered reagents	3 ml. black tar
Ethyl acetate	30	Recovered reagents	1 ml. black tar
Acetonitrile	30	Recovered reagents	5 ml. water-soluble solid
Phenylacetonitrile	32	Some recovered reagents	10-12 ml. viscous brown water-insoluble liquid
Benzonitrile	32	Recovered reagents	3 ml. brown water-soluble viscous liquid
<u>alpha</u> -Picoline	33	Recovered reagents	3 ml. black water-soluble liquid
<u>gamma</u> -Picoline	33	Recovered reagents	5 ml. black water-soluble liquid
Nitromethane	33	None	Black tar

reagents and the flask stoppered.

After standing at 0° for 72 hours the mixture was allowed to warm to room temperature and the excess ethylene oxide was removed under reduced pressure. Fractional distillation under reduced pressure yielded only ethyl phenylacetate as a high-boiling fraction.

Trial II

The experiment described above was carried out using acetylacetone (25 ml., 0.25 mole) in place of the ethyl phenylacetate. Upon fractional distillation of the reaction mixture, only acetylacetone was obtained as a high-boiling fraction.

Discussion

The failure to obtain enolate anion-ethylene oxide reactions in the experiments described in this section may be due to the failure to form enough enolate anion, an unfavorable rate and/or equilibrium in the enolate anion-ethylene oxide reaction, or the occurrence of unfavorable side reactions.

A failure to form enough enolate anion may be attributed to either low acidity on the part of the enolate or low basicity of the base, or both. It does appear that diethyl malonate, ethyl acetoacetate and ethyl cyanoacetate, all successfully converted into enolate anions by ethoxide ion, are stronger acids than the ones now tried with the probable exception of nitromethane. Sodium metal is active enough to attack even very weak acids but causes too much hydrogenation. That this is the case has been indicated by the relatively small amount of hydrogen evolved during the course of the reactions between sodium sand and ethyl acetate or methyl acetate. Ethyl phenylacetate is surely more acidic, but even here results were unsatisfactory and probably would always be so with sodium metal. Once started and maintained, the reaction of nitromethane with sodium sand apparently goes without reduction of the nitro group as evident from the amount of hydrogen evolved. However, the hazards encountered when the reaction got out of control discouraged further studies. The explosive nature of the sodium salts of nitroparaffins has been reported before (32,58). If an inert non-aqueous solvent could be found for the salt, the otherwise attendant hazards would probably be greatly minimized and the reaction of the enolate with ethylene oxide would probably have a good chance of success.

The failure to obtain reaction in the experiments involving aqueous sodium hydroxide or alcoholic sodium ethoxide media indicates that the

hydroxide and ethoxide ions are probably too weak as bases and therefore the enolate-enolate anion equilibrium is unfavorable. For an example from other work, ethyl isobutyrate is unaffected by ethoxide ion but reacts readily with triphenylmethyl anion to yield an enolate anion capable of reacting with ethylene oxide (36). The use of triphenylmethylsodium as a source of triphenylmethyl anion would probably guarantee carbanion formation in a number of the active methylene compounds studied but such a reagent is exceedingly expensive to use in time and money. Conceivably it could be made more simply from triphenylmethane and sodium, but triphenylmethane is not cheap and its equivalent weight is high. Hydride ion (from sodium hydride) is a possibility but it still might cause hydrogenation, though it is less likely to than sodium metal itself. Aside from its expense, the use of NH_2^- from sodium amide might be a useful enolate anion-forming reagent if the ammonia liberated during the enolate anion formation did not cause undesirable side reactions.

