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THE PREPARATION

OF

SOME DERIVATIVES

OF

PENTAERYTHRITOL

BY

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PENTAERYTHRITOL DERIVATIVES

GULEN

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ABSTRACT

The reaction between pentaerythrityl dichloride and sodium methoxide (ethoxide) in methyl (ethyl) alcohol gives 3-hydroxymethyl-3-chloro-methyl-oxacyclobutane in 40% yield. The structure of this compound was demonstrated by its conversion to pentaerythrityl dichloride in quantitative yield, by the action of concentrated hydrochloric acid.

The trimethylene oxide ring of 3-hydroxymethyl-3-chloromethyl-oxacyclobutane is readily attacked by hydrobromic acid and hydriodic acid giving 2-chloromethyl-2-bromomethyl 1,3, propanediol and 2-chloromethyl-2-iodomethyl 1,3 propanediol in 82% and 73% yield respectively.

An independent synthesis of 2-chloromethyl-2-bromomethyl 1,3 propanediol has been carried out by a four step process, starting from pentaerythritol.

Pentaerythrityl monoiodide, has been prepared in 63% yield by the action of hydriodic acid on 3,3-bis-(hydroxymethyl)-oxacyclobutane.

The reaction of 3,3-bis-(hydroxymethyl)-oxacyclobutane with ethoxyethanol in the presence of sodium at 140° gives pentaerythrityl- β -ethoxyethyl ether.

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PART I

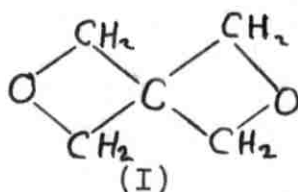
STUDIES ON THE PREPARATION

OF

2,6-DIOXASPIRO(3.3) HEPTANE

INTRODUCTION

Pentaerythritol forms intramolecular ether linkages giving 2,6-dioxaspiro(3,3) heptane (I)



This compound has been described in the literature as a white solid melting at 89-90° and possessing a camphor-like odor. All the preparative methods that have been published thus far, give very low yields of the product.

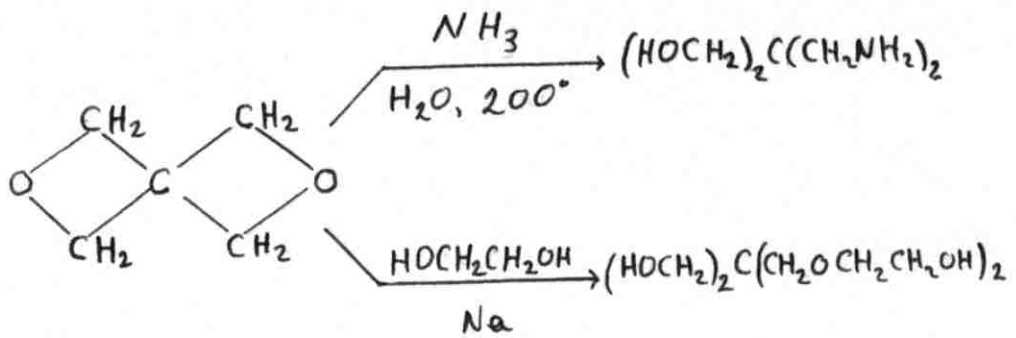
The purpose of this research was to study further the preparation of 2,6-dioxaspiro(3,3) heptane and to find a new method for its synthesis in satisfactory yields.

HISTORICAL

Attempt to prepare 2,6-dioxaspiro(3,3) heptane (I) by the action of sodium on pentaerythrityl dibromide¹, sulfuric acid on pentaerythritol¹, potassium hydroxide on pentaerythrityl dichloride, potassium hydroxide on pentaerythrityl dibromide diacetate¹ were without any success. The compound was finally obtained in 20-25% yield by the action of excess alcoholic potassium hydroxide on pentaerythrityl dibromide¹. This method was modified by Govaert and Beyaert³ who, using the theoretical amount of potassium hydroxide, obtained, a very pure product in somewhat smaller yields. Substitution of pentaerythrityl dichloride for the dibromide gave only 17% yields of 2,6-dioxaspiro(3,3) heptane⁴. Recently the spirocyclic compound was obtained by a combination of the methods of Backer and Keuning and of Beyaert and Hansens. The maximum yield reported was 20%⁵.

The importance of 2,6-dioxaspiro(3,3) heptane as a useful synthetic intermediate is a result of its 1,3-epoxide structure. Under special conditions, the heterocyclic ring of this compound can be opened up by various types of reagents to give certain derivatives of pentaerythritol, which are very difficult to prepare by more direct methods. For example, treatment of the spirocyclic compound (I) with aqueous ammonia⁶ in a sealed tube or with the sodium salt

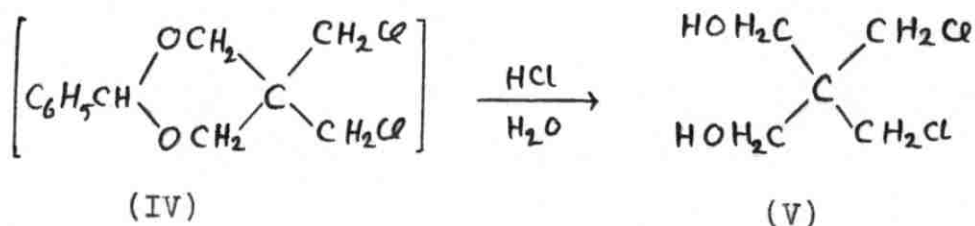
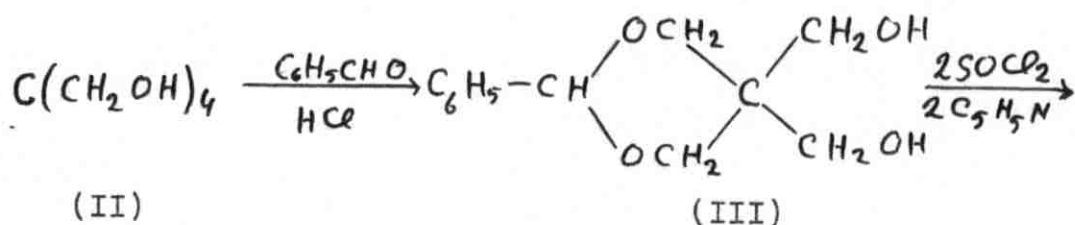
of ethylene glycol at reflux temperatures⁴ gives the corresponding diamines and diethers of pentaerythritol:



(I)

RESULTS

Pentaerythrityl dichloride (V) was used as the starting material for this investigation. It was obtained by the following sequence of reactions:



