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The Reactions of Ethyl Acetoacetate With Certain Halogen Derivatives of Alcohols

Harold E. Sullivan
Fort Hays Kansas State College

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THE REACTIONS OF ETHYL ACETOACETATE WITH CERTAIN
HALOGEN DERIVATIVES OF ALCOHOLS

being

A thesis presented to the Graduate Faculty
of the Fort Hays Kansas State College in
partial fulfillment of the requirements for
the Degree of Master of Science

by

Harold E. Sullivan, A. B.

Fort Hays Kansas State College

Date

July 20, 1949

Approved

Harold D. Choquill
Major Professor

F. J. Robertson

Chairman Graduate Council

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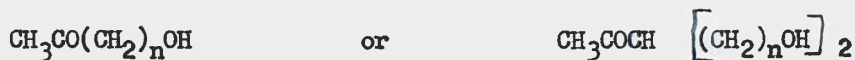
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INTRODUCTION

Chemical literature records many series of compounds produced by the acetoacetic ester synthesis, but in no instance is combination of the acetoacetic ester with the halogenated alcohols, of which the chlorohydrins are examples, mentioned. The products of these reactions are substituted derivatives of the acetoacetic ester. These products yield, upon hydrolysis, hydroxy-ketones.



and hydroxy-acids.



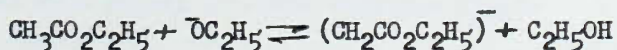
These acids and ketones may serve as intermediates for synthesizing other compounds. Many compounds which have medicinal value, such as pyrazolones and other ring compounds, may be synthesized from the acetoacetic ester derivatives.

This study of the reactions of the acetoacetic ester with certain halogen derivatives of alcohols was undertaken in an effort to prepare new intermediates. These intermediate compounds in turn may be used to synthesize new drugs and other organic compounds.

THE ACETOACETIC ESTER CONDENSATION

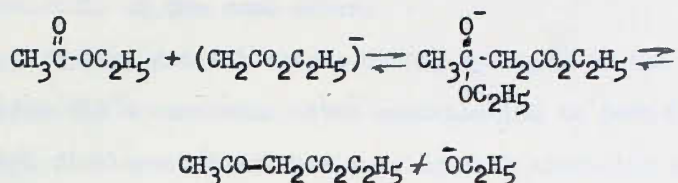
The acetoacetic ester condensation, also called the Claisen reaction, consists of the reaction, in the presence of certain bases, of an ester having hydrogen on the α -carbon atom with a second molecule of the same ester or with another ester (which may or may not have hydrogen on the α -carbon atom) to form a β -keto-ester. The bases capable of effecting such reactions include sodium alkoxides, triphenylmethylsodium, sodium amide, and certain Grignard reagents such as mesitylmagnesium bromide and isopropylmagnesium bromide. Also, metallic sodium effects certain condensations, the sodium alkoxide which is formed in the reaction mixture probably serving as the active condensing agent (17).

The classical example of the acetoacetic ester reaction is the formation of ethyl acetoacetate itself by condensation of two moles of ethyl acetate by means of sodium ethoxide. This reaction probably involves an ionic mechanism (10,6), the first step of which is an acid-base exchange; in the presence of the ethoxide ion the hydrogen on the α -carbon atom is ionized as a proton to form the ester anion (enolate anion), which is probably a resonance hybrid of the two structures ${}^{-}\text{CH}_2\text{-C}=\text{O}(\text{OC}_2\text{H}_5)$ and $\text{CH}_2=\text{C}-\text{O}^{-}(\text{OC}_2\text{H}_5)$.

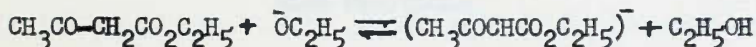


The second step involves the condensation of the ester anion with the carbonyl group of a molecule of unchanged ester, presumably forming an intermediate anion (with the charge on the oxygen) which,

on release of the ethoxide ion, forms acetoacetic ester.



Acetoacetic ester is then converted into its anion by the reaction of the ethoxide ion; this third step involves an acid-base reaction in which a hydrogen on the α -carbon atom of the β -ketoester is ionized.



Evidence has been furnished that esters form anions according to the first step of the mechanism, by the racemization of esters of optically active disubstituted acetic acids in the presence of ethoxide ion (7), and by the hydrogen-deuterium exchange of ethyl acetate and other esters with α -hydrogen atoms in the presence of this base and deuterio alcohol (2). That ester anions are the active intermediates in the condensation is shown by the fact that they may be prepared by means of the stronger base, the triphenylmethyl ion, and condensed with esters or other reagents (7,2).

Scope and Limitations

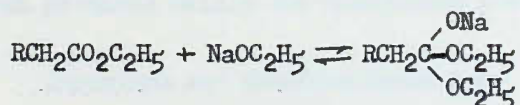
The acetoacetic ester type of reaction is used to prepare a variety of β -ketoesters and certain other compounds. The self-condensation of esters having hydrogen on the α -carbon atom may be

effected readily; this amounts to an acylation of the ester by another molecule of the same ester.

Apparently, not all esters having hydrogen on the α -carbon atom undergo the acetoacetic ester condensation to form β -ketoesters. Thus, ethyl dichloroacetate when treated with alcoholic sodium ethoxide yields ethyl oxalochloroacetate, diethyl acetal and ethyl diethoxyacetate (3). Although methyl diphenylacetate is converted by triphenylmethylsodium into its sodium enolate (which may be condensed with acid chlorides to form β -ketoesters) (9), the self-condensation of this ester apparently has not been effected.

Side Reactions

Probably the most important type of side reaction that is encountered when the acetoacetic ester condensation is carried out involves the reaction of the carbonyl group of the ester with the base used as condensing agent; this type of reaction is frequently the most characteristic reaction of the ester. Sodium alkoxides may react reversibly with the carbonyl group of the ester (9).

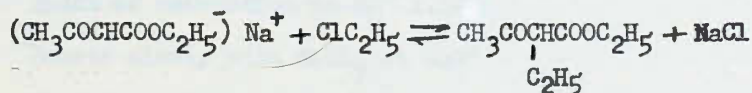


However, other bases of sufficient strength to ionize the α -hydrogen of esters and effect condensations are also capable of reacting irreversibly with the carbonyl group of esters. Thus, sodium amide effects the ammonolysis of esters (9), and the Grignard reagent react with esters to form ketones or carbinols.

