

SOME ASPECTS OF THE CHEMISTRY OF DIHYDROPYRAN

by

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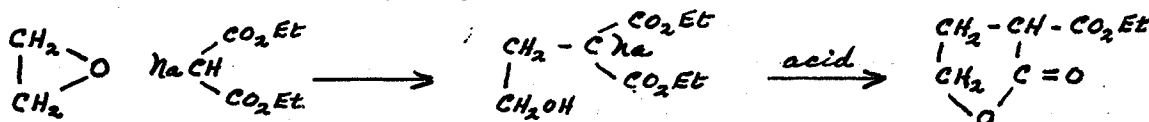
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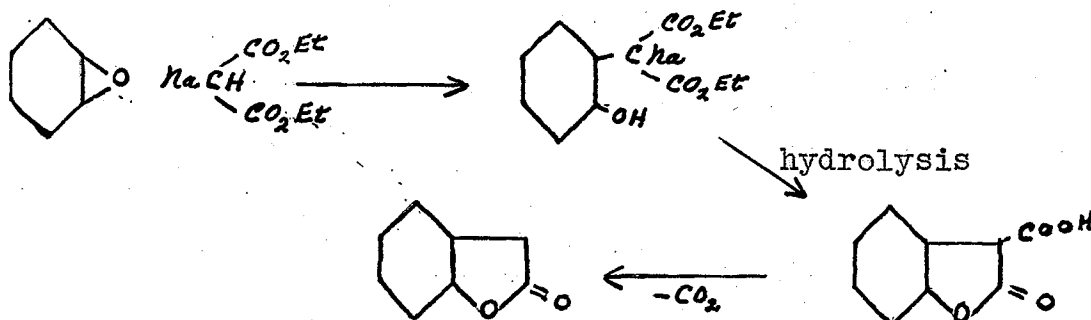
INTRODUCTION

Several investigators have reported the condensation of ethylenic oxides with sodio-activated methylene groupings to produce, on certain further treatment, a variety of lactones and acids. Traube and Lehmann (52, 53) condensed ethylene oxide with ethyl sodio-malonate and on acidification obtained 2-carbethoxybutyrolactone:

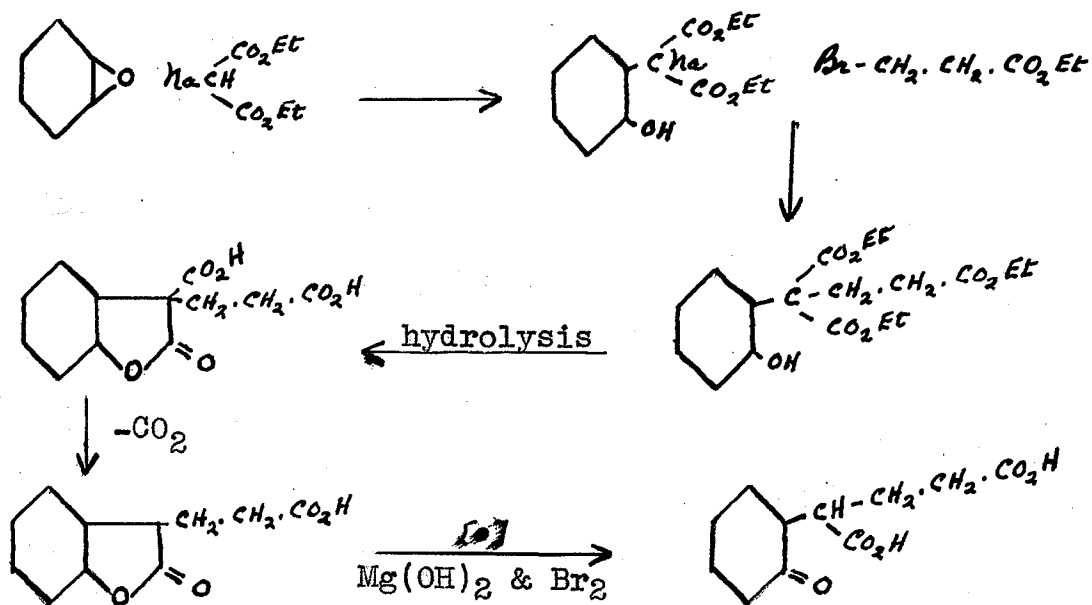


They carried out a similar reaction with epichlorhydrin and also condensations in which they replaced the malonic ester with acetoacetic ester. Haller and Blanc (12) used the same type of condensation in a synthesis of terebic acid.

Coffey (5) condensed cyclohexene oxide with ethyl sodio-malonate and, after hydrolysis and elimination of carbon dioxide, isolated cyclohexanol acetic lactone:



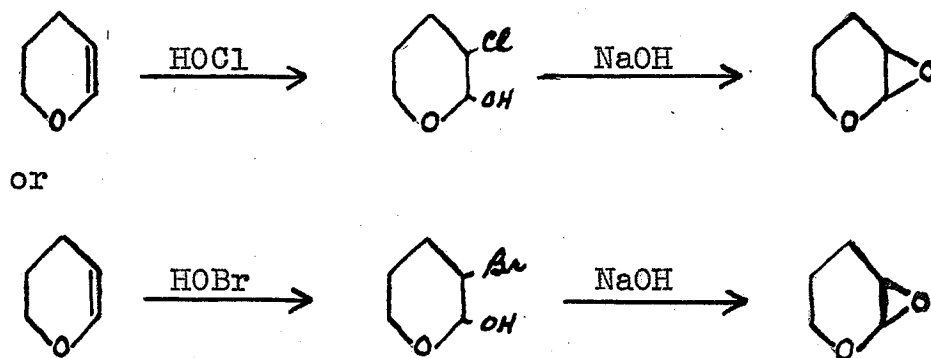
Kendall, Osterberg, and MacKenzie (18, 19), starting with the same condensation, synthesized  $\alpha$ -(2-ketocyclohexyl)-glutaric acid by condensing the first condensation product with  $\beta$ -bromopropionic ester, hydrolyzing, decarboxylating, and then oxidizing the resulting lactone with magnesium hydroxide and bromine:



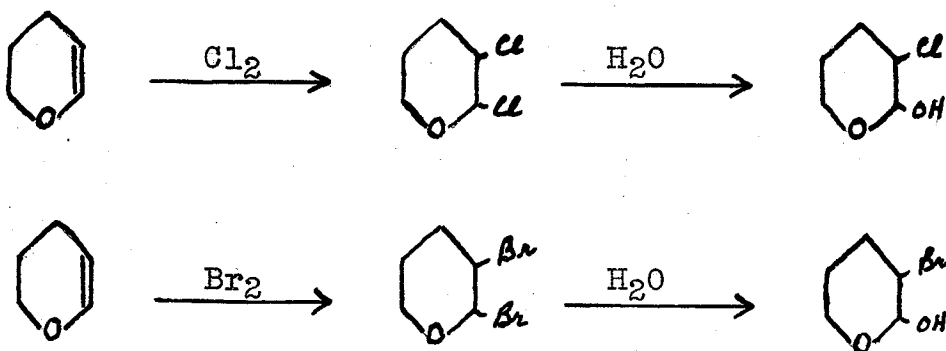
McRae, Charlesworth, and Alexander (21) used Kendall's method to synthesize 2-ketocyclohexyl succinic acid by using ethyl bromoacetate in place of the ethyl  $\beta$ -bromopropionate. They showed also that alkyl halides may be used in place of the bromoacetic ester or the bromopropionic ester to prepare ketocyclohexyl substituted acids. In another paper (22) McRae, Charlesworth, and co-workers report similar reactions with ethylene oxide and propylene oxide.

Recently a comparatively new ethylenic compound, dihydropyran, first reported in 1933, became available to us through the courtesy of E. I. Du Pont de Nemours & Company. It was thought that this substance might show reactions similar to those of cyclohexene and that it might be possible to repeat with it the reactions carried out with cyclohexene by the earlier workers mentioned. It was to check this hypothesis that the work to be described was undertaken.

The oxide of dihydropyran is not reported in the literature. It was decided to attempt to prepare it by the method used for cyclohexene oxide by McRae, Charlesworth, and Alexander (21). This involved carrying out the following reactions:



Both hypochlorous and hypobromous acid seemed to add to the dihydropyran readily enough, but efforts to isolate the halohydrins from the reaction mixtures failed. It was found possible, however, to prepare both the chlorohydrin and the bromohydrin by the hydrolysis of the dihalides:

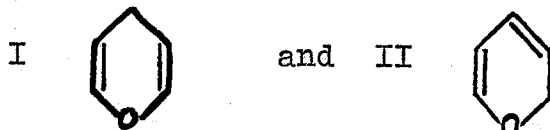


Both the chlorohydrin and the bromohydrin were found to react readily with sodium hydroxide solution, but the desired oxide has not as yet been isolated from the resulting solution.