Monobenzal pentaerythritol (III) was obtained in 75% yield from pentaerythritol (II) and benzaldehyde in the presence of catalytic amounts of hydrochloric acid⁷. This reaction is always accompanied by the formation of varying amounts of dibenzal pentaerythritol. However, the two products may be easily separated by virtue of their different solubilities in water and toluene. Monobenzal pentaerythritol was then converted to monobenzal pentaerythrityl dichloride (IV) by the action of thionyl chloride in the presence of pyridine⁴. The acetal dichloride (IV) was not isolated, but was hydrolyzed directly to give

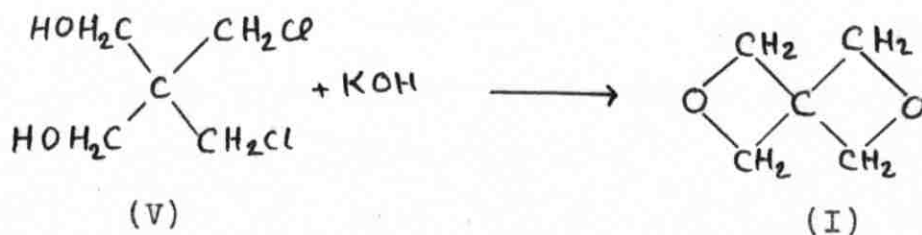
pentaerythrityl dichloride (V) in 70-75% yield.

Treatment of pentaerythrityl dichloride (V) with a suspension of potassium hydroxide in ether or sodium methoxide in ether at reflux temperatures, gave no traces of the spirocyclic compound. Pentaerythrityl dichloride was, however, recovered quantitatively.

Quinoline was also used as a dehydrohalogenation agent⁸ for the dichloride, but only very small amounts of the desired product, 2,6-dioxaspiro(3,3) heptane, were isolated.

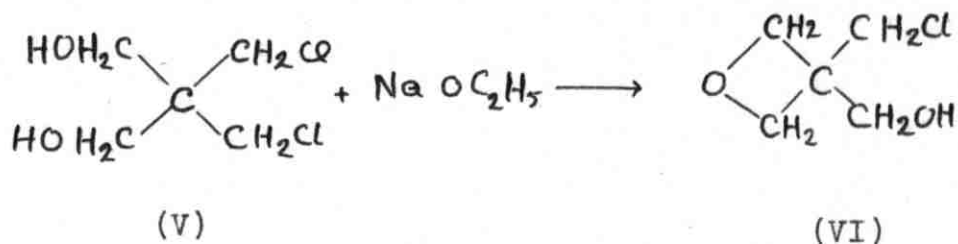
Treatment of pentaerythrityl dichloride with glycidyl phenyl ether in the presence of catalytic amounts of pyridinium ethiodide¹⁴ followed by slow distillation of the reaction mixture at reduced pressure gave only an unsaturated liquid.

A slight modification of the method described in the literature⁴ for the preparation of 2,6-dioxaspiro(3,3) heptane (I) by the action of a small excess of alcoholic potassium hydroxide on pentaerythrityl dichloride gave the desired product, but the yield never exceeded 17%.



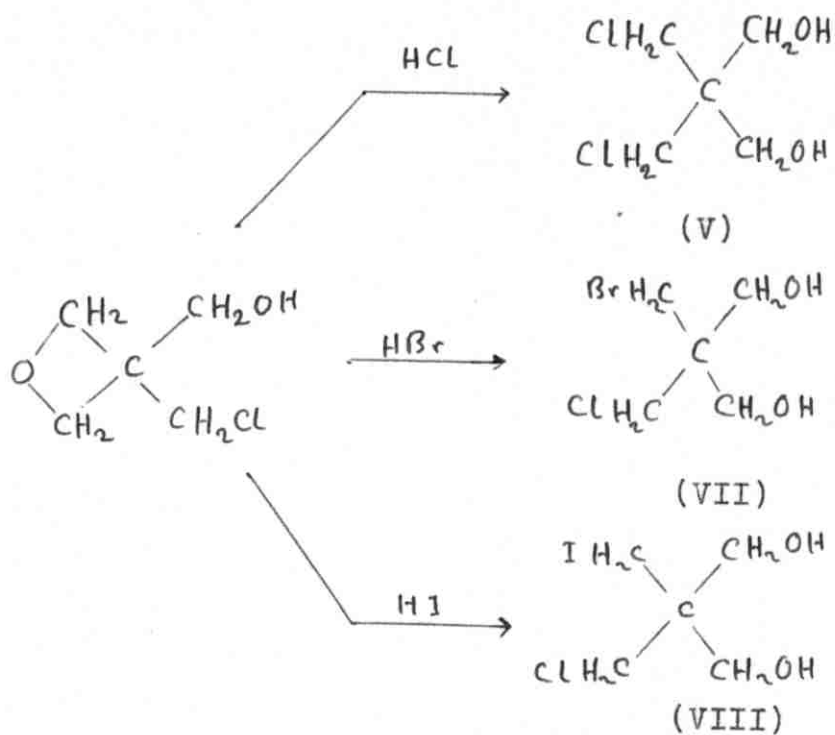
The reaction of pentaerythrityl dichloride (V) with

sodium ethoxide in ethyl alcohol gave, 3-hydroxymethyl-3-chloromethyl-oxacyclo butane (VI), presumably a new compound.

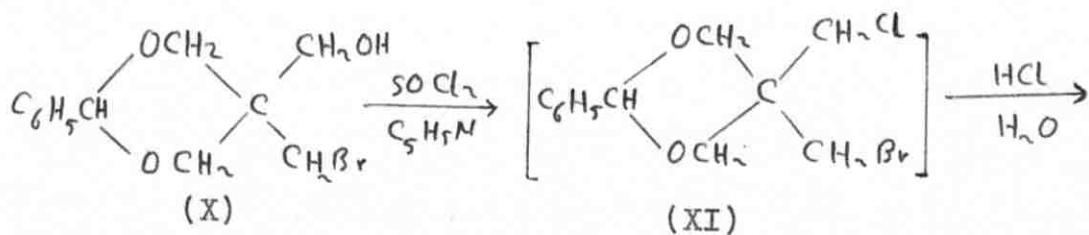
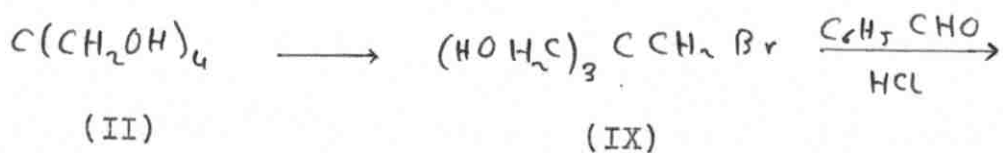


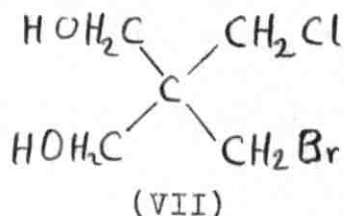
By varying the conditions and relative amounts of the reagents, the yield of 3-hydroxymethyl-3-chloromethyl-oxacyclo butane (VI) was 31 to 39%. The same compound was also obtained from pentaerythrityl dichloride (V) and sodium methoxide in 43% yield.