Metallic sodium is capable of reacting with the carbonyl

group of esters to form acyloins (RCHOHCOR) and diketones (9) (RCOCOR), but in the presence of excess of ethyl acetate or ethyl propionate, metallic sodium effects only the acetoacetic ester condensation (16). With ethyl *n*-butyrate or ethyl isobutyrate and sodium, however, the acetoacetic ester condensation does not take place even in the presence of an excess of the ester; instead, acyloins, diketones, and higher-boiling products are formed (16).

Closely related to acylation of esters with esters (as occurs in the acetoacetic ester reaction) is the acylation of esters with acid chlorides or anhydrides. For example, ethyl acetoacetate in the form of its sodium enolate may be acylated with ethyl chloride, the reaction being essentially irreversible, to give ethyl- α (ethyl) acetoacetate. This reaction may be represented by the following equation.



This acylation of the sodium enolate usually does not stop at one substitution but produces mainly the diacylated product (8).

Structure and Reaction Mechanism

It is well agreed that the acetoacetic ester is tautomeric, that is, the molecule consists of two resonating forms, called the enol form and the keto form. The enol form contains a hydroxyl group on the α -carbon atom; the keto form has a double bonded oxygen on the α -carbon atom. These tautomeric formulas are listed on a following page.

In 1911 Knorr (1), a German chemist, succeeded in isolating the keto and enol forms. The keto form was obtained by dissolving the ester in hexane and cooling the solution to -78° with solid carbon dioxide. The pure ketonic compound separated in crystalline condition and was removed from the solution by filtration. The enol form was procured by suspending the sodium salt of the ester in hexane, cooling to -78° , and introducing gaseous hydrogen chloride. The precipitate of sodium chloride was removed, and the enol form was obtained by evaporation of the hexane in vacuo.

A comparison of the properties of the keto and enol modifications of the ester is shown in the following (1).

Properties of Ethyl Acetoacetate

Keto Form

Colorless, needle-shaped crystals melting at -30°

Index of refraction is n_D^{20} 1.4225

Reacts slowly with FeCl_3 at -40°

Reacts slowly with bromine

In the absence of a catalyst it remains unchanged at -78° for long periods of time

Attains equilibrium with the enol form at room temperature in about one month

Enol Form

Colorless oil at -78° but solidifies when cooled in liquid air

Index of refraction is n_D^{20} 1.4480

Reacts instantly with FeCl_3 even at -78°

Reacts instantly with bromine

In absence of a catalyst it remains unchanged
at -78° for long periods of time

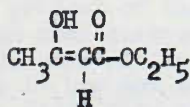
Attains equilibrium with the keto form at room
temperature in 10-14 days

Knorr also determined, by index of refraction, that about two percent of the equilibrium mixture was of the enol form. Fieser (4) states that according to Kurt Meyer, the percentage of enol was seven, which is probably somewhat high.

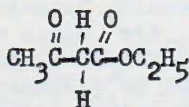
An interesting article by Kato and Goto (12) stated that the absorption spectrum of vaporized keto acetoacetic ethyl ester heated from 20° to 270° shows that the band due to the keto group, which begins to appear at about 60° , is changed at about 200° , and the appearance of a new band shows the formation of the enol group, while the spectrum of the vapor heated from 20° to 200° and then cooled down to 20° shows no absorption due to the keto ester. Thus it is verified that the vapor of the keto ester heated to about 200° is changed into the enol form and that the enol ester formed at about 200° is condensed.

Brewster (1) states that the amount of the two tautomers vary in different solvents and that the enol form is capable of chelation.

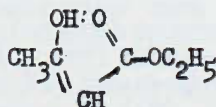
The acetoacetic ester can, therefore be represented by the three formulas.



Enol Form



Keto Form



Chelate Form

It is in the reaction in which a compound is added to the methylene carbon atom of the acetoacetic ester that much disagreement has taken place. The compounds are united by means of a sodio derivative of the ester. Some chemists hold that the sodium atom attaches to the carbon atom, whereas others hold that it joins to the oxygen atom, quoting from Michael (13).

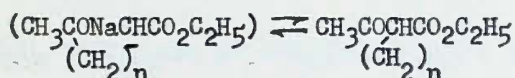
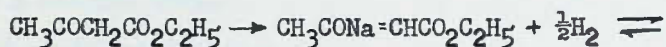
The partition principle of Thomsen was based upon the distribution of an insufficient amount of base for complete neutralization between two acids. This principle was extended to the course of organic reactions, and was verified experimentally with a number of typical organic reactions. Accordingly, the distribution of the sodium in a compound capable of reacting in more than one enolic form would be expected to follow the partition law, and the ratio of the amounts of sodium enolates should stand to one another in a definite relation to the avidities of the corresponding enolic structures.

Geuther represented the structures of acetoacetic ester and the sodium derivative by $\text{CH}_2\text{C}(\text{OH})=\text{CHCOOEt}$ and $\text{CH}_2\text{C}(\text{ONa})=\text{CHCOOEt}$ and although this conception was accepted by Claisen, Nef and other chemists, the commonly accepted view was that of Frankland and J. Wislicenus who considered the formulas $\text{CH}_2\text{COCH}_2\text{COOEt}$ and $\text{CH}_2\text{COCHNaCOOEt}$, respectively, to represent these compounds. In 1888 it was shown, theoretically and experimentally, that the chemical relations of these substances could be explained only from the keto structure $\text{CH}_2\text{COCH}_2\text{COOEt}$ for the ester and the enol structure $\text{CH}_2\text{C}(\text{ONa})=\text{CHCOOEt}^2$ (I), for the derivative. However, it was emphasized that a solution of the sodium compound should also contain some of the isomeric derivative $\text{CH}_2\text{CO}-\text{CH}(\text{ONa})\text{OEt}$ (II), since malonic ester yields an enolate, and the formula of acetoacetic ester may be derived from that of the malonic ester by replacing one of the carbethoxy groups of the former by the more negative acetyl group; further, that the relative amount of (I) should largely exceed that of (II), since acetyl is a much more negative radical than carbethoxyl.

This view is supported by the fact that along with the main product of the action of chlorocarbonic ester upon the sodium enol acetoacetic ester, viz., $\text{CH}_2\text{C}(\text{OCOEt})=\text{CHCOOEt}$ (III), some of the isomeric $\text{CH}_2\text{COCH}(\text{COOEt})_2$ (IV) is formed. Since it has not been possible to convert the O-carbethoxy ester (III) into the enolic sodium derivative of (IV), it would appear that (III) and (IV) are formed from the corresponding sodium derivatives (I) and (II).