### NOMENCLATURE

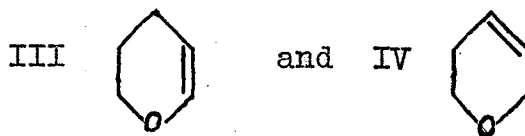
The dihydropyran used in this investigation is referred to in the literature by such a variety of names that it is advisable to review the naming system for the pyrans and dihydropyrans before discussing the substance further.

There are two possible pyrans:



Of these, I is called 1,4-pyran or  $\gamma$ -pyran and II is called 1,2-pyran or  $\alpha$ -pyran. Neither of them is known but derivatives of both have been prepared.

Partial hydrogenation of the two pyrans can lead to two dihydropyrans:



III may be derived from either I or II and hence may be referred to by any one of the following names:

5,6-dihydro-1,4-pyran, 5,6-dihydro- $\gamma$ -pyran,  
2,3-dihydro-1,4-pyran, 2,3-dihydro- $\gamma$ -pyran,  
3,4-dihydro-1,2-pyran, 3,4-dihydro- $\alpha$ -pyran.

IV is derivable from II only and hence may be called:

5,6-dihydro-1,2-pyran or 5,6-dihydro- $\alpha$ -pyran.

Both of the dihydropyrans are also sometimes referred to as epoxides. Thus III is called epoxy-1,5-pentene-4 or epoxy-1,5-pentene-1 and IV epoxy-1,5-pentene-3 or epoxy-1,5-pentene-2.

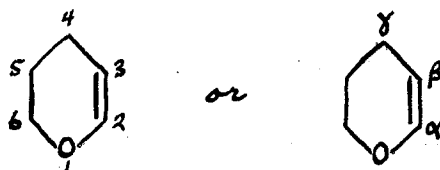
Obviously, either III or IV by the addition of another molecule of hydrogen gives the same tetrahydropyran. This tetrahydropyran is also called pentamethylene oxide and



epoxy-1,5-pentane.

Both of the dihydropyrans and the tetrahydropyran are known.


The dihydropyran III, first reported in 1933, is the substance used in this investigation. To avoid the constant repetition of the cumbersome names in the discussion which follows, it will be called simply dihydropyran and the ring positions will be designated as follows:

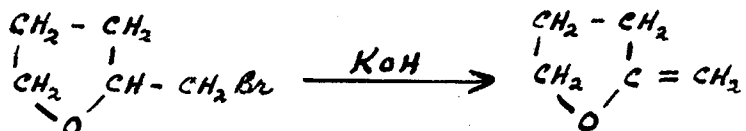


The dihydropyran IV, first reported in 1947, will be mentioned two or three times in this thesis. To distinguish it from the dihydropyran III, it will be called the new dihydropyran and its structure will be indicated.

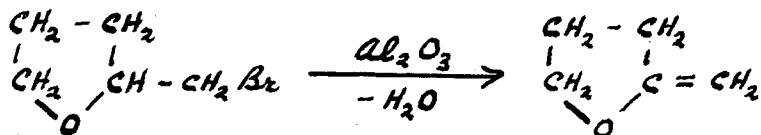
The saturated ring will be called tetrahydropyran and the ring positions numbered as for dihydropyran.


### HISTORY OF DIHYDROPYRAN

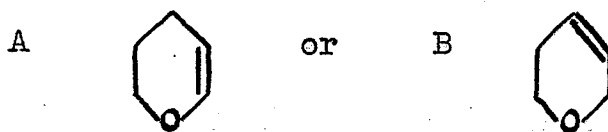
The dihydropyran  was first isolated in 1933 by the French chemist, Raymond Paul (32), while he was studying furan derivatives. He had prepared epoxy-1,4-pentene-4, but in meagre yields, from tetrahydrofurfuryl bromide by treatment with caustic potash:



In an effort to prepare the same substance by the dehydration of tetrahydrofurfuryl alcohol with alumina:

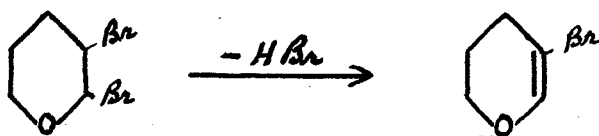


he obtained instead a new olefinic product. This new substance readily added a molecule of hydrogen to form a known pyran derivative, tetrahydropyran , reported by Clarke (4) in 1912. This suggested that the new compound was a dihydropyran and therefore had one of two possible structures:

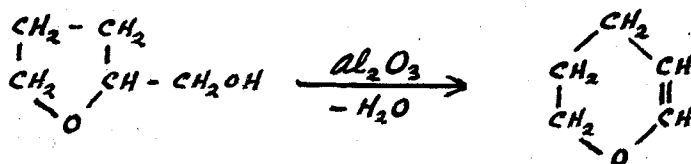


Of these Paul (33) chose structure A, because the reactions of his dihydropyran suggested the presence of a vinyl group  $-\text{CH}=\text{CH}-\text{OR}$ . He found, for instance, that acid hydrolysis opened the ring to form an aldehyde, a reaction which he considered "inconceivable" in the case of structure B. He found also that the dibromide of his dihydropyran, which was formed readily, tended to fume in moist air, presumably due

to the liberation of hydrogen bromide as follows:

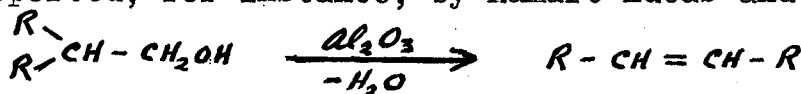


The dibromide of structure B would be expected to be more stable. Paul (32) points out also that the methylenic transposition which takes place on the dehydration of tetrahydrofurfuryl alcohol with alumina:

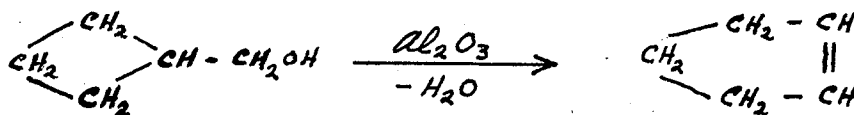


is a type of reaction which has been observed by others.

It is reported, for instance, by Ramart-Lucas and Amagat (46):





and by Dojarenko (8):



Subsequent work with Paul's dihydropyran, which will be dealt with later, has confirmed the structure which he assigned to it.

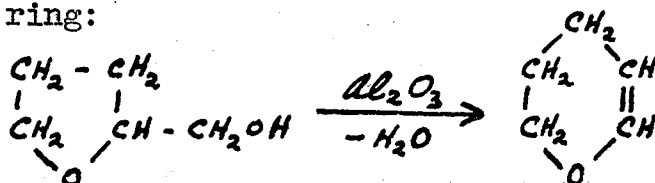
For some years after his discovery of the new compound Paul seems to have been the only chemist interested in dihydropyran. Many of its reactions were studied in his laboratory and a series of papers thereon published in the French journals. After the outbreak of war in 1939 the chemists of I. G. Farbenindustrie in Germany and those of Imperial Chemical Industries in Great Britain began to take an interest in the compound. Some of the results of their work were published during the war in the form of patents in

Germany and France and in Britain respectively. At the end of the war some of the confidential reports on dihydropyran of a Dr. Ritter of I. G. Farbenindustrie fell into American hands and attracted the attention of the chemists of E. I. Du Pont de Nemours & Company. Recent work in the field has been done mainly by them. The reactions that have been carried out by all these workers will be referred to in the next section.

It is interesting to note here that the other possible dihydropyran  has now been prepared also and its reactions  studied, again in the laboratory of Raymond Paul (42). A comparison of its reactions with those of the earlier dihydropyran confirms that these substances have the assigned structures.

THE CHEMISTRY OF DIHYDROPYRAN AND OF ITS DERIVATIVES

Dihydropyran can be prepared by passing the vapor of tetrahydrofurfuryl alcohol over heated alumina, the method originally used by Paul (33). The alcohol loses water and a methylenic transposition enlarges the furan ring to the pyran ring:



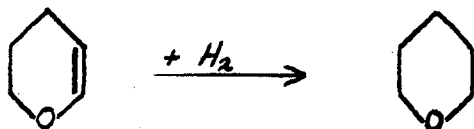
According to Paul, thorium dioxide may be used in place of aluminum oxide but acidic dehydrating agents such as phosphoric anhydride do not give results. On the other hand, Bremner and McNeil (2) of Imperial Chemical Industries have patented a process using a mixture of aluminum oxide and phosphoric anhydride. Limited quantities of dihydropyran, for research, are now available from E. I. Du Pont de Nemours & Company, who hope to have it on the market shortly at a reasonable price.