The trimethylene oxide ring of 3-hydroxymethyl-3-chloromethyl-oxacyclo butane was found to be extremely sensitive to attack by halogen acids. Thus, treatment of the compound with concentrated hydrochloric acid gave pentaerythrityl dichloride in almost quantitative yield. In a similar fashion, the action of concentrated hydrobromic acid and hydriodic acid on the epoxy ring of the compound resulted in the formation of two new mixed halides of pentaerythritol: Pentaerythrityl monochloride monobromide (3-bromomethyl-3-chloromethyl-1,3-propanediol) (VII), and Pentaerythrityl monochloride monoiodide (3-iodomethyl-3-chloromethyl-1,3-propanediol) (VIII).



The structures of these mixed halides were proved by independent synthesis of pentaerythrityl monochloride monobromide (VII) from pentaerythritol (I) by the series of reactions summarized below:





Monobromopentaerythritol (IX) was prepared according to the method of Beyaert and Hansens¹⁹ by the action of hydrobromic acid on pentaerythritol in glacial acetic acid, followed by transesterification of the bromoacetates formed. Treatment of monobromopentaerythritol (IX) with benzaldehyde in the presence of catalytic amounts of hydrochloric acid gave monobenzalpentaaerythrityl monobromide (X). The acetal was then converted to monobenzalpentaaerythrityl monobromide-monochloride (XI) with thionyl chloride, in the presence of pyridine. The intermediate was not isolated but hydrolyzed directly to pentaerythrityl monochloride monobromide (VII), a product which was identical with that isolated from the reaction between 3-chloromethyl-3-hydroxymethyl oxacyclo butane and hydrobromic acid.

A further example of the ease with which mineral acids can open the trimethylene oxide ring is given by the reaction between 3,3-bis-(hydroxymethyl)-oxacyclo butane (XII) and concentrated hydriodic acid. The reaction gives monoiodopentaerythritol (2-hydroxymethyl-2-iodomethyl-1,3-propanediol) (XIII) in 63% yield.



The compound had been previously prepared only as a by-product in the preparation of pentaerythrityl diiodide¹⁶.

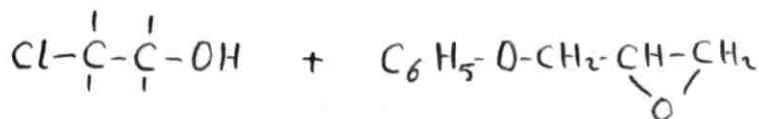
DISCUSSION

It has been reported that the reaction between pentaerythritol (II) and benzaldehyde in the presence of catalytic amounts of hydrochloric acid gives monobenzalpentaaerythritol (III), but no mention of formation of any by-product was made⁷. During this investigation, evidence was obtained that the reaction is always accompanied by the formation of varying amounts of dibenzalpentaaerythritol, depending on the duration of the reaction. Longer reaction times invariably increase the amount of dibenzalpentaaerythritol formed. Furthermore, it was found that when a saturated aqueous solution of monobenzalpentaaerythritol is treated with traces of acid, some dibenzalpentaaerythritol is formed after several hours. The reaction between benzaldehyde and pentaerythritol at room temperature probably involves a relatively fast reversible step forming monobenzalpentaaerythritol, and a second slower reaction giving dibenzalpentaaerythritol practically irreversibly due to the extremely small solubility of this product in water. During this investigation it was found that the best yield of monobenzalpentaaerythritol is obtained when the reaction is carried out within a period of about five hours. Under these conditions, only small amounts of dibenzalpentaaerythritol are formed.

Several methods for the preparation of pentaerythrityl

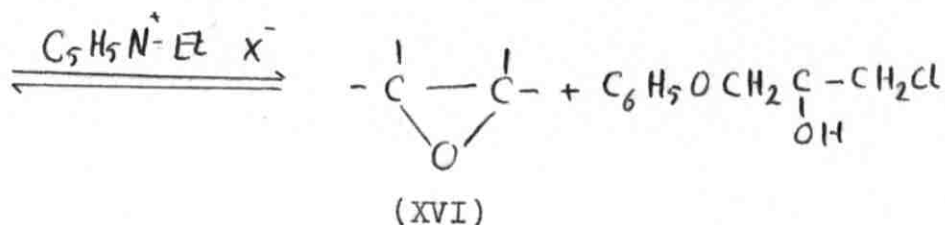
dichloride (V) have been reported in the past. The compound can be obtained from pentaerythritol and sulfur monochloride¹¹, from pentaerythritol and concentrated hydrochloric acid at elevated temperatures¹² or from monoisopropyledenepentaerythritol and p-toluene sulfonyl chloride in the presence of pyridine⁹. All these methods give poor yields of the dichloride. Better yields were obtained by the action of thionyl chloride on pentaerythritol¹⁰ but the reaction gives a mixture of products, thus making the isolation of the dichloride tedious. The procedure used in this investigation is convenient and gives very good yields of pure product, the melting point (80 - 81°) of which is in close agreement with that reported by Rapoport⁹ (79 - 80°) and by Mooradian and Cloke¹⁰ (83°), but widely differing from that reported by Bougault¹¹ (65°) and by Fecht¹² (95°).

A new method of preparation of epoxides has been described recently by Bradley and his co-workers¹³. This method involves transfer of hydrogen chloride from a halohydrin (XIV) to glycide phenyl ether (XV) in the presence of pyridinium salts to give a new epoxide (XVI) and the halohydrin derived from glycide phenyl ether.