The most recent theory (15,30,31) is that since the sodium compound is of ionic nature, it is likely that the formula $(\text{CH}_3\text{CO}-\text{CHCO}-\text{OC}_2\text{H}_5)^- \text{Na}^+$ in which the sodium is not joined to either carbon atom or oxygen atom, most clearly represents the state of the molecule.

Scheibler (4) postulated an intermediate, in the reaction



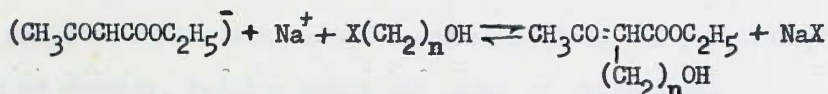
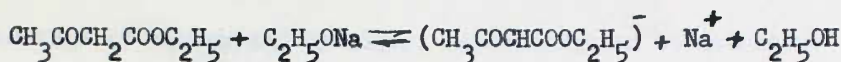
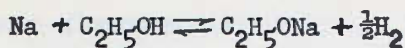
which he recovered as a primary residue; but Snell (16) attempted to duplicate his work and was completely unsuccessful.

All of the following equations will be based on the latest theory, using the ionic formula.

GENERAL METHODS OF INVESTIGATION

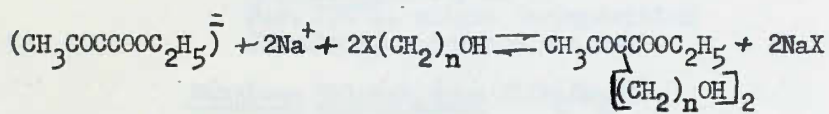
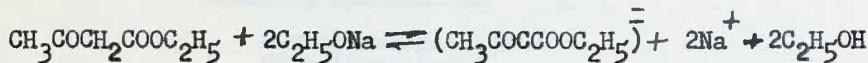
General Procedure

The basic reaction investigated in this problem consists essentially of reacting the acetoacetic ester with sodium alcoholate using ethyl alcohol as a carrier. The sodium enolate of the acetoacetic ester formed then reacts with the halohydrin to form an α -substituted hydroxy ester. This substitution may involve the addition of either one or two moles of the halohydrin to one mole of the ester. These reactions might be represented by the following equations.

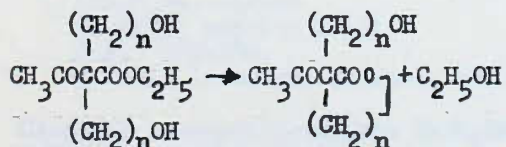
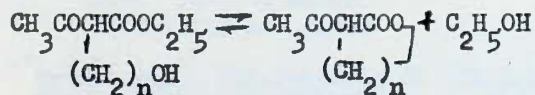


where X is a halogen atom.

In the case of di-substitution,



Cyclization of these products may occur to form a lactone. This would involve the splitting off of alcohol from the acid group and a rearrangement of the substituted alcohol group on the methylene carbon atom.



After the basic reaction has been completed, the products

are purified by means of vacuum distillation. Identification of the products formed involves: Carbon-hydrogen combustion to find the percentage of carbon and hydrogen; saponification to determine structure and molecular weight; and various other tests to determine the presence of certain radicals and some of of the physical properties such as density, boiling point and index of refraction.

PROPERTIES OF THE REAGENTS USED IN THE REACTION MIXTURE

(Taken from Lange's Handbook of Chemistry 6th Ed.)

Ethylene Bromohydrin $\text{BrCH}_2\text{CH}_2\text{OH}$

Formula weight 124.98
Colorless liquid
Specific gravity 1.772
B.p. 170°C . slight decomposition
Soluble in water and alcohol

Ethylene Chlorohydrin $\text{ClCH}_2\text{CH}_2\text{OH}$

Formula weight 80.52
Colorless liquid
Specific gravity 1.213
B.p. 85°C . @25mm.
Soluble in water, alcohol and ether

Propylene Bromohydrin $\text{CH}_3\text{CHBrCH}_2\text{OH}$

Formula weight 139.0
Colorless liquid
Specific gravity not given
B.p. $52-3^\circ\text{C}$. @16mm.
Solubility not given

Trimethylene Chlorohydrin $\text{Cl}(\text{CH}_2)_3\text{OH}$

Formula weight 94.54
Colorless liquid
Specific gravity 1.131
B.p. $160-2^\circ\text{C}$.
Soluble in water, alcohol, and ether

Glycerol α -monochlorohydrin $\text{ClCH}_2\text{CHOHCH}_2\text{OH}$

Formula weight 110.54
Yellow liquid

Specific gravity 1.318
 B.p. 213°C.
 Soluble in water, alcohol and ether

Epichlorohydrin $\text{CH}_2\overset{\text{O}}{\text{C}}\text{HCH}_2\text{Cl}$

Formula weight 92.53
 Colorless liquid
 Specific gravity 1.183
 B.p. 117°C. @756mm.
 Slightly soluble in water, soluble in alcohol
 and ether

Acetoacetic Ester (Ethyl Acetoacetate) $\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$

Formula weight 130.14
 Colorless liquid
 Specific gravity 1.025
 B.p. 180°C. @765mm.
 Soluble in water, alcohol, chloroform and ether

EXPERIMENTAL

Purification

The sample was purified by means of vacuum distillation. It might be well to note that the distillate receiver was of a type that improves the fractionating of the mixture, and also measures the amount of each fraction. Most distillations were made at about 7 mm pressure.

Determination of the Empirical Formula by the Carbon-Hydrogen Combustion Method (5)

The method of determination of carbon-hydrogen given below is a modified version to suit the needs and the apparatus available.