Dihydropyran is a mobile, colorless liquid, which boils at 86°C. at normal pressure. It is slightly soluble in water and soluble in most organic solvents. It is a very reactive compound. It shows both the addition reactions characteristic of olefines and ring-opening reactions which produce a variety of open-chain compounds. Many of its derivatives are themselves very reactive and promise to be useful in the synthesis of a variety of new products. The important derivatives that have been made, the methods of preparing them, and their outstanding reactions, so far as

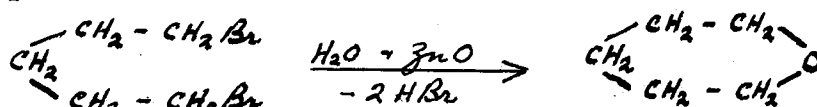
they have been studied, are summarized in the following paragraphs.

Tetrahydropyran

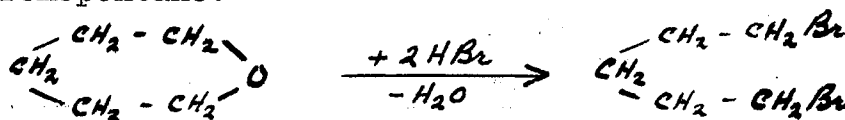
Paul (33) found that dihydropyran, in the presence of platinum black, adds a molecule of hydrogen in the cold, forming tetrahydropyran:



This compound had previously been prepared by Clarke (4), who had obtained it by the hydrolysis of 1,5-dibromopentane in the presence of zinc oxide:

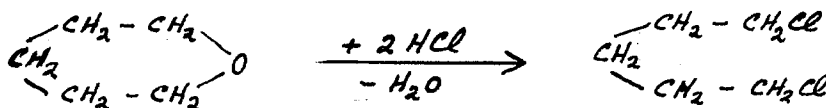


To confirm that his hydrogenation product was tetrahydropyran, Paul reversed Clarke's reaction by submitting his compound to the action of gaseous hydrogen bromide and obtained 1,5-dibromopentane:



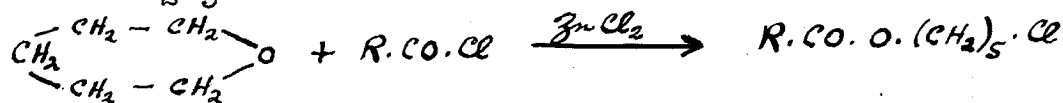
So good was the yield of this reaction that he recommends it as an excellent source for the dibromopentane, which had been difficult to obtain in pure form by the earlier method of von Braun (1).

The chemists of I. G. Farben (27) found that hydrogen chloride similarly opened the ring of tetrahydropyran to produce 1,5-dichloropentane:

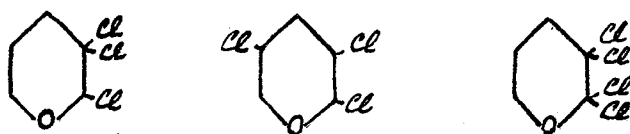


They opened the ring also by the action of acid chlorides,

in the presence of zinc chloride, forming esters of the type  $R.CO.O.(CH_2)_5.Cl$ :



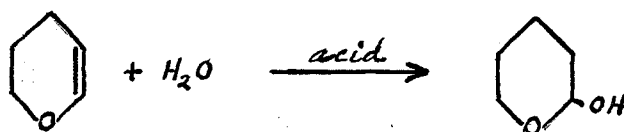
Hawkins and Bennett (15) claim that chlorine substitutes readily in the tetrahydropyran ring. They passed chlorine into tetrahydropyran at  $70^\circ$  and isolated the following trichloro- and tetrachloro- derivatives:



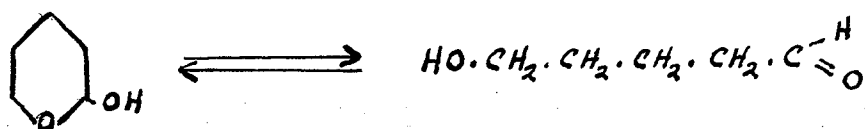
The chlorination process is facilitated by the use of chlorination catalysts such as ferric chloride or aluminum chloride, iron turnings, iodine, or actinic radiation, particularly if it is desired to produce a highly chlorinated body.

#### Hydrolysis Products

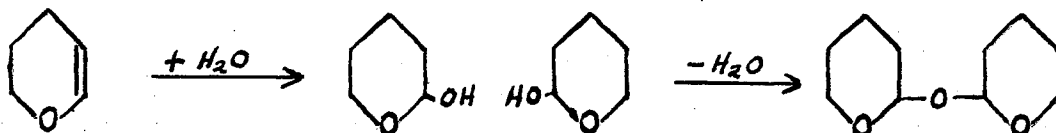
Paul (34, 37) reports that dihydropyran, in the presence of mineral acid, readily adds a molecule of water. The hydrolysis is effected rapidly by boiling but the yields are better when the reactants are simply left in contact at room temperature. The product is the expected epoxy-pentanol:



This cyclic alcohol has aldehyde properties, leading Paul (37) to conclude that it exists in equilibrium with the open-chain aldehyde form,  $\delta$ -hydroxyvaleraldehyde:

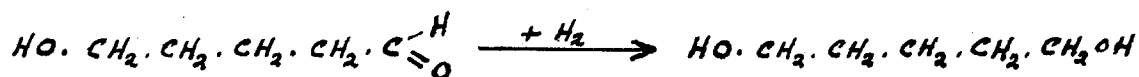


The Du Pont chemists (9) have apparently isolated a bicyclic ether, di-2-tetrahydropyryl ether, as one of the products of hydrolysis:

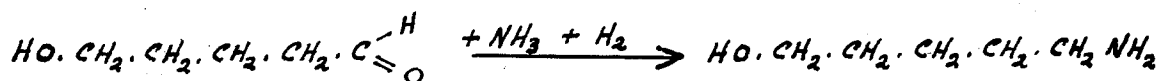


They claim there is equilibrium between  $\delta$ -hydroxyvaleraldehyde and this ditetrahydropyryl ether but that the two forms can be separated by distillation from neutral solution.

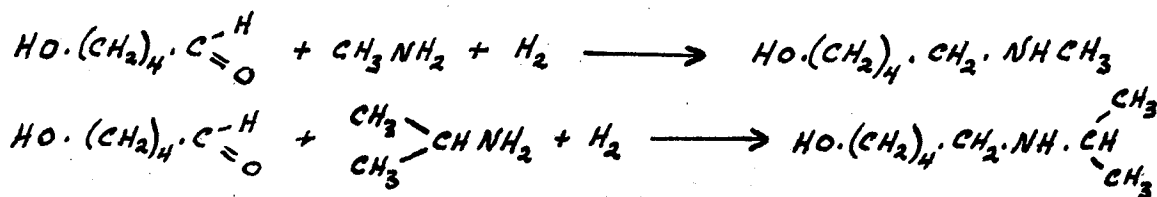
So far as reactions are concerned,  $\delta$ -hydroxyvaleraldehyde is the important form. It is apparently a very useful intermediate in the preparation of a variety of compounds. Schniepp and Geller (50) submitted it to catalytic hydrogenation and obtained 1,5-pentanediol:



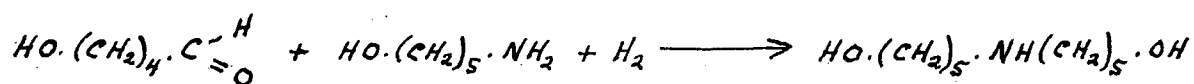
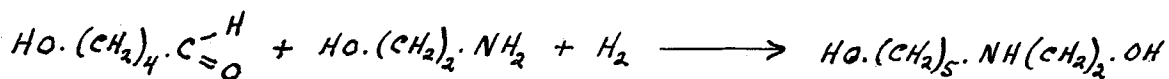
Woods and Sanders (57) treated it with liquid ammonia and hydrogen, in the presence of a catalyst, and obtained 5-aminopentanol-1:



This last reaction was carried out earlier by the chemists of I. G. Farbenindustrie (27, 28), who extended it to a number of amines:

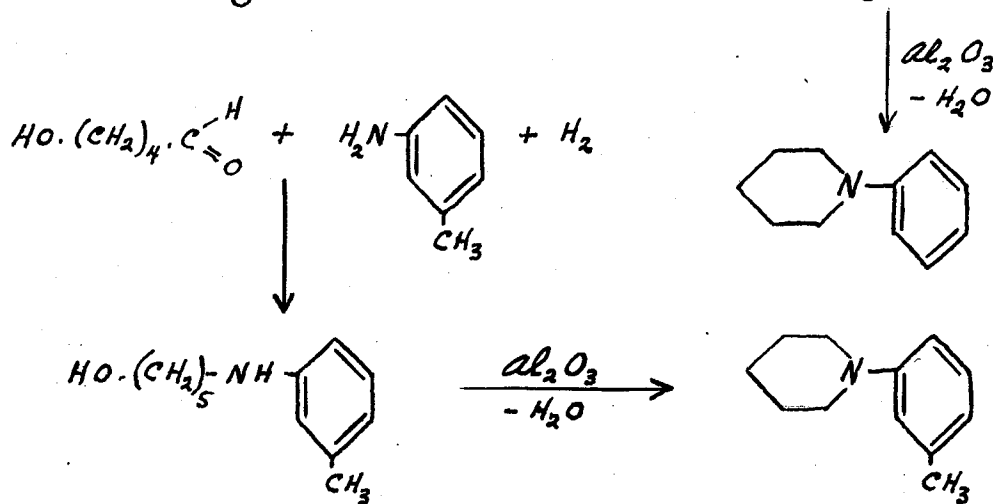
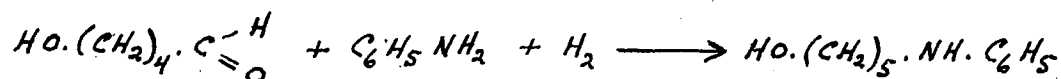




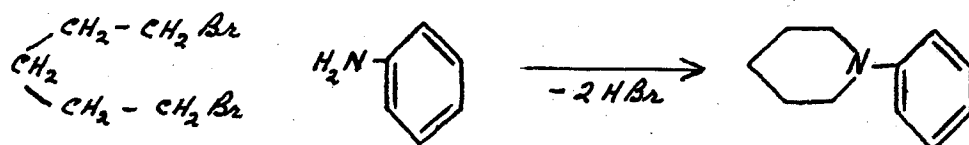


From these and similarly constituted substances, by condensation with aliphatic di-isocyanates, they claim to have obtained polyamides of interest to the textile industry.

Using aromatic amines similarly and dehydrating the resulting phenylaminopentanol by passing them over heated alumina they prepared N-phenylpiperidines:

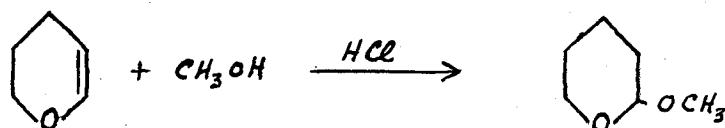


It is interesting to note here that Paul (33) prepared N-phenylpiperidine from his 1,5-dibromopentane by condensing it with aniline:



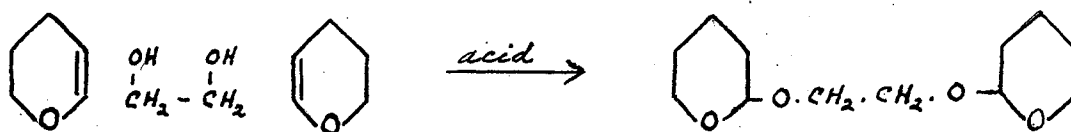
### Alcohol Addition Products

Paul (34, 37) reports that dihydropyran boiled with alcohols, in the presence of a trace of hydrochloric acid, adds the alcohol to the double bond forming alkyl tetrahydropyryl ethers. For example, with methanol one obtains 2-methoxy-tetrahydropyran:

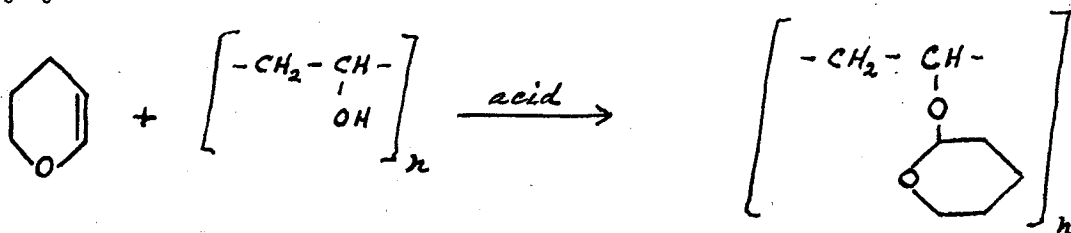


These ethers have no aldehyde properties. They probably do not exist to any appreciable extent in the open-chain form as does 2-hydroxytetrahydropyran, which exists mainly as  $\delta$ -hydroxyvaleraldehyde. The alkyl group apparently stabilizes the ring.

The Du Pont chemists (9) have extended this reaction to glycols and polyvinyl alcohols. For instance, with ethylene glycol they obtained di-2-tetrahydropyryl glycol ether:



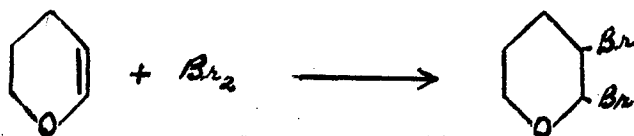
With polyvinyl alcohols they obtained polyvinyl 2-tetrahydropyryl ethers:



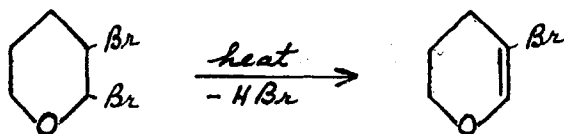
They claim that these products have possible application as plasticizers, e.g. in vinyl chloride resins.

Halogen Derivatives

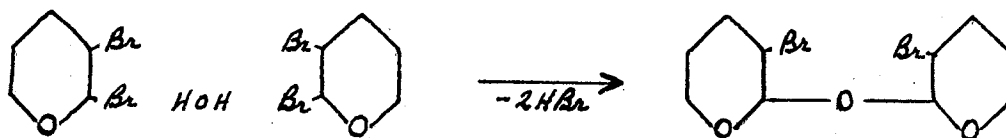
Paul (35, 38) reports the preparation of a number of bromine derivatives of dihydropyran. He found that dihydropyran reacted energetically with bromine in the cold, adding a molecule of bromine to the double bond:



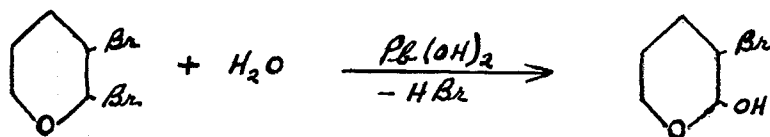
This dibromide is not very stable. When heated, it loses a molecule of hydrogen bromide, forming the unsaturated monobromide, 3-bromodihydropyran:



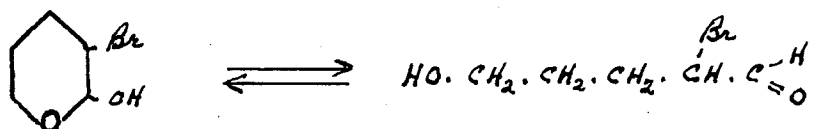
It also reacts readily with water, forming different products according to the conditions. Left in contact with water for some time at room temperature it forms a symmetric ether:



In the presence of an alkaline reagent -- Paul used lead hydroxide -- the hydrolysis gives the bromohydrin, 2-hydroxy-3-bromotetrahydropyran:

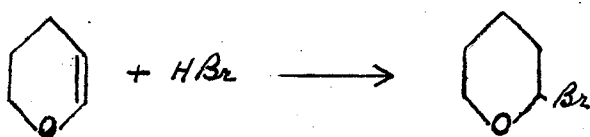


The bromohydrin was found to have aldehyde properties, indicating that it exists to some extent in the aldehyde form,  $\alpha$ -bromo- $\delta$ -hydroxyvaleraldehyde:

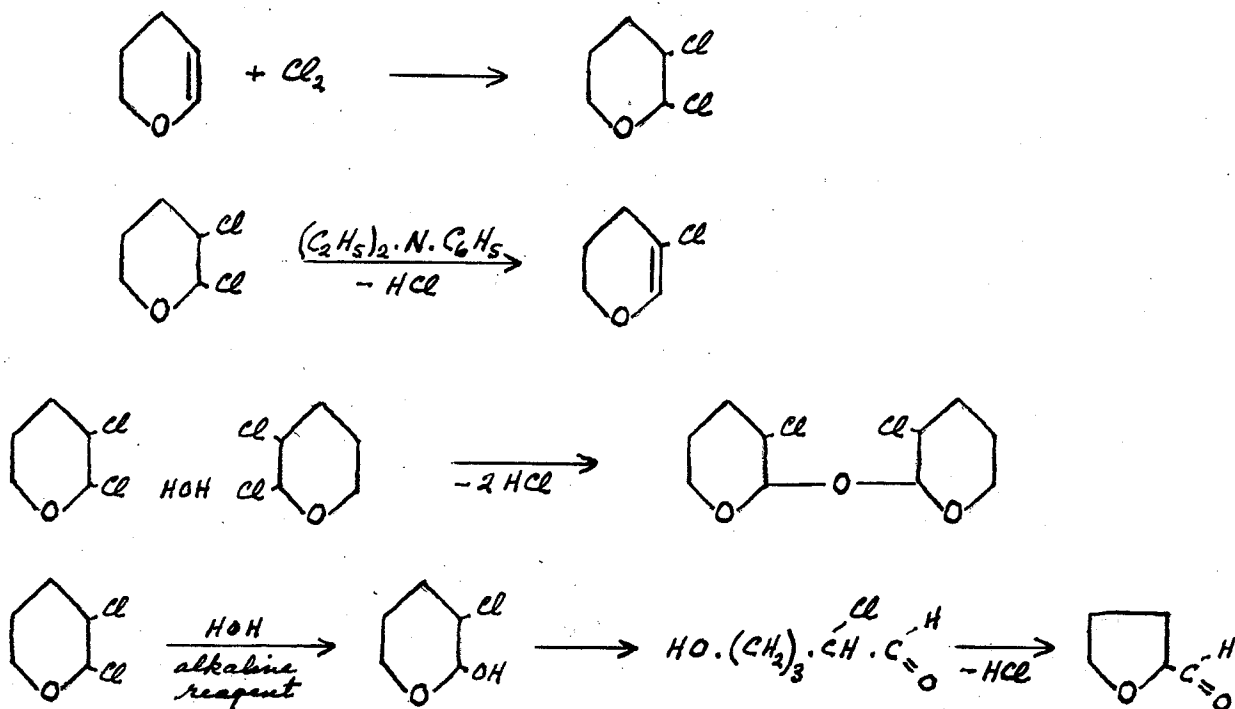


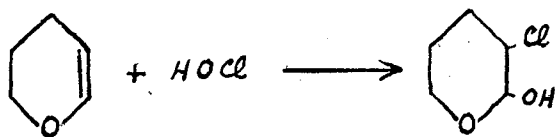
Titration with sodium hydroxide, of which it neutralized a nearly equivalent quantity, showed that it readily lost a molecule of hydrogen bromide.

Paul found also that dihydropyran rapidly adds dry hydrogen bromide in the cold, forming 2-bromotetrahydropyran:



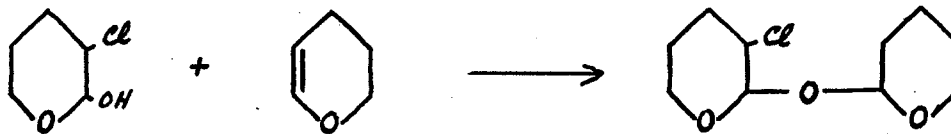
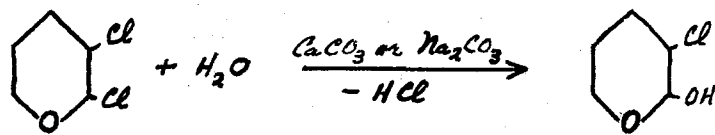
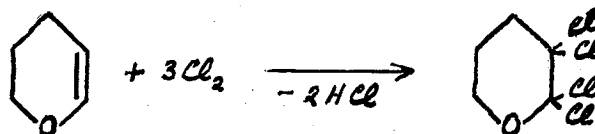
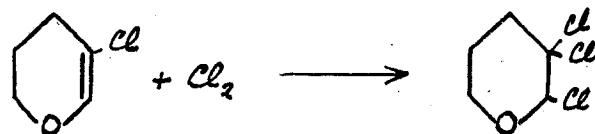
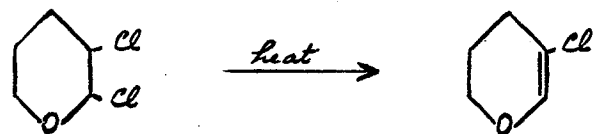
The corresponding chlorine derivatives, as well as others, were first reported by the chemists of I. G. Farben (27, 28, 29). They secured a patent in France and in Germany in 1943 (58) for some of their methods of preparation. The publication of these results prompted Paul (41) to report that he had carried out, earlier than the Germans, the following reactions:





He found that chlorine, like bromine, added readily to the double bond of dihydropyran, forming 2,3-dichlorotetrahydropyran. When distilled with diethylaniline at normal pressure, the dichloride loses a molecule of hydrogen chloride forming the more stable 3-chlorodihydropyran. Left in contact with water at room temperature, the dichloride, like the dibromide, forms a symmetric bicyclic ether. Paul claims, however, and here other workers in the field disagree with him, that when the hydrolysis is carried out in the presence of an alkaline reagent, the chlorohydrin can not be isolated, as can the bromohydrin under similar conditions. He found that in the presence of an alkaline reagent the dichloride dissolved rapidly in water and that the resulting solution had all the characteristics of aldehydes. On treating it with hydroxylamine he extracted, in good yield, the oxime of tetrahydrofurfural, indicating that the reaction had gone as pictured by the equation. He did obtain the chlorohydrin, but with a poor yield, by direct addition of hypochlorous acid to dihydropyran, using acetic monochlorurea solution as the source of hypochlorous acid.

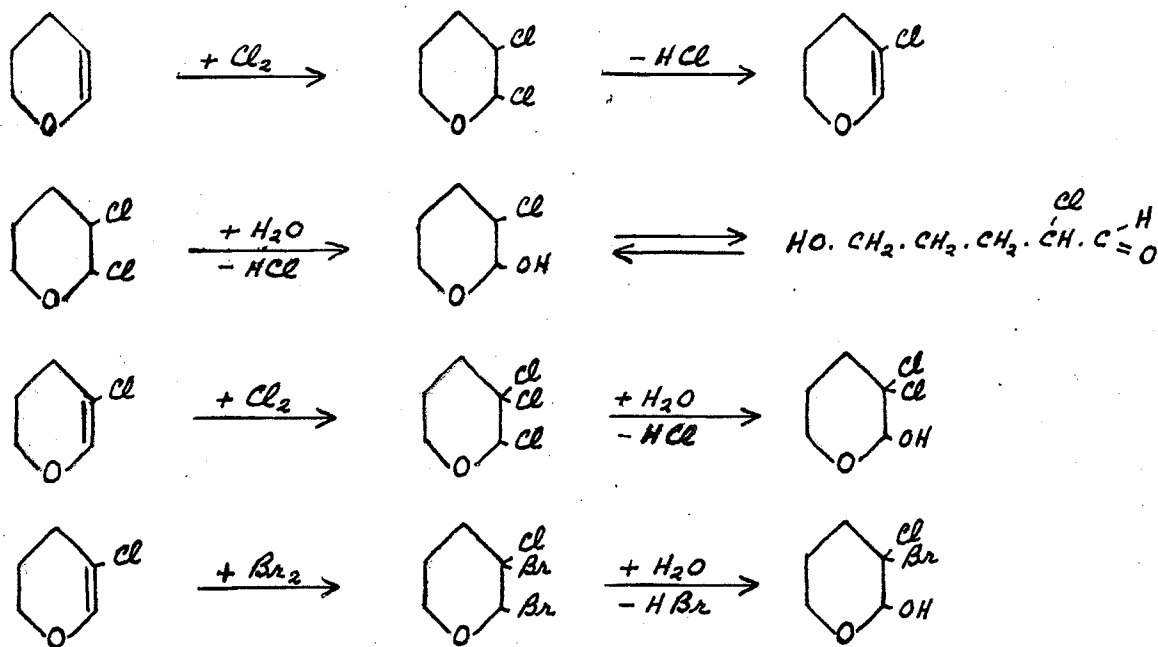
In the meantime in Great Britain the chemists of Imperial Chemical Industries were working along the same lines. In 1945 they patented (13, 15, 16) their methods for the following reactions:



It should be noted that they prepared 2,3,3-trichlorotetrahydro-pyran by adding a molecule of chlorine to the double bond of 3-chlorodihydro-pyran. They also extended the chlorination beyond the addition reaction to produce 2,2,3,3-tetrachloro-

tetrahydropyran. Disagreeing with Paul (41), they claim that the chlorohydrin, 2-hydroxy-3-chlorotetrahydropyran, can be prepared by hydrolysis of the dichloride in the presence of alkaline reagents. They also obtained the chlorohydrin by the addition of hypochlorous acid to dihydropyran. They found also that the symmetric ditetrahydropyryl ether, made by Paul by the hydrolysis of the dichloride, could be made by condensing the chlorohydrin with 3-chlorodihydropyran and a similar ether by condensing the chlorohydrin with dihydropyran itself.