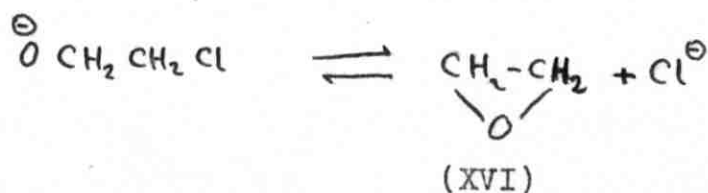
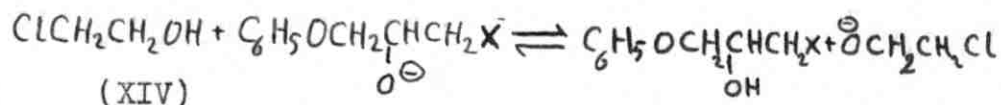
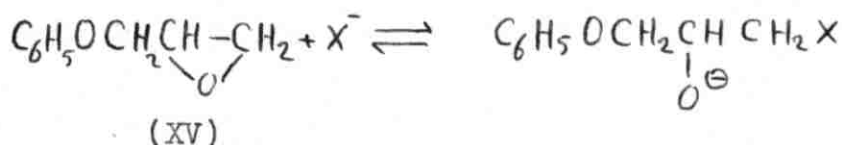


(XIV)

(XV)

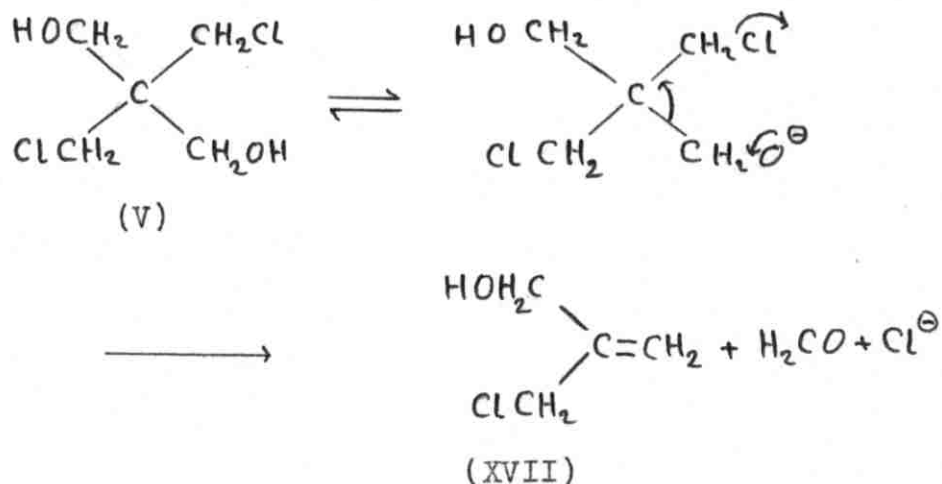


If the epoxide formed is more volatile than glycide phenyl ether it may be isolated by slow fractionation. The equilibrium is thus displaced to the right, giving excellent yields of the product. The mechanism for this reaction is probably as follows:



Since the boiling points of 2,6-dioxaspiro(3,3) heptane and of glycide phenyl ether are appreciably different and since the mechanism is theoretically possible also for 1,3 halohydrins, the attempt was made to apply this method to penta-

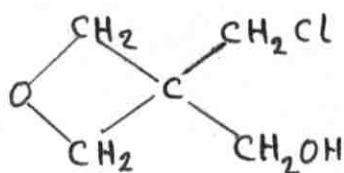
erythrityl dichloride (V). However, instead of the expected spirocyclic compound, an unsaturated liquid containing chlorine and alcoholic hydroxyl groups was isolated from the reaction. The possibility of an elimination reaction^{14,15}:



is probably excluded in this case since the boiling point of the product is much too high for a compound of the type (XVII) (b.p. 160°/33 mm.). Work on the identification of this product is in progress.

The viscous oil which was isolated from the reaction between pentaerythrityl dichloride (V) and sodium ethoxide in absolute alcohol contained chlorine and hydroxyl groups. The presence of ethoxyl groups was excluded, since the same product was isolated when methanol and sodium methoxide were substituted for ethanol and sodium ethoxide. Treatment of the compound with concentrated hydrochloric acid gave pentaerythrityl dichloride (V) in almost quantitative yields. In view of this evidence, the structure 2-chloro-

methyl-2-hydroxymethyl-oxacyclo butane (VI) was assigned to the product*.



(VI)

This structure is supported by further reactions of this compound with hydrobromic acid and hydriodic acid to give the corresponding mixed dihalides of pentaerythritol. The structure of one of these (pentaerythrityl monochloride monobromide (VII)) was proved by independent synthesis.

* Preliminary microanalytical results indicate that the product is not pure, but that it is probably contaminated with some 2,6 dioxaspiro(3,3) heptane(I). Work on the purification of this product is in progress.

EXPERIMENTAL

Preparation of Pentaerythrityl Dichloride

Preparation of Monobenzalpentaaerythritol (III): The procedure adopted for the preparation of this compound was a modification of the method described by Bograchov⁷.

In a 3 liters, three-necked, round-bottomed flask were placed 180 g (1.32 moles) of pentaerythritol and 1.3 liters of water. The flask was fitted with an efficient mechanical stirrer and a graduated dropping funnel containing 147 g (140 ml, 1.32 moles) of benzaldehyde. The third neck was left open and used later on for the addition of hydrochloric acid and for the introduction of the thermometer. The mixture in the flask was heated until all the solid dissolved, and then it was allowed to cool undisturbed. When the solution cooled to 25° stirring was started and 6.6 ml of concentrated hydrochloric acid were added through the open neck of the flask followed by 30 ml of benzaldehyde from the dropping funnel. When the precipitate of monobenzalpentaaerythritol started forming, benzaldehyde was allowed in dropwise. The addition took about 2½ hours, and the temperature of the mixture was kept between 25 and 29°. After the addition of benzaldehyde was completed the mixture was stirred for 3 more hours. The precipitate was collected in a Buchner funnel and washed with cold water made slightly alkaline by the addition of sodium carbonate. The solid was

transferred to a 3 liters round-bottomed flask, 1 liter of water (made alkaline with sodium carbonate) was added and the mixture was heated with stirring at 100°. After about 10 minutes at this temperature, the hot mixture was filtered through a fluted filter paper using a hot water funnel. The solid remaining in the filter paper was then washed with 50 ml of hot water. After drying, the solid was recrystallized from butanol to give 1 gram of dibenzal-pentaerythritol melting at 159-160°. The combined aqueous filtrates were cooled in an ice bath for several hours and the crystals collected on a Buchner funnel and dried. The dried product was refluxed for 15 minutes with 200 ml of toluene and the hot mixture was allowed to cool to room temperature with continuous stirring to prevent the formation of hard lumps. Finally the mixture was cooled in an ice bath for 5 hours and the solid was collected on a Buchner funnel, washed with 100 ml. of cold toluene and dried. The yield of monobenzal-pentaerythritol melting at 134-135° was 215-227 grams [73-77%) of the theoretical based on pentaerythritol].