Secondary and tertiary amines, which are certainly weak bases, have caused reactions of enolate-forming compounds such as diethyl malonate and ethyl acetoacetate with ethylene oxide. It is uncertain whether or not an enolate anion is formed in these cases. The triethylamine-catalyzed reactions in the present work probably failed largely because most of the ethylene oxide escaped before it could react. Even so, the nature of some of the residues indicated that reaction had started to take place. The black undistillable tar obtained by the interaction of nitromethane with ethylene oxide under the influence of triethylamine is like that obtained by Strong (93) in a similar reaction catalyzed by ethylene diamine. Although the ethylene oxide was retained in the two trials using diethylamine as catalyst, the temperature was apparently so low that no

detectable reaction took place.

The results described above may also be due to an unfavorable rate and/or equilibrium in the enolate anion-ethylene oxide reaction. Raising the temperature would help the rate but would also tend to increase the rate of competing reactions. One would think that the driving force of the ethylene oxide ring opening would minimize any unfavorable equilibrium factor, but perhaps an excess of the oxide would be required to provide additional driving force. It would appear that the reagents (with an excess of ethylene oxide) will have to be sealed in glass and allowed to stand at room temperature, or above, for some time before the desired reaction will take place to any substantial degree.

There was no direct evidence of side reaction but there is a chance that some may have taken place. The principal side reaction would certainly be what may be called the generalized aldol reaction in which the carbanion adds into the multiple bond of another molecule of its own kind ($C=O$, $C\equiv N$). There may be subsequent changes, as there are in the Claisen condensation when the alkoxide anion splits out. There is no obvious way to judge whether the addition of the enolate carbanion will be more to the $C=O$ or $C\equiv N$ of another molecule or to the epoxide linkage.

There appears to be a striking similarity of required reaction conditions and yields obtained in the alkylation and beta-hydroxyalkylation of certain enolizable compounds. The statements of yields and general reaction conditions cited below were obtained from Synthetic Organic Chemistry by R.B. Wagner and H.D. Zook (100). Olefin oxide react with the sodium enolates of malonic esters, cyanoacetic esters and acetoacetic esters in yields of approximately 85%, 75%, and 60%, respectively. Alkylation of the sodium enolates of the same esters by primary alkyl halides takes place to the extent of 75-90% for malonic ester, 65-76% for cyano-

acetic ester, and 50-70% for acetoacetic ester. In all cases the enolates were formed by the action of sodium ethoxide on the ester. However, the action of sodium ethoxide does not suffice to convert acetylacetone, substituted acetic acid esters, nitroparaffins, or nitriles into enolates which are then capable of being alkylated by alkyl halides.

Treatment of powdered sodium in ethyl ether with acetylacetone followed by the addition of an alkyl halide gives only 30-32% yields of the 3-alkyl-2,4-pentanedione. When esters of dialkylacetic acids are treated with triphenylmethylsodium and then an alkyl halide, yields of esters of trialkylacetic acids ranging from 42 to 61% are obtained. alpha-Alkylated nitriles are obtained in yields of 60-88% when an alkyl halide is added to a mixture of a nitrile and sodium amide. The condensation of para-nitrobenzyl chloride with the sodium salt of nitroethane gives an 83% yield of 1-para-nitrobenzyl-1-nitroethane.

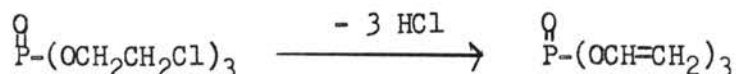
The discussion in the preceding paragraph has been presented by way of illustration of the types of reaction conditions which might have to be used, and the kinds of yields that might be expected, if the reaction of olefin oxides with the classes of active hydrogen compounds listed is to be studied further. It would seem reasonable that since the alkylation and beta-hydroxyalkylation of malonic, cyanoacetic, and acetoacetic esters appear to be analogous, similar alkylations of acetylacetone, dialkyl- or diarylacetic acid esters, nitroparaffins and partially substituted or unsubstituted acetonitriles should also be analogous. Further work is required to prove or disprove the viewpoint presented above.