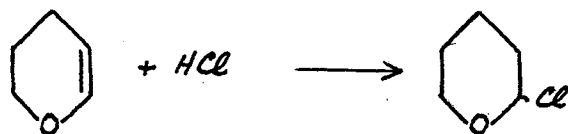
The I. G. Farben chemists (27) had prepared some of the same compounds, as well as others. They mention the following reactions:



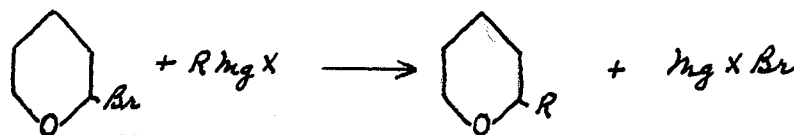
It should be noted that the German chemists, like the British chemists (15), claim the preparation of the chlorohydrin by the hydrolysis of the dichloride, disagreeing with Paul (41). Moreover, they claim that the chlorohydrin, like the bromohydrin, exists in equilibrium with an aldehyde form. In

addition to 2,3,3-trichlorotetrahydropyran, which the British chemists also prepared, the Germans made 2,3-dibromo-3-chlorotetrahydropyran by adding a molecule of bromine to 3-chlorodihydropyran. They also hydrolyzed both of these compounds, obtaining 2-hydroxy-3,3-dichlorotetrahydropyran and 2-hydroxy-3-chloro-3-bromotetrahydropyran. Both of these hydroxy derivatives were found to have no aldehyde properties, differing in this respect from 2-hydroxy-3-chlorotetrahydropyran. Apparently two halogen atoms attached to the carbon in the 3-position tend to stabilize the ring.

In another report (29) the German chemists claim the preparation of 2-chlorotetrahydropyran by the addition of a molecule of hydrogen chloride to dihydropyran, a reaction which Paul (35) had accomplished with hydrogen bromide:

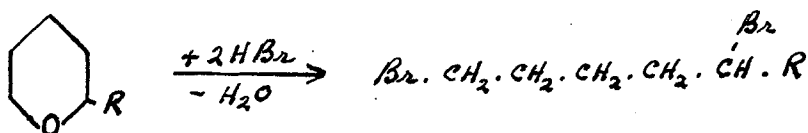


Many of the bromine and chlorine compounds mentioned have been found useful in the synthesis of other compounds. Paul (36) used 2-bromotetrahydropyran to prepare  $\alpha$ -alkyl and  $\alpha$ -aryl tetrahydropyrans by the Grignard reaction:

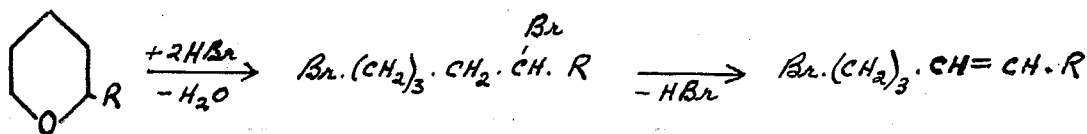


He made in this way  $\alpha$ -ethyl,  $\alpha$ -propyl, and  $\alpha$ -phenyltetrahydropyran. Then, by the action of hydrogen bromide and heat, he opened the tetrahydropyran ring and obtained 1,5-dibromides, where R was alkyl:

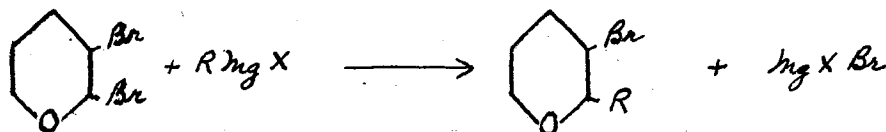




and olefinic monobromides where R was aryl, the dibromides being unstable in this case:



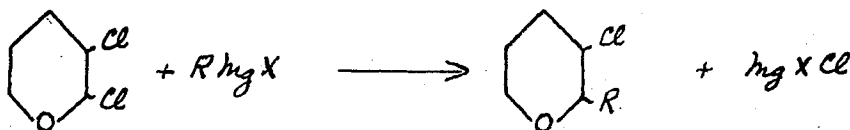
He also used the dibromide in a Grignard reaction and obtained, but in smaller yields, 2-R-3-bromotetrahydropyrans:



He made in this way 2-ethyl- and 2-phenyl-3-bromotetrahydropyran.

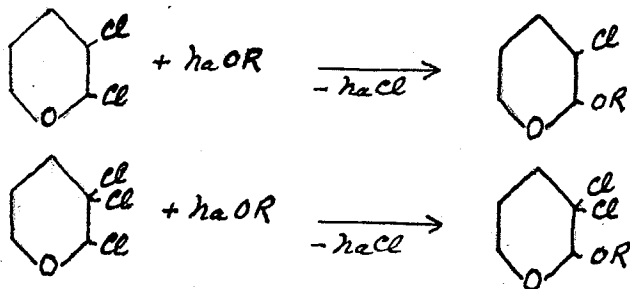
Later (41) he used the dichloride similarly to obtain

2-R-3-chlorotetrahydropyrans:

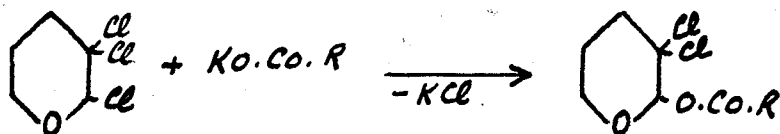
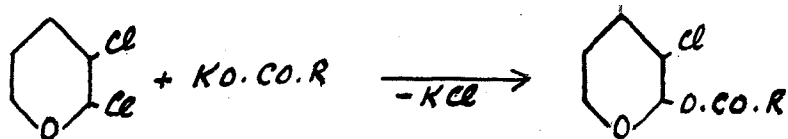


Thus he obtained 2-n-butyl- and 2-phenyl-3-chlorotetrahydropyran.

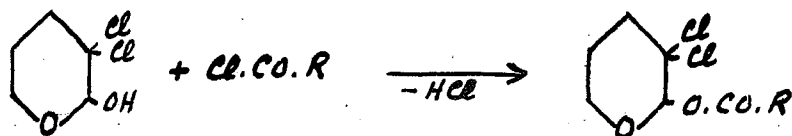
The German chemists carried out a variety of reactions with the chlorine derivatives of dihydropyran. They claim (27) that both the dichloride and trichloride react readily with the sodium derivatives of hydroxy-compounds to form the corresponding ethers:



Also, both of these chlorides are readily converted to esters, presumably by reaction with potassium or silver salts of carboxylic acids:

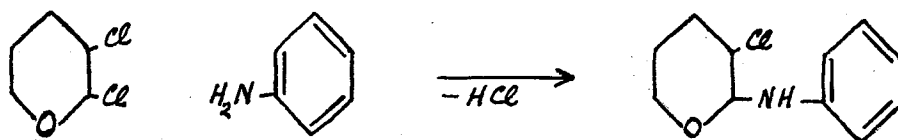


The last ester may be produced also by acylation of the corresponding 2-hydroxy-derivative mentioned earlier:



In all of these reactions R may be either alkyl or aryl. It should be noted that in all cases the substitution takes place on the  $\alpha$ -carbon atom.

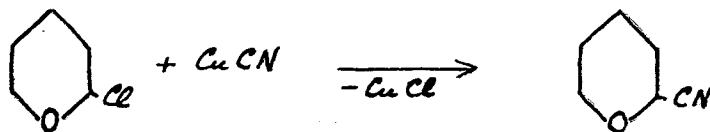
In another report (28) it is pointed out that the dichloride will not condense with ammonia to form an amino-chlorotetrahydropyran but that the reaction takes place readily with aniline:



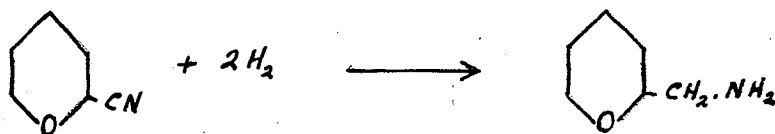
Tertiary bases like pyridine and dimethylaniline will not react in this way.

The Germans also used the chlorides to prepare nitriles (29). They had found earlier (27) that hydrocyanic acid would not add to dihydropyran to form the expected 2-cyanotetrahydropyran.