Preparation of Monobenzal-pentaerythrityl Dichloride and Hydrolysis to Pentaerythrityl Dichloride (V): The procedure described is a modification of the method of Wawzonek and Issidorides⁴.

In a 3 liters, three necked, round-bottomed flask with ground glass fittings are placed 314 grams (1.4 moles) of

monobenzalpentaaerythritol, 221.4 g. (225.3 ml, 2.8 moles) of dry pyridine and 175 ml of dry chloroform. The flask was fitted with a mercury-sealed stirrer, a dropping funnel and a reflux condenser which was connected through a calcium chloride tube to a gas absorption trap. The flask was surrounded by an ice and salt bath and the stirrer was started. When the temperature of the mixture dropped to about 5°, 666 g (413 ml, 5.6 moles) of thionyl chloride dissolved in 300 ml of dry chloroform were added slowly through the dropping funnel. The addition took about 8 hours. After the addition was completed, the mixture was stirred overnight at room temperature and then heated on a water bath for 4 hours at 70°, after which chloroform and the excess of thionyl chloride were removed under reduced pressure, without application of heat. After removal of the volatile components, the residue in the flask was treated with 1.2 liters of 0.5N hydrochloric acid and 200 ml of dioxane. The mixture was refluxed for 4 hours. The hot solution was then steam distilled until the distillate ceased to be cloudy. The solution in the flask was then concentrated under reduced pressure to about 500 ml and extracted with five 200 ml portions of ether. The combined ether extracts were dried over 50 g of anhydrous sodium sulfate and filtered. The ether was removed on a water bath and the residue was transferred to a 225 ml Claisen flask provided with a ground-glass fitting for the thermometer.

The flask was connected to an air condenser provided with an electric heating tape, and arranged for vacuum distillation. Almost all the product distilled at 145-149°/5mm.

The solid obtained from the distillation was refluxed with a mixture of 200 ml of chloroform, 200 ml of carbon tetrachloride and 55 ml of toluene for about half an hour. The hot solution was filtered through a steam heated funnel and cooled in an ice bath for several hours. The crystals were collected in a Buchner funnel and dried in a vacuum dessicator at 40 mm, over calcium chloride and paraffin wax. The yield of pentaerythrityl dichloride melting at 80-81° was 170-187 grams (70-77% of the theoretical).

The product was also purified by the following procedure: After removal of the ether, the product was refluxed with 300 ml of water and 3 g of charcoal and filtered. After cooling, the aqueous solution was extracted with five 150 ml portions of ether. The combined ether layers were dried over 50 g of anhydrous sodium sulfate and filtered. The ether was removed on a steam bath and the product was recrystallized from a mixture of chloroform, carbon tetrachloride and toluene.

Studies on the Formation of 2,6-Dioxaspiro(3,3) heptane

Alcoholic Potassium Hydroxide Method: The method

described is essentially that of Backer and Keuning¹.

Pentaerythryl dichloride (40 g, 0.23 moles) dissolved in 80 ml of absolute ethyl alcohol was added to a solution of 36 g (85% assay, 0.54 moles) of potassium hydroxide in 140 ml of absolute ethyl alcohol. The mixture was refluxed on the water bath for 30 minutes. After cooling in an ice bath, the precipitated potassium bromide was separated by filtration. The solution was then neutralized with dilute acetic acid and the excess of alcohol was removed under reduced pressure. The residue was distilled under diminished pressure and the fractionated at atmospheric pressure. The product which boiled at 168-173°/750 mm was recrystallized from petroleum ether (b.p. 60-70°). The yield of 2,6-dioxaspiro(3,3) heptane (I) melting at 89-90° was 4 g. (17% of the theoretical).

Potassium Hydroxide in Ether Method: In a 1 liter round-bottomed flask, provided with a mercury-sealed stirrer and a reflux condenser were placed 40 g (0.23 moles) of pentaerythryl dichloride dissolved in 500 ml of dry ether and 36 g (85% assay, 0.54 moles) of potassium hydroxide. Stirring was started and the mixture was refluxed for 10 hours and then filtered. After removal of the ether on the water bath, unchanged starting material was isolated almost quantitatively.

Sodium Methoxide in Ether Method: Substitution of 27 g (0.5 moles) of sodium methoxide for potassium hydroxide gave the same result.

Quinoline Method: A mixture of 40 g (0.23 moles) of pentaerythryl dichloride and 129 g (1 mole) of dry quinoline was heated at 180-200° for 10 hours, and then distilled through a Vigreux column. Small amounts of distillate were collected below 200°. The distillate was acidified with dilute acetic acid and extracted with ether. The ether was removed on the water bath and the residue recrystallized from petroleum ether, to give less than 1 g of 2,6-dioxaspiro(3,3) heptane, melting at 88-90°.

Glycide Phenyl Ether-Pyridinium Ethiodide Method¹³

Condensation of phenol with epichlorohydrin: A mixture of 188 g (2 moles) of phenol, 194 g (2.09 moles) of epichlorohydrin and 2 g of pyridine was heated to 85-90°. An exothermic reaction occurred, necessitating cooling to prevent rise in temperature. The red-brown solution was heated at 90° for a further 13 hours and then distilled. The following fractions were collected:

- 1.- 85 g of α,γ -dichlorohydrin, boiling at 85°/3mm.
- 2.- Small amount of glycide phenyl ether, boiling at 90-105°/3mm.
- 3.- 150 g of 1-chloro-3-phenoxy-propane-2-ol, boiling at 120-135°/3mm.

No further fractions were collected.

Cyclization of 1-chloro-3-hydroxy-propane-2-ol to glycide phenyl ether: A solution of 240 g of sodium

hydroxide (6 moles) in 1 liter of water was mixed with 870 g of 1-chloro-3-phenoxy-propane-2-ol (4.6 moles) and stirred for 2 hours at 25°. The reaction mixture was transferred to a separatory funnel and allowed to stand overnight. The organic layer was separated and the aqueous layer was extracted with three 250 ml portions of ether. The ether extracts were combined with the organic layer and dried. The ether was removed and the product was distilled under reduced pressure to give 474 g of glycide phenyl ether (67% of the theoretical) boiling at 89-90°/2mm.

Preparation of Pyridinium Ethiodide¹⁷: A mixture of 39.5 g (40 ml, 0.5 moles) of pyridine and 70 g (40 ml, 0.5 moles) of ethyl iodide was heated over a low flame for a few minutes, allowed to cool to room temperature and finally cooled in an ice bath. The crystals were collected on a Buchner funnel, washed with ether and then recrystallized from a mixture of ethyl alcohol and ethyl acetate. After drying, the product melted at 90°.