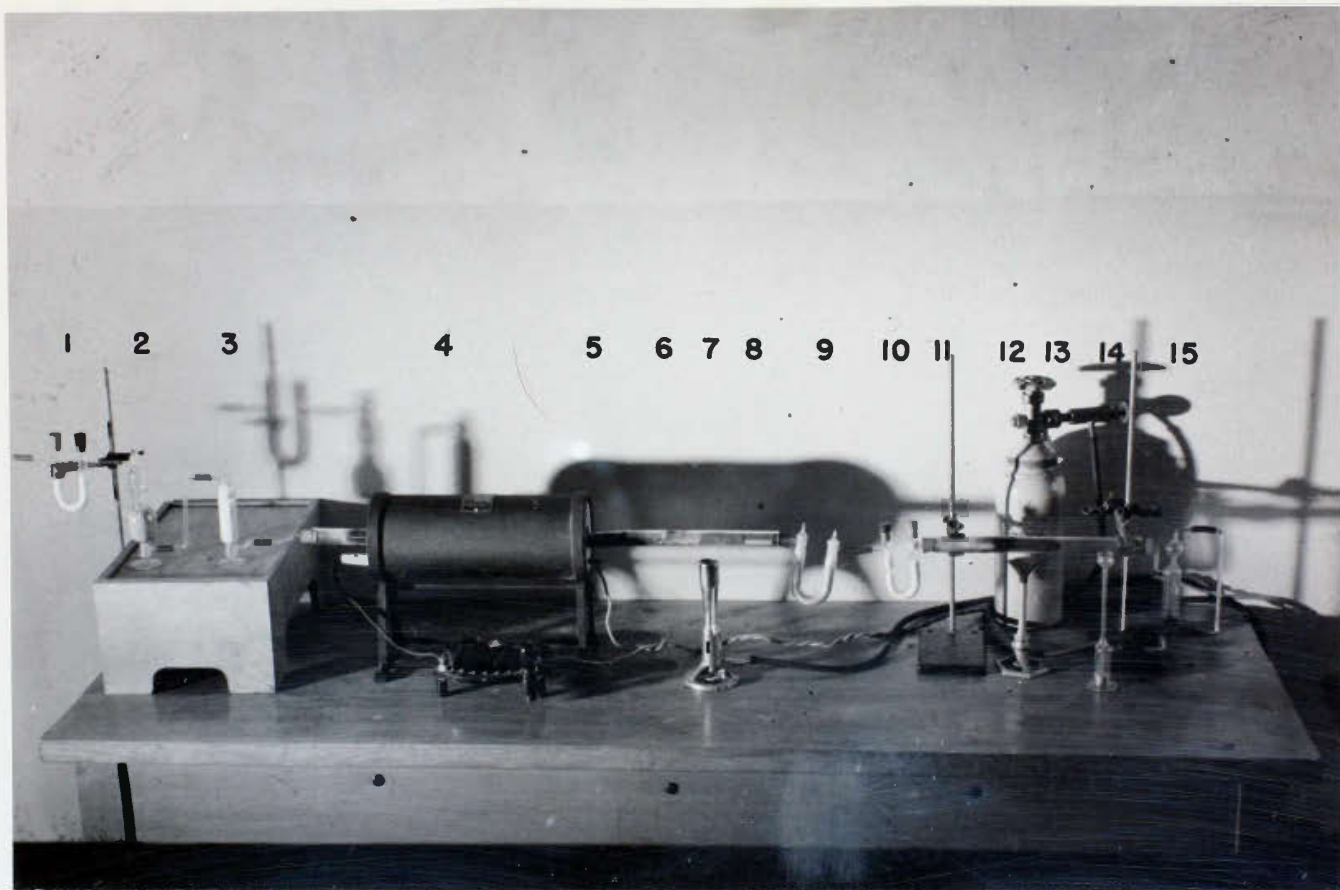
Chemicals and Apparatus used:

Electric combustion furnace
 Bunsen burner for preheater

Two Fisher burners for combustion tube
Pyrex combustion tube, 76 cm. long and 15 cm.
inside diameter, for combustion furnace
Copper gauze
Gas bubble counter
Rubber stoppers
Rubber tubing
Three U-tubes
Two absorption bottles
Porcelain boat
Special sample weighing tube, ground glass
stopper
Desiccator and crucible tongs
Ascarite
Calcium chloride
Magnesium perchlorate
Glass wool
Asbestos shreds
Concentrated sulfuric acid for bubble counter
Copper oxide pellets

Explanation of Photograph of Carbon-Hydrogen Combustion Unit

1. U-tube filled with calcium chloride to prevent moisture entering the system
2. Carbon dioxide absorption bottle filled with ascarite
3. Water absorption bottle filled with magnesium perchlorate
4. Electric furnace for heating of copper oxide
5. Pyrex combustion tube
6. Sample boat.
7. Fisher burner to ignite the sample
8. Copper oxide roll to prevent backflow of any gases
9. U-tube filled with ascarite to remove CO_2 from oxygen gas
10. U-tube filled with calcium chloride to dry oxygen gas
11. Pyrex tube for preheater
12. Bunsen burner for preheater
13. Oxygen cylinder
14. Mercury safety trap
15. Gas bubble counter



PHOTOGRAPH OF CARBON-HYDROGEN COMBUSTION UNIT

A special glass bulb was used to contain the sample since it was of a volatile nature. The tip of this bulb was broken just before placing in combustion boat and tube. The oxygen was purified by passing it over hot copper oxide in the preheater and then through the purifying U-tubes. The first U-tube contained calcium chloride to remove the water. The other U-tube contained ascarite to remove the carbon dioxide.

The first absorption bottle at the end of the combustion tube contained magnesium perchlorate for water absorption. The other absorption bottle was filled with ascarite for carbon dioxide absorption.

A final U-tube was placed in the system to prevent outside moisture and carbon dioxide from entering the absorption bottles. This tube was filled with ascarite and calcium chloride.

Since there was the possibility of many errors in the apparatus and chemicals, a blank determination was run before a regular combustion was attempted.

After the apparatus had been set up (without the boat and the absorption train), the combustion tube was heated to the same temperature that was used later in an actual determination. The preheater was also heated to the proper temperature and oxygen gas was passed through for a period of about four hours. After this period of "blowing out", the absorption bottles were weighed and connected into the system. The system was again allowed to run but for a period of about one hour. The absorption bottles were immediately weighed and the differences in weight were recorded. This difference was not greater than the possible error in weighing

so the system was ready for an actual combustion.