EXPERIMENTAL - PART D

Other Reactions Involving Ethylene Oxide

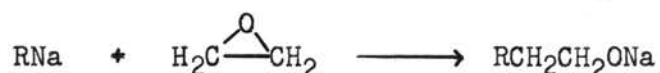
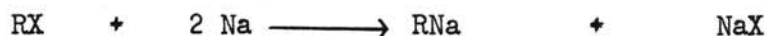
Introduction

A. Although there were no vinyl phosphates recorded in the literature it was thought possible to dehydrohalogenate tris-2-chloroethyl phosphate so as to obtain trivinyl phosphate. Such an ester would be of considerable interest as a monomer for polymerization. The hoped-for reaction is illustrated below.



The tris-2-chloroethyl phosphate is readily prepared by the interaction of ethylene oxide and phosphorus oxychloride, which is of course the reason for its study here. During the time this work was in progress Upson (97) published a paper dealing with the dehydrohalogenation of diethyl 2-chloroethyl phosphate to diethyl vinyl phosphate.

B. The reaction of an alkyl halide with sodium to yield a hydrocarbon (the Wurtz reaction) probably proceeds via an organosodium compound. By the use of excess metal and low temperature, it was hoped to stop the reaction at the organometallic stage long enough to trap such a compound with ethylene oxide. The reaction of ethylene oxide with Grignard reagents is well known, so that such a procedure has no great novelty as a synthesis, but it might have some additional convenience.



The reaction would be directly analogous to the sodium-promoted condensation of organic halides and carbonyl compounds recently reported (26a).

Procedure and Results

Attempted Dehydrohalogenation of tris-2-Chloroethyl Phosphate

The tris-2-chloroethyl phosphate was successfully prepared according to the method of Daly and Lowe (19) by treating phosphorus oxychloride with ethylene oxide in the presence of aluminum chloride.

Two dehydrohalogenation experiments were conducted.

Apparatus

A 200-ml. round-bottom flask was equipped with a reflux condenser. A glass tube was fitted to the top of the condenser and by means of two right-angle bends was brought down so as to reach the bottom on an eight-inch side-arm test tube. The test tube was set in an ice bath and the side-arm was vented. The flask was heated by means of a Glas-Col heating mantle controlled by a Powerstat.

Trial I

Tris-2-chloroethyl phosphate (30 g., 0.11 mole) was placed in the reaction flask. Benzene (100 ml.) and potassium hydroxide pellets (18.5 g., 0.33 mole) were added. At the end of a six-hour reflux period, the material in the flask had become a pale yellow.

During the reflux period, 3 ml. of a water-white liquid collected in the ice trap. From its volatility, lack of acetaldehyde odor, and its vigorous reaction with sulfuric acid, it was decided that the substance was ethylene oxide.

The mixture in the reaction flask was separated into two portions, liquid phase A and solid phase B.

Distillation of phase A gave a water-white to cloudy distillate boiling between 65 and 78°. This material showed no active unsaturation toward bromine in carbon tetrachloride or to 1% aqueous potassium permanganate. Hydrolysis of 10 ml. of the distillate with 25 ml. of 2N

hydrochloric acid for 30 minutes at 65° on a steam bath gave no detectable amount of acetaldehyde. It was concluded that the distillate contained no vinyl compound, since any vinyl ester, on hydrolysis, should give acetaldehyde.

A yellow residue from the distillation gave a slightly positive unsaturation test with the bromine in carbon tetrachloride and 1% aqueous potassium permanganate. Hydrolysis of 10 ml. of the residue with 25 ml. of 2N hydrochloric acid for 30 minutes on a steam bath at 65-75° gave some benzene with a slight trace of acetaldehyde odor. However, no acetaldehyde itself was received.

Trial II

This experiment was set up as in Trial I except that 100 ml. of isopropylbenzene were used in place of benzene.

As the mixture was heated and came up to the reflux temperature, a very vigorous reaction took place and most of the liquid boiled over into the ice trap. The pot material became viscous and dark brown in color. After the reaction had subsided and the pot cooled down, the liquid in the trap was poured back into the reaction flask. After being allowed to stand an additional two hours the mixture was separated into a yellow liquid (phase A) and a pasty brown wax (phase B).