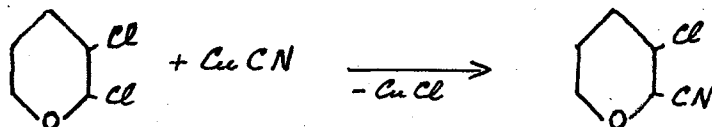
An attempt using 2-chlorotetrahydropyran and cuprous cyanide, however, produced this compound:



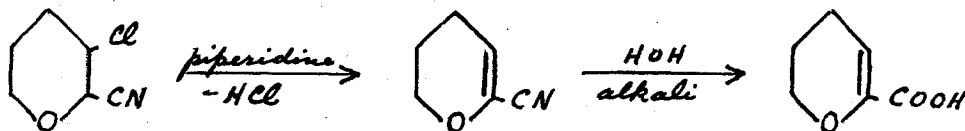
Hydrogenation of this cyanide gave a small yield of aminomethyltetrahydropyran:



The 2,3-dichlorotetrahydropyran also reacted readily with cuprous cyanide to form 2-cyano-3-chlorotetrahydropyran:



Heating this cyanide with piperidine produced 2-cyanodihydropyran, which, by alkaline hydrolysis, formed dihydropyran-2-carboxylic acid:



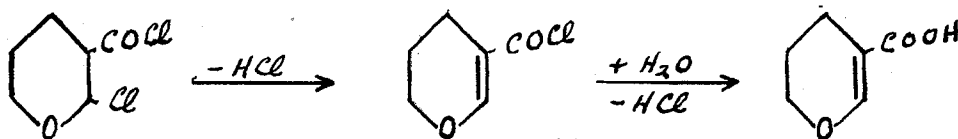
#### Phosgene Addition Product

Hawkins and Bennett (14) report that phosgene, when dissolved in dihydropyran and left standing at room temperature, adds to the double bond as follows:



The product readily loses hydrogen chloride to form

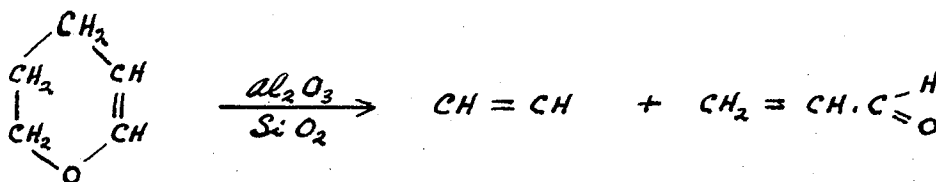
dihydropyran-3-carbonyl chloride, which hydrolyzes to the corresponding acid:



Esters and amides of this acid are easy to prepare from the chloride. Hawkins and Bennett prepared a number of these.

### Products of Pyrolysis

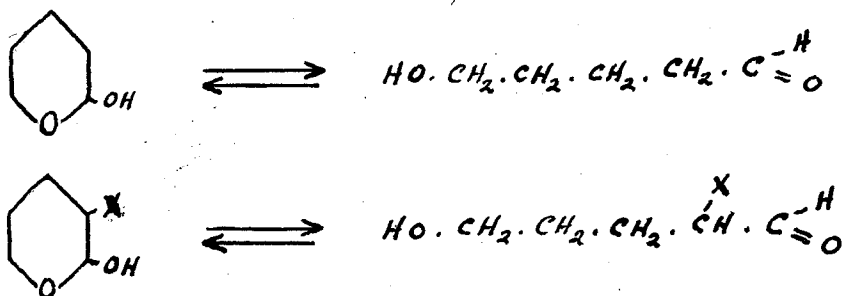
Wilson (55) heated dihydropyran with a mixture of equal parts of alumina and silica and obtained a mixture of ethylene and acrolein in yields as high as 62%:



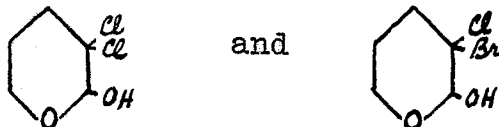
Other catalysts which can be used are basic aluminum phosphate, titanium dioxide, and thorium dioxide.

### Opening of the Hydropyran Ring

As has been mentioned earlier, the tetrahydropyran ring tends to open when there is an -OH group attached to the  $\alpha$ -carbon atom. Both the 2-hydroxytetrahydropyran and the 2-hydroxy-3-halotetrahydropyrans exist in equilibrium with open-chain aldehyde forms:

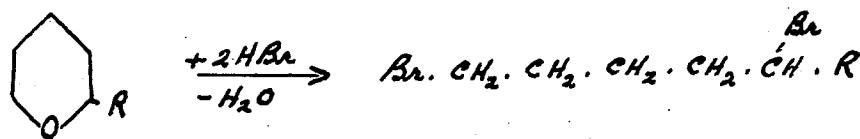
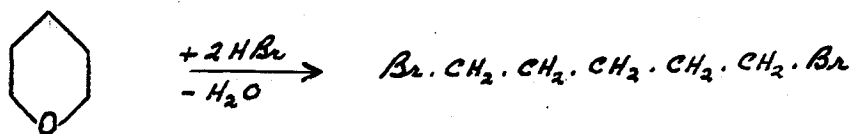


It should be noted, however, that the halohydrins are somewhat more stable in the cyclic form than the 2-hydroxytetrahydropyran, and that when there are two halogen substituents on the  $\beta$ -carbon as in

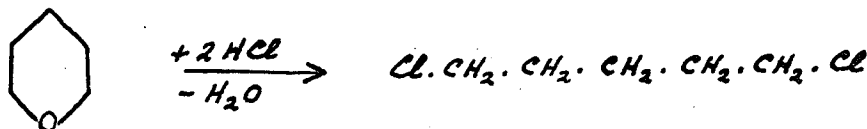


the substances do not normally exist in aldehyde forms. For all the other tetrahydropyran derivatives that have been mentioned the ring is reasonably stable.

At higher temperatures certain acidic reagents will open the ring at the oxygen bridge. Paul (33, 36), as has been mentioned previously, accomplished the reaction with dry hydrogen bromide, at a maximum temperature of  $100^{\circ}$ , and obtained in this way 1,5-dibromides from tetrahydropyran and  $\alpha$ -R-tetrahydropyrans:



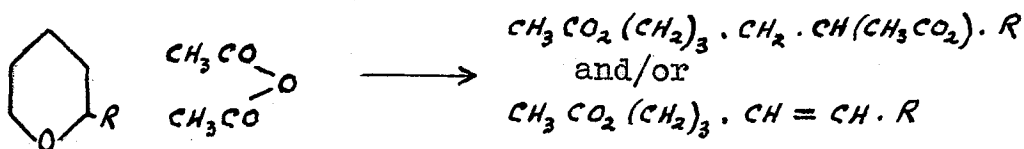
The Farben chemists (27) found that dry hydrogen chloride accomplished the same purpose:



They found that the ring could be opened also by the use of acid chlorides, in the presence of zinc chloride:



Paul (39, 40) made a thorough study of the opening of hydroxyran and hydrofuran rings, using as reagent acetic anhydride, in the presence of anhydrous zinc chloride. He found that a temperature of 190° or higher was needed to open the ring and that two types of products tended to form, a diacetate and an ethylenic acetate:



The extent of ring opening and the relative proportions of the two types of products depended on the nature of the  $\alpha$ -substituent R. Paul found that the more positive and polar R was, the more difficult the ring was to open and the smaller was the yield of the ethylenic acetate. When R was H, i.e. for tetrahydroxyran itself, the ring opened to a much smaller extent than when R was an alkyl group, and the diacetate was the only product. When R was alkyl the ring opened more readily and the ethylenic product tended to predominate, although the diacetate was still formed. The longer alkyl side chains tended to give more of the ethylenic product. When R was aryl resinification resulted.

Mechanisms of the Reactions of the Hydropyrans  
and of their Derivatives

Paul (35) points out that dihydropyran is essentially a vinyl ether and shows the great reactional aptitude of this type of compound.

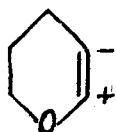
The exceptional reactivity of the double bond of the vinyl ether group  $-\text{CH}=\text{CH}-\text{O}-\text{R}$  first attracted the attention of Meyer and Lenhardt (23). After studying a large number of ethylenic addition reactions, they concluded that the double bond of this group was specially "activated" as compared with ordinary ethylenic bonds. Modern theory -- see, for example, Kharasch and Mayo (20) -- gives the following explanation for this phenomenon: (i) when an electron-attracting group is attached to a carbon atom, the shared pair of electrons is closer to this group than it is to the carbon atom; (ii) when one of the carbon atoms in a double bond has an electron-attracting group attached to it, one of the two pairs of shared electrons is closer to that carbon atom which has the least electron-attracting groups attached to it. Hence, in the vinyl ether group, where an oxygen atom is attached to one of the carbon atoms of the ethylenic bond, (i) the pair of electrons shared by the oxygen and the  $\alpha$ -carbon are closer to the oxygen atom, since it has a nuclear charge of +6 compared with the carbon's +4, and (ii) the electrons of the double bond are displaced in the direction of the  $\beta$ -carbon, as follows:

$$\begin{array}{c} \text{:}\ddot{\text{C}}\text{:} \\ \text{H} \end{array} \text{:}\ddot{\text{C}}\text{:} \begin{array}{c} \text{:}\ddot{\text{O}}\text{:} \\ \text{R} \end{array}$$

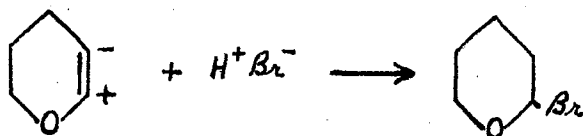
In this arrangement one would expect the  $\alpha$ -carbon to be somewhat positive and the  $\beta$ -carbon somewhat negative:

$\bar{\text{C}}\text{H}=\overset{+}{\text{C}}\text{H}-\text{O}-\text{R}$ . This is what may be called the "normal ionization" of the double bond in vinyl ethers. This ionization explains the greater than normal activity of this type of double bond as compared with the ordinary ethylenic bond.