Reaction of Pentaerythrityl Dichloride with Glycide Phenyl Ether: A mixture of 40 g (0.23 moles) of pentaerythrityl dichloride, 39 g of glycide phenyl ether (0.26 moles), 1.9 g of pyridinium ethiodide was slowly fractionated through a Vigreux column at reduced pressure. A liquid (21 g) was isolated, boiling 158-163°/33mm.,
 n_D^{25} 1.5210, d_4^{28} 1.120.

Preparation of 3-Hydroxymethyl-3-Chloromethyl-Oxacyclo-
Butane

Method A (using excess of the alkoxide): Pentaerythrityl dichloride (40 g, 0.23 moles) in 80 ml of absolute ethyl alcohol was refluxed with a solution of 11.5 g (0.5 moles) of sodium in 300 ml of absolute ethyl alcohol for 2 hours. The mixture was then cooled in an ice bath and the precipitated sodium chloride was removed by filtration. In order to destroy the excess of sodium ethoxide, 20 ml of water was added to the filtrate and carbon dioxide was bubbled through the solution. After cooling in an ice bath for five hours, the precipitated sodium carbonate was separated by filtration. The alcohol was removed on the steam bath and the residue was fractionated under reduced pressure. After a small amount of forerun, the main product distilled at 108-110°/1mm. (144-146°/5mm.). The yield of 3-hydroxymethyl-3-chloromethyl-oxacyclobutane was 12.5 (39.3% of the theoretical) n_D^{19} 1.4819.

Substitution of methyl alcohol for ethyl alcohol gave 13.6 g of 3-hydroxymethyl-3-chloromethyl oxacyclobutane (42.7% of the theoretical), boiling at 144-146°/5mm., n_D^{19} 1.4820.

Method B (using theoretical amounts of sodium methoxide): The reaction was carried out in a manner similar to that described above, using 40 g of pentaery-

thrityl dichloride (0.23 moles) and 5.3 g of sodium (0.23 moles). After this final distillation, 10 g of 3-hydroxymethyl-3-chloromethyl oxacyclo-butane (31.4% of the theoretical) was obtained.

Anal. Calcd. for $C_5H_9ClO_2$: C, 43.96; H, 6.64; Cl, 25.96.

found : C, 46.02; H, 6.88; Cl, 22.66.

Reaction of 3-Hydroxymethyl-3-Chloromethyloxacyclobutane With Halogen Acids

Reaction with Hydrochloric Acid. Preparation of 2,2-bis(chloromethyl)1,3-Propanediol (Pentaerythrityl Dichloride)(V): A mixture of 2.5 g of 3-hydroxymethyl-3-chloromethyl-oxacyclobutane (0.018 moles) and 25 ml. of concentrated hydrochloric acid was refluxed for 2 hours. The mixture was diluted with 75 ml of water and extracted with five 25 ml portions of ether. The combined ether layers were dried over anhydrous sodium sulfate and filtered. The ether was removed on the water bath and the residue was recrystallized from a mixture of carbon tetrachloride (5 ml), chloroform (5 ml) and toluene (0.5 ml) to give 3.1 g of pentaerythrityl dichloride (theoretical amounts), melting at 80-81°.

A mixture with an authentic sample melted at the same temperature.

Reaction with Hydrobromic Acid. Preparation of 2-Chloromethyl-2-Bromomethyl-1,3-Propanediol (Pentaerythrityl Monochloride Monobromide)(VII): A similar procedure was employed, using 2.5 g of 3-hydroxymethyl-3-chloromethyl-oxacyclobutane (0.018 moles) and 25 ml of 40% hydrobromic acid. The crude product was recrystallized from a mixture of carbon tetrachloride, chloroform and toluene to give 3.2 g of 2-chloromethyl-2-bromomethyl-1,3-propanediol (82% of the theoretical), melting at 95.5-96°.

Anal. Calcd. for $C_5H_{10}O_2ClBr$: C, 27.67; H, 4.64; combined halogens, 53.07.

found : C, 27.89; H, 4.73; combined halogens, 53.80.

Reaction with Hydriodic Acid. Preparation of 2-Iodomethyl-2-Chloromethyl-1,3-Propanediol (Pentaerythrityl Monobromide Monoiodide)(VIII): A mixture of 2.5 g (0.018 moles) of 3-hydroxymethyl-3-chloromethyl-oxacyclobutane was refluxed with 25 ml of 45% hydriodic acid for half an hour, and then diluted with 75 ml of water. The mixture was neutralized with solid sodium carbonate and cooled in an ice bath for several hours. The precipitated crude monochloride monoiodide (3.5 g) was separated by filtration. An additional 1.5 g of material was obtained by extracting the filtrate with ether and evaporating the solvent. The combined crude product was recrystallized

from a mixture of carbon tetrachloride and small amounts of toluene. The yield of pentaerythrityl moniodide monochloride was 4.3 g (72% of the theoretical) melting at 95-95.5°.

Anal. Calcd. for $C_5H_{10}O_2ClI$: C, 22.70; H, 3.81; combined halogen, 61.38.

found : C, 22.70; H, 3.64; combined halogen, 61.70.

Independent Synthesis of 2-Chloromethyl-2-Bromomethyl-1,3-Propanediol.

Preparation of Monobromopentaerythritol (IX): The procedure used was for the preparation of this compound was a modification of the method described by Beyaert and Hansens¹⁹.

In a 2 liters, two-necked flask fitted with ground-glass joints were placed 200 g (1.47 moles) of pentaerythritol, 1.5 liters of glacial acetic acid and 283 ml of 48% hydrobromic acid. A reflux condenser and a dropping funnel were attached to the flask. The mixture was refluxed for 7½ hours. The solution was heated under reduced pressure to remove as much of the acetic acid and water as possible and was finally heated for 15 minutes at 140-150°/10mm. pressure. The viscous residue was treated with 750 ml of 98% ethyl alcohol, and 50 ml of 48% hydrobromic acid. The flask was provided with an efficient fractionating column

and the solution was fractionated slowly until about 500 ml of distillate was collected. Then a second 750 ml of 98% ethyl alcohol was added and the distillation was continued slowly until 750 ml more distillate were collected. The boiling point during the collection of the first 500 ml of distillate remained constant (72°) corresponding to the ethanol-ethyl acetate azeotrope. The flask was then fitted with a Claisen head and a condenser set for downward distillation and the remaining alcohol was removed as completely as possible under reduced pressure. Benzene (500 ml) was added to the residue and distilled off at atmospheric pressure. The last traces of benzene were removed by heating for 15 minutes at $150^{\circ}/8\text{mm}$. The same procedure was repeated using a second 500 ml portion of benzene. The viscous residue was then refluxed for several hours with 500 ml of dry ether, with frequent shaking until it became white and granular. After cooling thoroughly the ether was decanted and the solid was washed with two 200 ml portions of dry ether. The solid was powdered and extracted exhaustively in a Soxhlet extractor with 600 ml of dry ether. At the end of the extraction, 30-35 g of unchanged pentaerythritol remained in the extraction thimble. The ether extract was cooled overnight in an ice bath and the precipitated monobromopentaerythritol was collected by filtration and washed with 200 ml of dry ether. The yield of the crude product, melting at $72-73^{\circ}$, was 146-160 g