Distillation of phase A, with 1-2 g. of hydroquinone added as a polymerization inhibitor, gave a yellow liquid boiling between 100 and 142°. The distillate showed active unsaturation toward bromine in carbon tetrachloride and toward 1% aqueous potassium permanganate. Hydrolysis of 10 ml. of the distillate with 25 ml. of 2N hydrochloric acid for 30 minutes on a steam bath at 95° gave no detectable amount of acetaldehyde. It is thought that the positive unsaturation tests were due to traces of hydroquinone carried over into the distillate.

Acid hydrolysis of the distillation residue and of the pasty brown mass from the reaction (phase B) likewise gave no detectable quantities of acetaldehyde.

Attempts at the Formation of Butylsodium and its Reaction with

Ethylene Oxide

Apparatus

A one-liter three-neck flask was equipped as follows. The center neck was fitted with a cone-drive stirrer. Each side neck was fitted with a two-neck addition tube. One of the necks of each addition tube was joined to a 60 cm. air condenser. One of the condensers was left open to the air while the other was connected to a tank of nitrogen. The nitrogen was first passed through a mineral-oil bubbler to give an indication of flow rate. The other neck of the addition tube was furnished with a thermometer whose bulb reached into the contents of the reaction flask if at least 200 ml. of material were present. The fourth neck of the addition tubes was fitted with a rubber stopper, the removal of which allowed the addition of material to the flask.

The reaction flask was placed in a four-liter stainless-steel beaker containing 2.5 liters of kerosene. The stainless-steel beaker was placed in a 10-quart enameled bucket containing crushed ice. This arrangement provided a means for cooling the reaction vessel without the danger of sodium coming in contact with water in the event that the reaction flask broke.

Trial I

Ethylene oxide (150 ml., 3 moles) was placed in the reaction flask and a nitrogen atmosphere introduced. Sodium metal (46 g., 2 moles) cut into small, clean pieces was washed with anhydrous ethyl ether and added to the ethylene oxide. Then n-butyl bromide (b.p. 101-102°)(137 g.,

1 mole) was added to the reaction flask over a 1.5-hour period. The temperature of the reaction mixture remained at 5 to 10° during the addition.

After the sodium had been stirred in the ethylene oxide for about one hour a white coating was gradually splashed up onto the walls of the flask. After the addition of the n-butyl bromide was started the coating became thicker and slowly became yellow. After all the n-butyl bromide had been added, the mixture was allowed to stir at 0-5° for 8 hours and then allowed to warm to and stand at room temperature (35°) overnight. Provision was made to trap and condense any ethylene oxide which might distill over.

As the reaction mixture warmed up overnight, apparently some reaction took place since a considerable quantity of black material was found sprayed up into the necks of the flask and about 40-50 ml. of a dark liquid was obtained in the chilled receiver. This material was ethylene oxide with a small amount of tarry residue.

A total of 150 ml. of denatured alcohol was added in small portions to destroy the excess sodium. Upon removal from the kerosene bath the reaction mixture was a deep grey semi-fluid mass. Active pieces of sodium still remained and were destroyed by adding, in small portions and with stirring, a large excess of denatured alcohol.

The mixture was transferred to a one-liter beaker and the three-neck flask washed out with alcohol. Some black chips of residue remained. It was found that these black chips contained small bits of active sodium metal. The grey mixture was treated with glacial acetic acid until it was neutral to Hydrion paper. Just before the neutral point the contents of the beaker set into a solid mass, but upon treatment with 50 ml. of denatured alcohol and a little more acetic acid the

mass became fluid again. The grey mass was filtered with suction, washed with alcohol, dried at the pump and saved.