For the actual determination the glass bulb was carefully weighed, filled with the sample, sealed and reweighed to get the difference of weight or the weight of the sample. Since the sample was a volatile liquid, the absorption bottle was weighed and replaced in the system before the sample. The portion of the combustion tube that contained the sample was kept relatively cool for about one-half hour. Then heat was gradually applied to the sample to bring it slowly to the vapor state. After all the sample had vaporized, the system was run at full temperature for a period of about forty-five minutes. The oxygen was then turned off, the burners turned out and the absorption bottles removed from the system and immediately weighed. The percentage of hydrogen was calculated by the following formula.

$$\text{Per Cent H} = \frac{\text{Weight of H}_2\text{O} \times .1119 \times 100}{\text{weight of sample}}$$

The percentage of carbon was calculated by the following formula.

$$\text{Per Cent C} = \frac{\text{Weight Co}_2 \times .2727 \times 100}{\text{weight of sample}}$$

Determination of Molecular Weight by the Saponification Number

Diethylene Glycol Method (15). The reagent was made by dissolving 3 g of C.P. potassium hydroxide pellets in 15 ml of diethylene glycol. It was necessary to warm the mixture gently

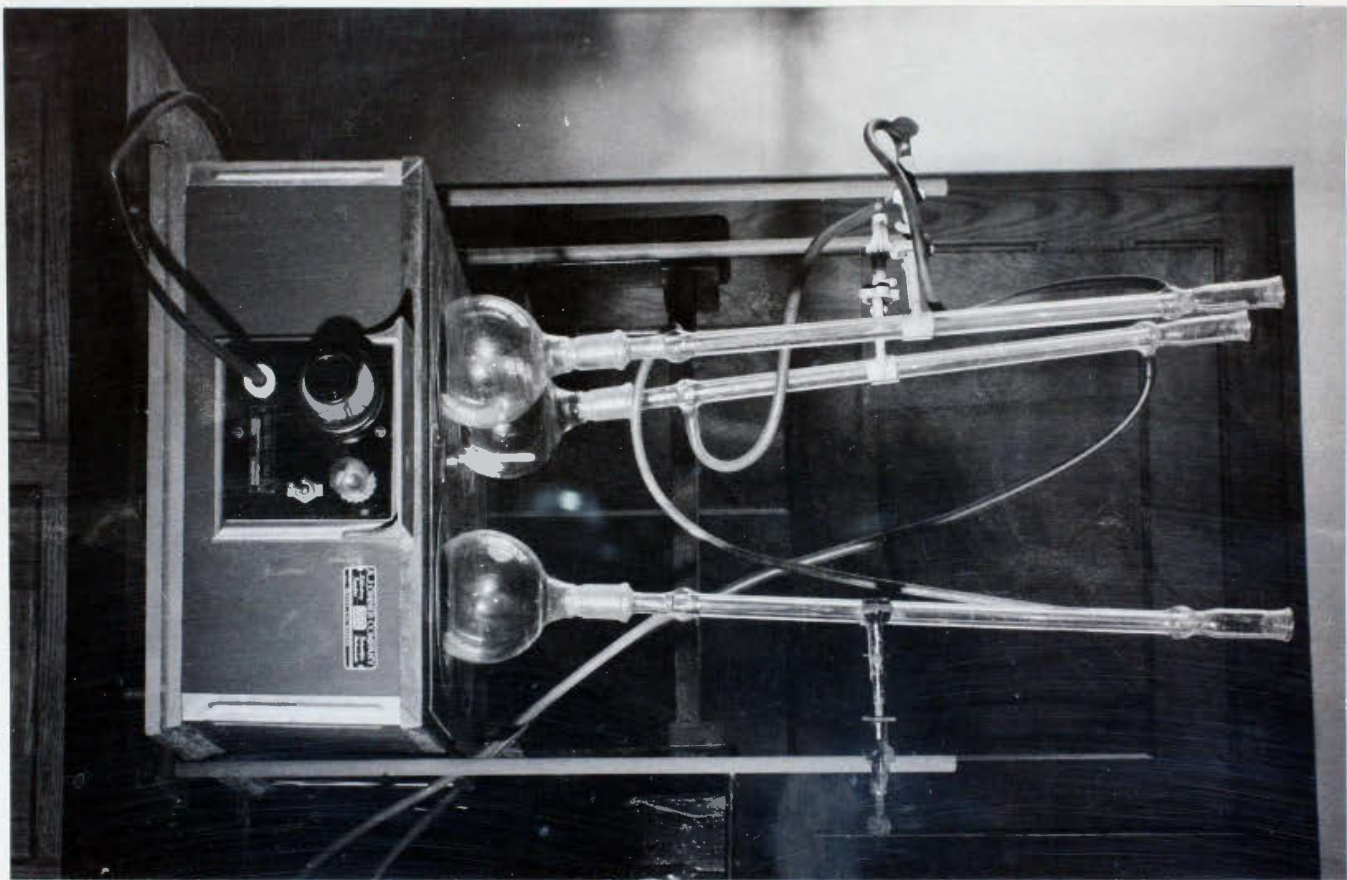
to effect solution. A thermometer was used for stirring and the mixture was not heated above 130° ; since higher temperatures would discolor the reagent. After all the solid was dissolved, the warm solution was poured into 35 ml of diethylene glycol and stored in a glass-stoppered bottle. The solution is standardized against 0.25 N hydrochloric acid.

Exactly 10 ml of the reagent was pipetted into a small glass-stoppered flask. A weighed amount of the ester was then added to the flask.