(49-54% of the theoretical). The product was recrystallized from a mixture of 120 ml of chloroform and 80 ml of ethyl acetate to give 124-136 g of monobromopentaerythritol melting at 75-76°.

Monobenzalpentaerythrityl Monobromide (X): A solution of 20 g (0.1 moles) of monobromopentaerythritol in 50 ml of distilled water was treated with 10.6 g (0.1 moles) of benzaldehyde and 0.6 ml of concentrated hydrochloric acid. The mixture was shaken mechanically for 48 hours. The precipitate was collected on a Buchner funnel and washed with water made slightly alkaline with sodium carbonate, and finally with distilled water. The dry product (24 g) was recrystallized from a mixture of one part of benzene and one part of aviation benzene (b.p. 60-70°) to give 20 g of monobenzalpentaerythrityl monobromide (69% of the theoretical) melting at 73.5-74.5°.

Anal. Calcd. for $C_{12}H_{15}O_3Br$: C, 50.19; H, 5.26

found : C, 50.14; H, 5.08

2-Chloromethyl-2-Bromomethyl-1,3-Propanediol(Pentaerythrityl Monochloride Monobromide)(VII): In a 100 ml, three-necked round-bottomed flask with ground-glass fittings were placed 17.2 g of monobenzalpentaerythrityl monobromide (0.06 moles), 4.7 g of dry pyridine (0.06 moles) and 8 ml of dry chloroform. The flask was equipped with a mercury-sealed stirrer, a dropping funnel and a condenser (protected with a calcium chloride tube). The flask was

surrounded by an ice bath and the stirrer was started. Thionyl chloride (7.2 g, 4.2 ml, 0.06 moles) dissolved in 8 ml of dry chloroform was slowly added through the dropping funnel in the course of 2 hours. After the addition was completed, the mixture was stirred overnight at room temperature and then heated on a steam bath for 4 hours. After cooling, chloroform and excess of thionyl chloride were removed under reduced pressure. The residue was refluxed with a mixture of 150 ml of 0.5N hydrochloric acid and 50 ml of dioxane for 4 hours. The hot solution was then steam distilled until all the benzaldehyde was removed. The solution in the flask was concentrated under reduced pressure to about 20 ml and then extracted with three 50 ml portions of ether. The ether was evaporated on the steam bath and the residue was refluxed with 100 ml of water and 1 gr of charcoal for 5 minutes and filtered while hot. The filtrate was extracted with four 50 ml portions of ether. The combined ether layers were dried over anhydrous sodium sulfate and filtered. After removal of the ether, the residue was recrystallized from a mixture of 20 ml of carbon tetrachloride and 5 ml of toluene. The yield of pentaerythrityl monobromide monochloride, melting at 94-95°, was 7 g (53% of the theoretical).

A mixture with pentaerythrityl monobromide monochloride prepared from 3-hydroxymethyl-3-chloromethyloxacyclobutane melted at the same point.

Preparation of 2-Hydroxymethyl-2-Iodomethyl-1,3-Propanediol (Pentaerythrityl Monoiodide)

Preparation of 3,3 bis(Hydroxymethyl) Oxacyclobutane (XII): The procedure was a modification of the method reported by Goveart and Beyaert¹⁸.

A solution of 40 g (0.2 moles) of pentaerythrityl monobromide in 160 ml of absolute ethyl alcohol was added to a solution of 13.8 g (85% assay, 0.2 moles) of potassium hydroxide in 190 ml of absolute ethyl alcohol. The mixture was stirred at room temperature for 2 hours and then refluxed for 5 minutes. The mixture was then cooled and the precipitated potassium bromide was removed by filtration. The alcoholic filtrate was neutralized with acetic acid and the alcohol was removed under reduced pressure. The residual oil was fractionated through a 15 cm Vigreux column. A small amount of 1,3-propanediol-2-methylene¹⁵ distilled at 98-102°/1mm. The yield of 3,3 -bis (hydroxymethyl) oxacyclobutane, distilling at 135-137°/1mm, was 15 g (63% of the theoretical).

Preparation of Pentaerythrityl monoiodide(XIII): A mixture of 21 g (0.17 moles) of 3,3 -bis (hydroxymethyl) oxacyclobutane and 79 g (52.7 ml, 0.27 moles) of 45% hydriodic acid was refluxed for half an hour. The mixture was then neutralized with sodium carbonate and cooled in an ice bath for 3 hours. The precipitate was removed by filtration, dried and extracted with 50 ml of ether in a Soxhlet extrac-

tor. The ether extract was cooled in an ice bath and then filtered to give 28.5 g (63% of the theoretical) of pentaerythrityl monoiodide, melting at 108-109°. The product, which was slightly yellowish, was recrystallized from a mixture of 150 ml of ethyl acetate and 70 ml of chloroform to give 27 g of colorless crystals, melting at 108-109°. The melting point of this product has been reported as 106°¹⁶.

Formation of Dibenzalpentaerythritol from Monobenzalpentaerythritol

A solution of 2.89 g of monobenzalpentaerythritol (0.012 moles) in 289 ml of distilled water was acidified with 1.5 ml of concentrated hydrochloric acid. The solution was allowed to stand at room temperature for 24 hours and then neutralized with sodium carbonate solution. The precipitate was collected by filtration and dried. After recrystallization from butanol, 0.5 g of dibenzalpentaerythritol (24.6% of the theoretical) was obtained, melting at 159-160°.

A mixture with an authentic sample of dibenzalpentaerythritol melted at the same point.