Part of the alcohol in the filtrate was evaporated under suction. The filtrate had a deep brown color and contained white crystals which were thought to be sodium acetate. The crystals were filtered off and the filtrate distilled through a Todd column. No material corresponding to the hoped-for n-hexyl alcohol was received.

Trial II

The apparatus described above was modified as follows. The air condensers were removed and the nitrogen inlet made directly to the addition tube. The exit tube led to a chilled trap to condense ethylene oxide. The inlet side was fitted with a glass tube which led below the level of the liquid in the reaction flask and which was used to bubble ethylene oxide through the reaction mixture. A copper coil through which ice water was circulated was placed in the kerosene cooling bath.

Decahydronaphthalene (200 ml.) was placed in the reaction flask and a nitrogen atmosphere was introduced. The cooling bath was temporarily replaced with a one-liter Glas-Col heating mantle. Clean sodium metal (27 g., 1.17 mole) was added to the liquid and the mixture was heated to 105°. After the sodium had melted, the mixture was stirred at the highest speed of a cone-driven stirrer with a 1.5-inch half-moon monel metal stirrer. The sodium was dispersed into particles about the size of sand grains. Upon cooling, the sand-grain-sized particles remained in suspension as long as the stirring was continued. When stirring was stopped, the particles settled out but were readily dispersed again upon resumption of stirring. The heating mantle was removed and replaced by the kerosene cooling bath.

n-Butyl chloride (62.2 g., 0.68 mole) was added slowly, over a three-hour period, to the sodium dispersion described above. Except for an initial rise to 50° , the temperature was maintained between 38 and 43° during the addition. By the time all of the alkyl halide had been added, the solution was deep purple in color.

About 300 ml. of ethylene oxide was condensed and then slowly distilled through the purple butylsodium solution. A sharp rise in temperature (to about 60°) was noted at the start of the reaction but this subsided upon cooling. Thereafter, without cooling, slowly bubbling ethylene oxide through the purple solution maintained the reaction temperature at 45 - 48° . The color of the mixture gradually changed from purple to black to brown. The purple color was completely discharged after about 1.5 hours but the black color still remained. After an additional hour the temperature began to drop slowly, and the entering ethylene oxide was recovered essentially without change.

The reaction mixture was then treated with denatured alcohol to destroy the excess sodium. Addition of 10 ml. of alcohol caused the temperature to rise rapidly to a peak of 120° . Upon cooling to 70° , the addition of another 40 ml. of alcohol caused the temperature to rise to 85° . After cooling to 70° again, the addition of 100 ml. of alcohol caused no further temperature rise.

The mixture was a deep brown paste at this time. The mixture was cooled to below 50° and treated dropwise with concentrated sulfuric acid. The mixture was neutral as indicated by Hydrion paper after 15 ml. of the acid had been added. The neutralized, dark-brown mass was cooled overnight in the reaction flask.

The mixture was filtered to remove the solids. The filtrate formed two layers: a light-brown top layer and a deep brown bottom layer. The

layers were separated and each was distilled through a Todd column.

No material corresponding to the hoped-for n-hexyl alcohol was obtained. There was considerable decomposition in the distillation of the bottom layer, most of which formed a water-insoluble carbonaceous residue. The top layer was essentially decahydronaphthalene.

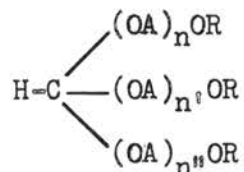
Discussion

The formation of trivinyl phosphate by treatment of tris-2-chloro-ethyl phosphate with a suspension of alkali metal hydroxide in an aromatic hydrocarbon was not successful. It is not certain whether the failure was due to any inherent instability on the part of the vinyl phosphate or simply a poor choice of reaction conditions. Before any definite statement can be made regarding the stability of the ester, other dehydrohalogenation attempts should be made, preferably seeking a mono-vinyl compound first. The use of alcoholic sodium hydroxide or alcoholic sodium ethoxide might prove practical in this respect.