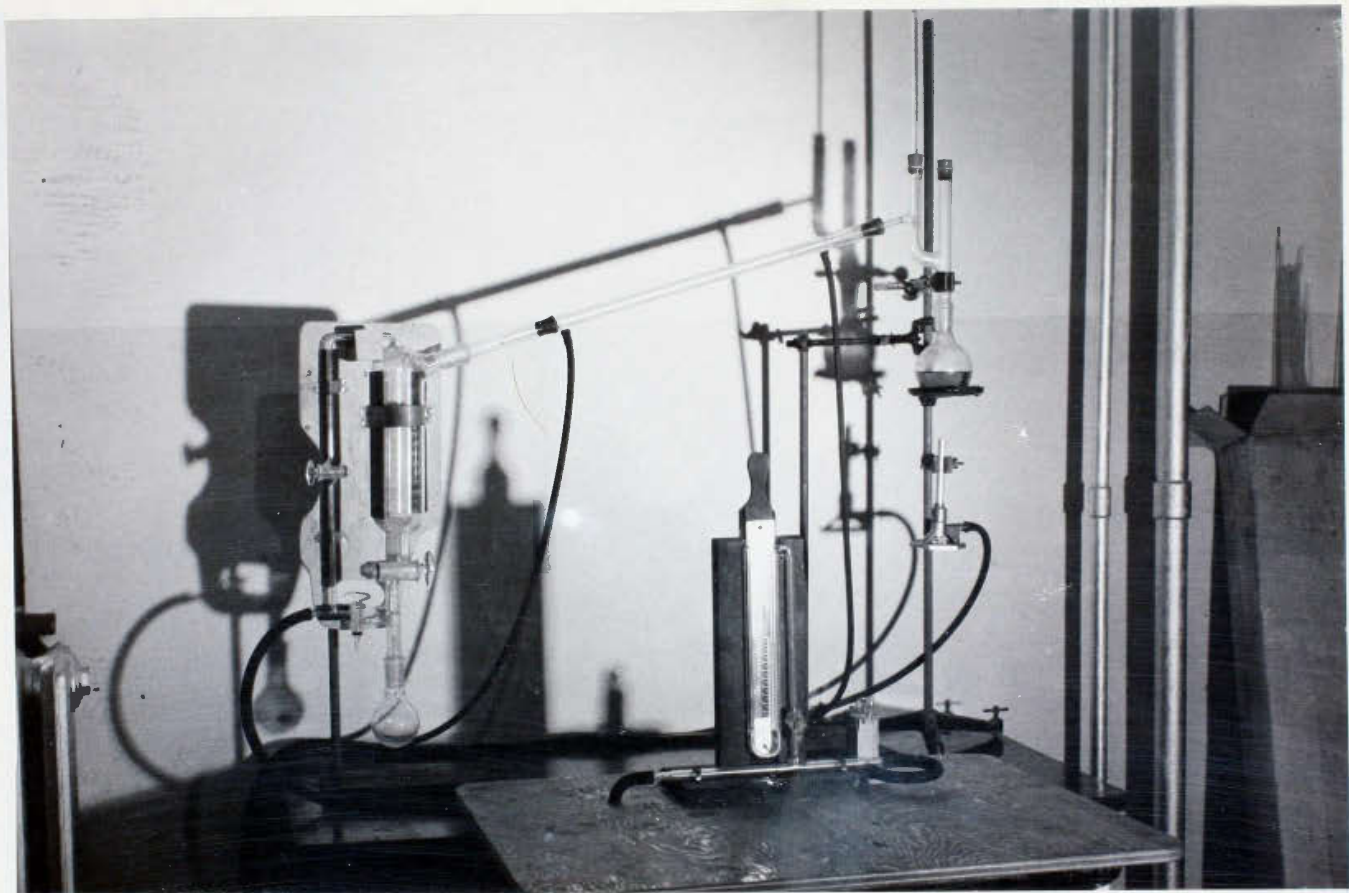
The ester was mixed with the reagent by a rotary motion of the flask. The stopper was held firmly in place and the mixture heated in an oil bath so that a temperature of $70-80^{\circ}$ was reached in two or three minutes. The liquid was agitated by a whirling motion during heating. At this point the flask was removed from the heating bath and shaken vigorously. The liquid was allowed to drain and the stopper was carefully loosened to allow air to escape. The stopper was replaced, and the temperature was raised to $120-130^{\circ}$.

After three minutes at this temperature the flask and its contents were cooled to $80-90^{\circ}$ and the stopper removed and washed with distilled water so that the rinsings drain into the flask. About 15 ml of distilled water was added, the contents mixed and then titrated with 0.25 N hydrochloric acid using brom cresol purple as an indicator. The saponification equivalent was calculated from the following equation.

$$\text{S.E.} = \frac{\text{weight of sample} \times 1000.}{\text{me. base} - \text{me. acid}}$$



PHOTOGRAPH OF INITIAL REACTION VESSEL AND WATER BATH



PHOTOGRAPH OF VACUUM DISTILLATION UNIT

Condensation of Acetoacetic Ester with Ethylene Bromohydrin (14)

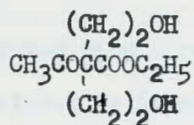
In a 500 ml flask fitted with a reflux condenser, 4.6 g of sodium was added in small pieces to 60 ml of absolute alcohol. After the sodium had dissolved, 26 g of ethyl acetoacetate was added dropwise, and then 25 g of ethylene bromohydrin was added dropwise. This mixture was slowly heated to 94° and refluxed for a period of three to ten hours. At the end of this time, the excess alcohol was distilled off and 50 ml of water was added to the distillation residue. The oil was then separated from the water and dried over calcium chloride. This oil was purified by vacuum distillation and the index of refraction taken on the different fractions. The fractions with the same index of refraction were recombined and again vacuum distilled to further purify the compound. The index of refraction found was 1.4273. The boiling point found was 68° at 7 mm pressure.

The purified sample showed the presence of a double bond between two carbon atoms by the Baeyer test with potassium permanganate, the presence of a hydroxyl group with acetyl chloride, and the carbonyl group with phenylhydrazine.

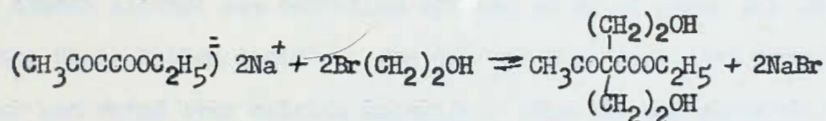
Next, the saponification number was determined and by it the molecular weight determined. The saponification number found was 109.32, which, assuming that the molecule was split in two places would give a molecular weight of 218.64.

A 0.2 g sample was used for the carbon-hydrogen combustion determination. The percentage of carbon was found to be 55.03. The percentage of hydrogen was 9.31.

If two moles of the ethylene bromohydrin attached to one mole of the acetoacetic ester, the molecular weight would be 218.17, the percentage carbon 55.04 and the percentage hydrogen 8.24. The percentage of hydrogen was high but in determination of a known sample the hydrogen also came out high in about the same proportions. It has therefore been indicated that the compound is ethyl- α , α '-bis-(β '-hydroxyethyl) acetoacetate, the formula of which would be represented as:

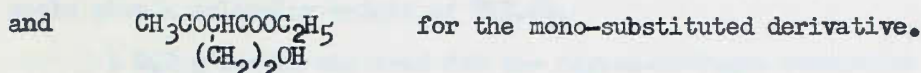
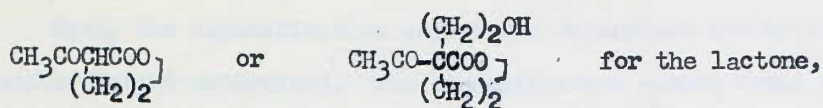


The equations which represent the reactions are:



It was found that the yield was the greatest when refluxed for about five hours and at a temperature of 96°. When a higher temperature was used, much of the product decomposed. A lower temperature and a longer time also promoted decomposition.