PART II

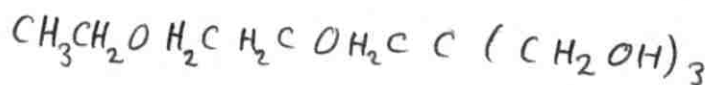
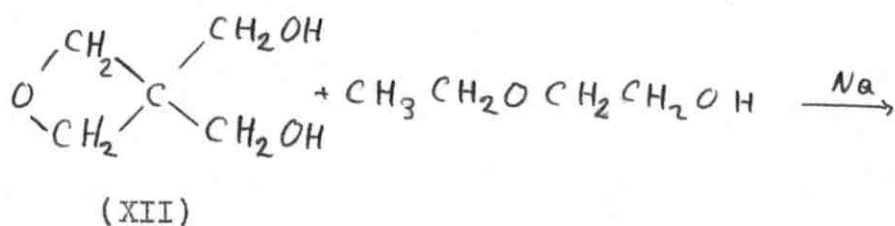
THE REACTION

of

3,3 bis(HYDROXYMETHYL) OXACYCLOBUTANE

WITH ETHOXY ETHANOL

In a previous work⁴ on the preparation of ethylene glycol ethers of pentaerythritol, it was found that the trimethylene oxide ring of 3,3-bis-(hydroxymethyl)-oxa-cyclobutane (XII) was attacked readily by the sodium derivative of ethylene glycol to give the monoethylene glycol ether of pentaerythritol. The work has now been extended to a study of the reaction between (XII) and ethoxyethanol to give pentaerythrityl β -ethoxyethyl ether (XVIII).



(XVIII)

The reaction proceeds smoothly at reflux temperatures to give (XVIII) in moderately good yield. The product is an oil and was characterized by conversion to the triacetate and the tritryl ether.

EXPERIMENTAL

Reaction of 3,3-bis-(Hydroxymethyl)-Oxacyclo-
butane (XII) with Ethoxyethanol: A solution of 26 g
(0.22 moles) of 3,3-bis-(hydroxymethyl)-oxacyclobutane in
200 ml of ethoxyethanol was added to a solution of 5.1 g
(0.22 moles) of sodium in 200 ml of ethoxyethanol during
the course of $1\frac{1}{2}$ hours at 140-150°. The mixture was kept
at this temperature for 24 hours. After cooling to room
temperature, the mixture was neutralized with dilute
hydrochloric acid. The solution was cooled in an ice
bath and the precipitated sodium chloride was removed by
filtration. The excess ethoxyethanol was removed under
reduced pressure (75-80°/55 mm). The residue was heated
at 100° for 12 hours with 400 ml of acetic anhydride and
2 g of pyridine²⁰. The excess acetic anhydride was
removed under reduced pressure (90-120°/120 mm) and the
viscous oil obtained was treated with 200 g of ice and
then neutralized with solid sodium bicarbonate. The oil
was separated and the aqueous layer was extracted with
ether. The ether extracts were combined with the oil,
dried over anhydrous sodium sulfate, and filtered. After
removal of the ether, the residue was fractionated under
reduced pressure to give 40 g (55% of the theoretical
based on the cyclic compound) of the triacetate of the
 β -ethoxyethyl ether of pentaerythritol, boiling at

184-189°/2 mm; n_D^{23} 1.4430.

Anal. Calcd. for $C_{15}H_{26}O_8$: C, 53.88; H, 7.84;

Sapn. equiv., 111.3.

found: C, 54.58; H, 7.95;

Sapn. equiv., 110.2.

Transesterification of Pentaerythrityl- β -Ethoxy-

ethyl Ether Tri-acetate to Pentaerythrityl- β -Ethoxy-

ethyl Ether: A solution of 10 g (0.03 moles) of the

tri-acetate of pentaerythrityl- β -ethoxyethyl ether in 50 ml of absolute ethyl alcohol was refluxed for one hour with a solution of 0.06 g of sodium in 100 ml of absolute ethyl alcohol. The solution was then fractionated very slowly through an efficient column, to remove the ethyl alcohol-ethyl acetate azeotrope. The residue was then neutralized with dilute hydrochloric acid and distilled under reduced pressure to give 6.2 g (theoretical amounts) of pentaerythrityl- β -ethoxyethyl ether, b.p.

172-178°/1 mm. n_D^{25} 1.4416.

Anal. Calcd. for $C_9H_{20}O_5$: C, 51.92; H, 9.57

found: C, ; H,

Preparation of Triphenylchloromethane (Trityl

Chloride)²¹: A mixture of 75 g of triphenyl carbinol and 22 ml of dry benzene was placed in a 250 ml round-bottomed flask provided with a reflux condenser. The condenser was provided with a calcium chloride tube at the top. The mixture was heated on a steam bath, and 15 ml of acetyl

chloride was added through the condenser. Heating was continued while the mixture was shaken vigorously. In about 5 minutes all the solid disappeared. In the course of 10 minutes an additional 30 ml of acetyl chloride was added. The solution was then refluxed for one half hour.

The flask was cooled under running water and during this operation 50 ml of petroleum ether were added through the condenser. The mixture was then cooled in an ice bath for 2 hours and the product was filtered and washed with 75 ml of petroleum ether. The colorless solid, after drying in a dessicator over soda lime and paraffin, weighed 70 g (80% of the theoretical) and melted at 111-112°.

Tritylation of the Product: The procedure used was a modification of the method described by Seikel and Huntress²².

A mixture of 4 g of pentaerythrityl- β -ethoxyethyl ether, 49.8 g of trityl chloride and 89 ml of dry pyridine was heated at 100° for 1½ hours. After cooling, 70 ml of water was added and the gum formed was removed from the flask and triturated with several portions of water. After cooling in an ice bath, the lumps were powdered and washed with water and alcohol. The product was refluxed with absolute alcohol and then filtered. The solid remaining on the filter paper was recrystallized first from acetone and then from a mixture of 50 ml of methanol and 60 ml of benzene to give 6.5 g of the trityl ether

melting at 198-199°.

Anal. Calcd for $C_{66}H_{12}O_5$: C, 84.79; H, 6.63

found : C, ; H,

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SUMMARY

1.- The reaction between pentaerythrityl dichloride and sodium ethoxide (methoxide) in ethyl (methyl) alcohol gives 3-hydroxymethyl-3-chloromethyl-oxacyclobutane.

2.- Monobromopentaerythrityl monochloride and monoiodopentaerythrityl monochloride have been prepared from 3-hydroxymethyl-3-chloromethyl-oxacyclobutane.

3.- A method has been described for the preparation of monobromopentaerythrityl monochloride from monobenzalpenterythrityl monobromide.

4.- A method for the preparation of pentaerythrityl monoiodide has been described.

5.- The reaction between 3,3-bis(hydroxymethyl)-oxacyclobutane and β -ethoxyethyl alcohol gives pentaerythrityl- β -ethoxyethyl ether.

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