One of the difficulties in preparing alkylsodium compounds seemed to be the coating of the sodium metal with sodium chloride, or the alkylsodium, thereby preventing further attack on the sodium metal by the alkyl halide. This was true even when sodium sand was used. The use of high-surface sodium might result in a cleaner preparation of the alkylsodium and thereby might increase the chances of getting reaction with ethylene oxide. Even though none of the expected product was detected in the two trials made, a different set of reaction conditions might serve to effect the reaction. Of the two serious side reactions noted by Frank and Foster (26a) -- metallation of an enolizable carbonyl compound and dehydrohalogenation of an alkyl halide -- only the latter is a factor here, since ethylene oxide cannot form an enolate.

SUMMARY

A new reaction between olefin oxides and alkyl orthoformates has been developed. The reaction results in the formation of compounds having the generic formula:



in which A is a bivalent hydrocarbon radical, simple or substituted, having free valence bonds on adjacent carbon atoms, such as ethylene or propylene; n is 1 or any larger integer; n' and n'' are any integers including zero; and R is an alkyl group such as methyl or ethyl. Products of the type mentioned above are formed in satisfactory yield by the interaction of an alkyl orthoformate with an olefin oxide in the presence of not more than 0.5% of boron trifluoride as catalyst and in the temperature range between 0 and 10°. Concentrated sulfuric acid, anhydrous stannic chloride, hydrated calcium silicate, and boron trifluoride etherate were not effective as catalysts for the reaction. Heating the reagents without catalyst in a sealed tube resulted in no reaction at 110-135° and explosion of the tubes at 145-147°.

Indication of a similar reaction between ethylene oxide and ethyl orthoacetate was obtained from indistinct plateaus of a distillation curve. However, the reaction does not proceed to any appreciable extent under the same conditions that gave good results in the orthoformate-olefin oxide work.

No reaction was observed between ethylene oxide and esters such as methyl orthobenzoate, methyl orthoborate, ethyl orthosilicate, methoxy-

methyl acetate, and methylene diacetate under conditions of boron trifluoride catalysis. n-Butyl vinyl ether also could not be thus condensed with ethylene oxide.

A novel, yet relatively simple procedure was developed for the preparation, in good yield, of methoxymethyl acetate and methylene diacetate by an acid-catalyzed reaction of acetic anhydride with methylal. The use of small amounts of catalysts such as concentrated sulfuric acid, 85% phosphoric acid, anhydrous stannic chloride, or commercial boron trifluoride etherate converted an equimolar mixture of methylal and acetic anhydride into methoxymethyl acetate in yields up to 80% of theory. Only concentrated sulfuric acid was studied as a catalyst for the conversion of methoxymethyl acetate or methylal into methylene diacetate. Such a conversion takes place in 70% and 50% yields, respectively. Preliminary studies indicated that the reaction is general for acid anhydrides and also for acetals.

Attempted condensations of ethylene oxide with acetylacetone, ethyl phenylacetate, phenylacetonitrile, and acetonitrile under conditions which are reported to result in reaction in the case of diethyl malonate and ethyl acetoacetate did not give any indication of the desired reaction. The treatment of sodium sand with methyl acetate, ethyl acetate, and ethyl phenylacetate in an attempt to form the sodium enolates of the esters followed by treatment with ethylene oxide did not yield any of the desired butyrolactone. From the smallness of the amount of hydrogen evolved it seemed that reduction of the esters took place to the exclusion of the enolate formation. Treating sodium sand in a similar manner with nitromethane apparently produced the sodium salt of nitromethane in high yield but the explosion hazards encountered in handling this material discouraged further studies.

The attempted formation of tris-vinyl phosphate by the dehydrohalogenation of tris-2-chloroethyl phosphate was not successful.

The attempted preparation of n-butylsodium followed by the addition of ethylene oxide did not give any detectable amount of the hoped-for n-hexyl alcohol.

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