It is probable that there were three other products, two lactones and a monosubstituted ester. These products were not available in a large enough quantity to be identified, but their respective predicted formulas would be:



Condensation of Acetoacetic Ester with Ethylene Chlorohydrin (14)

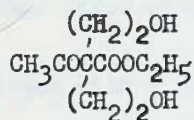
In a 500 ml flask fitted with a reflux condenser, 4.6 g of sodium was added in small pieces to 60 ml of absolute alcohol. After the sodium had dissolved, 26 g of ethyl acetoacetate was added dropwise, and then 16.04 g of ethylene chlorohydrin was added dropwise. This mixture was slowly heated to 94° and refluxed for a period of fifteen to twenty-five hours. At the end of this time, the excess alcohol was distilled off and 50 ml of water was added to the distillation residue. The oil was then separated from the water and dried over calcium chloride. This oil was purified by vacuum distillation and the index of refraction taken on the different fractions. The fractions with the same index of refraction were recombined and again vacuum distilled to further purify the compound. The index of refraction found was 1.4273. The boiling point found was 68° at 7 mm pressure.

The purified sample showed the presence of a double bond between two carbon atoms by the Baeyer test with potassium permanganate, the presence of a hydroxyl group with acetyl chloride, and the carbonyl group with phenylhydrazine.

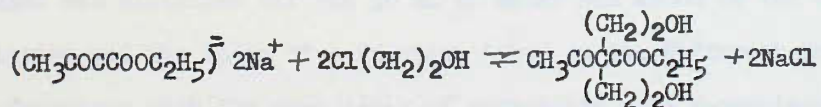
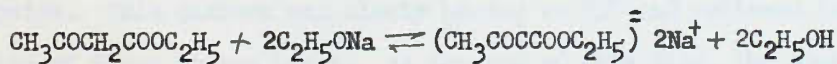
Next, the saponification number was determined and by it the molecular weight determined. The saponification number found was 109.32, which, assuming that the molecule was split in two places would give a molecular weight of 218.64.

A 0.2 g sample was used for the carbon-hydrogen combustion determination. The percentage of carbon was found to be 55.03. The percentage of hydrogen was 9.31.

If two moles of the ethylene chlorohydrin attached to one mole of the acetoacetic ester, the molecular weight would be 218.17, the percentage carbon 55.04 and the percentage hydrogen 8.24. The percentage of hydrogen was high but in determination of a known sample the hydrogen also came out high in about the same proportions. It has therefore been indicated that the compound is ethyl- α , β -bis-(β' -hydroxyethyl) acetoacetate, the formula of which would be represented as :



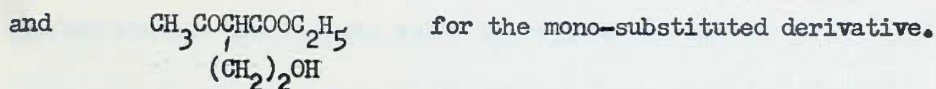
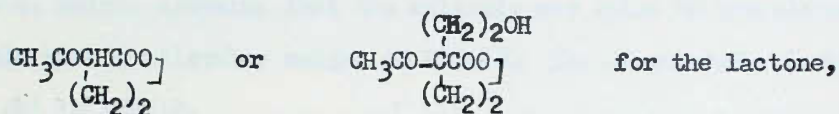
The equations which represent the reactions are:



It was found that the yield was the greatest when refluxed

for about twenty-one hours and at a temperature of 96°. When a higher temperature was used, much of the product decomposed. A lower temperature and a longer time also promoted decomposition.

It is probable that there were three other products, two lactones and a monosubstituted ester. These products were not available in a large enough quantity to be identified, but their respective predicted formulas would be:



Condensation of Acetoacetic Ester with Propylene Bromohydrin (14)

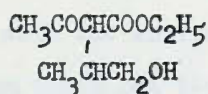
In a 500 ml flask fitted with a reflux condenser, 4.6 g of sodium was added in small pieces to 60 ml of absolute alcohol. After the sodium had dissolved, 26 g of ethyl acetoacetate was added dropwise, and then 27.8 g of propylene bromohydrin was added dropwise. This mixture was slowly heated to 94° and refluxed for a period of three to ten hours. At the end of this time, the excess alcohol was distilled off and 50 ml of water was added to the distillation and the index of refraction taken on the different fractions. The fractions with the same index of refraction were recombined and again vacuum distilled to further purify the compound. The index of refraction found was 1.4283. The boiling point found was 54° at

7 mm pressure.

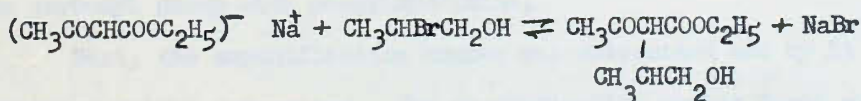
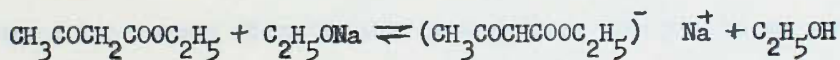
The purified sample showed the presence of a double bond between two carbon atoms by the Baeyer test with potassium permanganate, the presence of a hydroxyl group with acetyl chloride, and the carbonyl group with phenylhydrazine.

Next, the saponification number was determined and by it the molecular weight determined. The saponification number found was 95.04, which, assuming that the molecule was split in two places would give a molecular weight of 190.08. The calculated molecular weight is 188.12.

The compound would be ethyl- α -(α' methyl, β' hydroxyethyl)-acetoacetate. The formula would be represented as:



The equations which represent the reactions are:



It is probable that there were three other products, two lactones and a disubstituted ester. These products were not available in a

large enough quantity to be identified.

Condensation of Acetoacetic Ester with Glycerol- α -Monochlorohydrin (14)

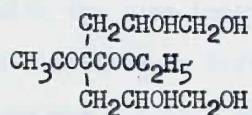
In a 500 flask fitted with a reflux condenser, 4.6 g of sodium was added in small pieces to 60 ml of absolute alcohol. After the sodium had dissolved, 26 g of ethyl acetoacetate was added dropwise, and then 22.1 g of glycerol- α -monochlorohydrin was added dropwise. This mixture was slowly heated to 94° and refluxed for a period of six to ten hours. At the end of this time, the excess alcohol was distilled off and 50 ml of water was added to the distillation residue. The oil was then separated from the water and dried over calcium chloride. This oil was purified by vacuum distillation and the index of refraction taken on the different fractions. The fractions with the same index of refraction were recombined and again vacuum distilled to further purify the compound. The index of refraction found was 1.4370. The boiling point found was 58° at 7 mm. pressure.

The purified sample showed the presence of a double bond between two carbon atoms by the Baeyer test with potassium permanganate, the presence of a hydroxyl group with acetyl chloride, and the carbonyl group with phenylhydrazine.

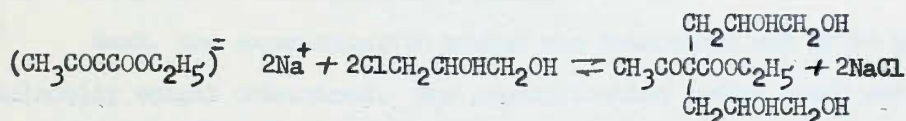
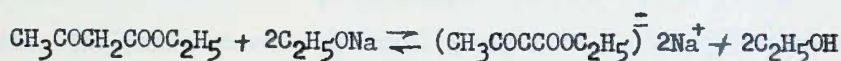
Next, the saponification number was determined and by it the molecular weight determined. The saponification number found was 139, which, assuming that the molecule was split in two places would give a molecular weight of 278.

If 2 moles of glycerol- α -monochlorohydrin attached to one mole of the acetoacetic ester, the calculated molecular weight would be 279.14.

It is, therefore, indicated that the compound is ethyl- α ,
 α' -bis(β' , γ' -dihydroxypropyl) acetoacetate, the formula of which would
 be represented as:



The equations which represent the reactions are:



It is probable that there were three other products, two
 lactones and a monosubstituted ester. These products were not
 available in a large enough quantity to be identified.

Condensation of Acetoacetic Ester with Trimethylene Chlorohydrin (14)

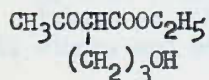
In a 500 ml flask fitted with a reflux condenser, 4.6 g
 of sodium was added in small pieces to 60 ml of absolute alcohol.
 After the sodium had dissolved, 26 g of ethyl acetoacetate was
 added dropwise, and then 18.9 g of trimethylene chlorohydrin was
 added dropwise. This mixture was slowly heated to 94° and refluxed
 for a period of three to ten hours. At the end of this time, the
 excess alcohol was distilled off and 50 ml of water was added to

the distillation residue. The oil was then separated from the water and dried over calcium chloride. This oil was purified by vacuum distillation and the index of refraction taken on the different fractions. The fractions with the same index of refraction were recombined and again vacuum distilled to further purify the compound. The index of refraction found was 1.4345. The boiling point found was 53° at 7 mm pressure.

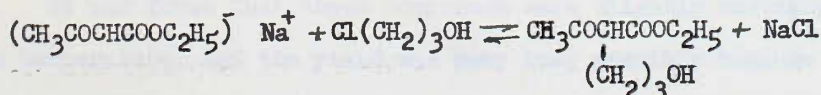
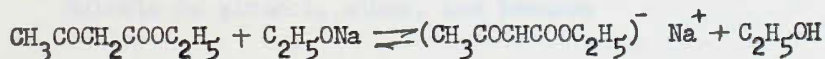
The purified sample showed the presence of a double bond between two carbon atoms by the Baeyer test with potassium permanganate, the presence of a hydroxyl group with acetyl chloride, and the carbonyl group with phenylhydrazine.

Next, the saponification number was determined and by it the molecular weight determined. The saponification number found was 188.2. Assuming that the molecule split in only one place, the calculated molecular weight would be 188.12.

It is indicated, therefore, that the compound would be ethyl- α -(γ -hydroxypropyl)acetoacetate. The formula would be:



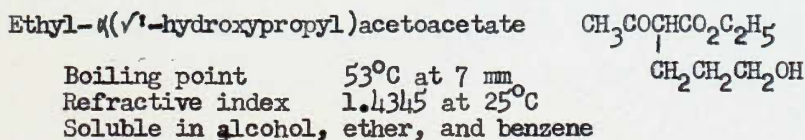
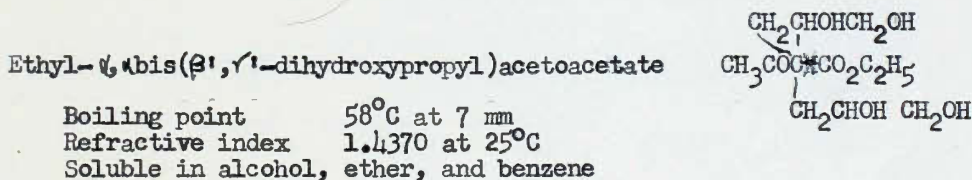
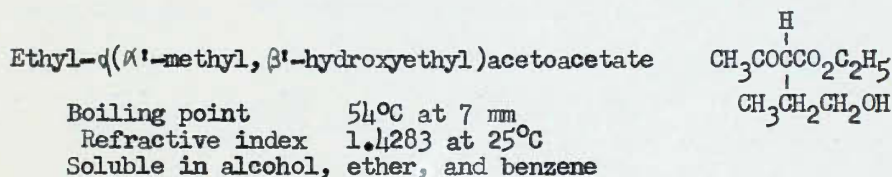
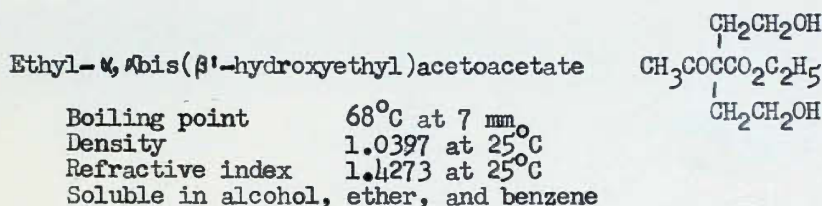
The equations for the reaction would be represented as:



It is probable that there were three other products, two lactones and a monosubstituted ester. These products were not available in a large enough quantity to be identified.

SUMMARY

Four new compounds were synthesized and identified. These compounds and the physical properties that were determined are:



It was found that these compounds were slightly unstable at room temperature, and the yield was very low, possibly because of the formation of other compounds. Also the yield could possibly

be increased by finding the optimum temperature, and length of time for refluxing. It seems that prolonged heating and using the bromohydrin favors the disubstituted product, while the use of the chlorohydrin favors the monosubstituted product.

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