According to this view dihydropyran normally has its  $\alpha$ -carbon slightly positively charged and its  $\beta$ -carbon slightly negatively charged:

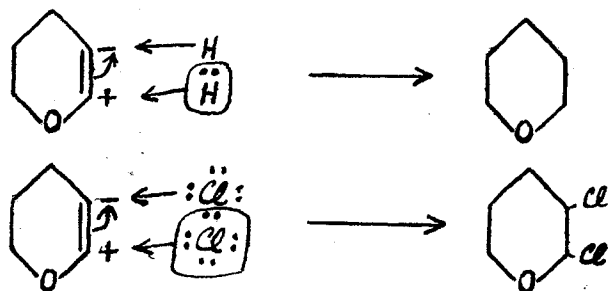


One would expect, therefore, that substances which ionize readily, such as hydrogen halides, would add very readily to the double bond of dihydropyran, the negative ion going to the  $\alpha$ -carbon and the positive ion to the  $\beta$ -carbon. This is, in fact, what happens. Paul (35) found that hydrogen bromide adds almost instantaneously:



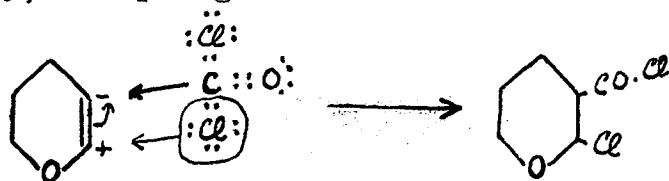
The I. G. Farben chemists (29) found that hydrogen chloride adds similarly, although one does not normally expect it to add so readily to an ethylenic bond.

Accepting this view of the addition reactions, one must assume that hydrogen, chlorine, and bromine add as follows:

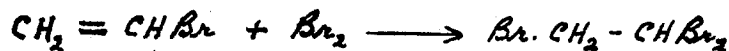




Similarly, for phosgene:

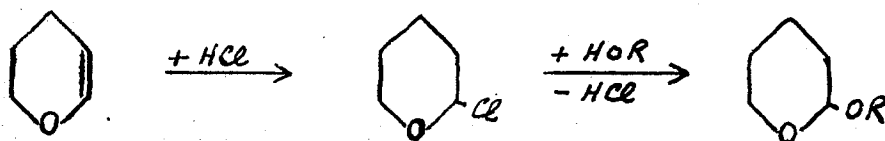


It is interesting to note, and perhaps of some importance, that there is evidence that the negative group adds first to the  $\alpha$ -carbon and then the positive group to the  $\beta$ -carbon. Nozaki and Ogg (26) found that lithium bromide and hydrogen bromide catalyze the addition of bromine to vinyl bromide:



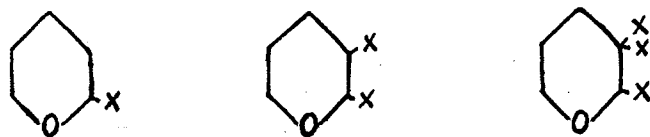
This means that the addition of the negative ion is the rate-determining factor. Since vinyl bromide should show the same ionization of the double bond as dihydropyran:  $\bar{\text{C}}\text{H} = \overset{+}{\text{C}}\text{H}-\text{Br}$ , it is to be expected that the negative ion adds first also to dihydropyran.

Water and alcohols do not normally add to ethylenic bonds. Paul (37) found, however, that in the presence of acid they do add to dihydropyran. Since they do not ionize appreciably, it is probable, as Paul points out, that there is an intermediate addition of acid and then displacement of the negative ion of the acid by  $-\text{OH}$  or  $-\text{OR}$ :

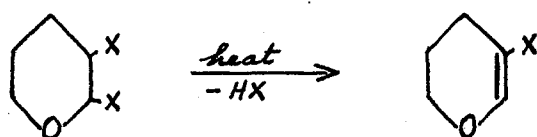


The ease with which a halogen atom in the  $\alpha$ -position is replaced by  $-\text{OH}$ ,  $-\text{OR}$ , as well as by  $-\text{O} \cdot \text{CO} \cdot \text{R}$ , is one of the striking properties of the halogen derivatives of dihydropyran, to which attention is drawn by the Germans (27) and by Paul (38).

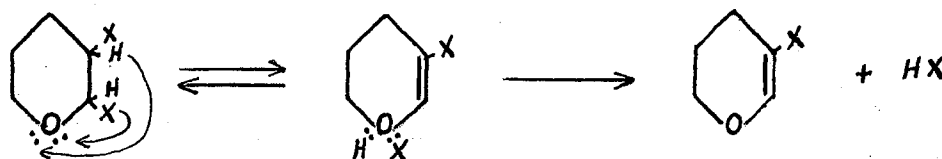
It is true of the three types:



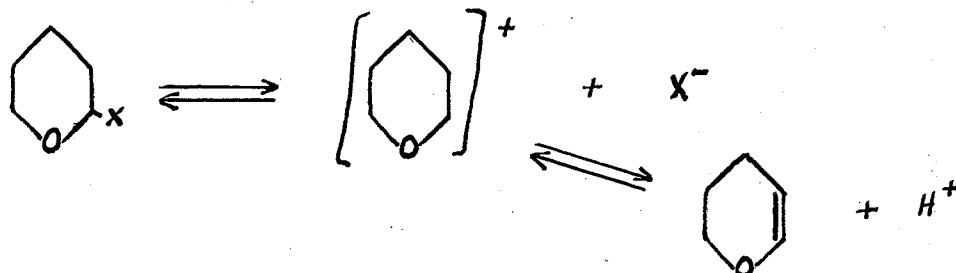
Paul says this property is common to all  $\alpha$ -halogen ethers but gives no other examples and does not explain further. Related to this property is the relative instability of the dihalides, which lose hydrogen halide on distillation to form 3-halodihydropyrans:



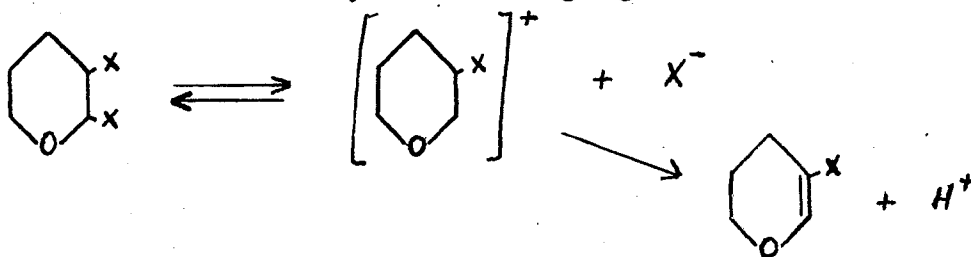
Paul (38) points out that this property is characteristic of  $\alpha$ - $\beta$ -dihaloethers and gives several other examples. He attempts to explain the phenomenon by assuming an equilibrium between normal and oxonium salt forms:



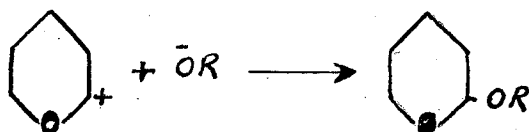
This would account for the ready loss of a molecule of hydrogen halide by the dihalide, which is all that Paul claims for it, but it does not explain the easy displacement of  $\alpha$ -halogen by  $-OH$ ,  $-OR$ , and  $-O.CO.R$ , which would seem to be a related property. Both properties could be explained by assuming an ionization equilibrium of the following type:

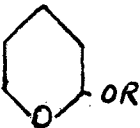
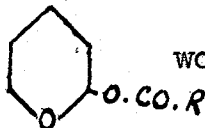
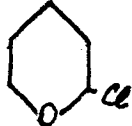


The dihalide would then decompose as follows, the hydrogen halide driven off by heat bringing the reaction to completion:

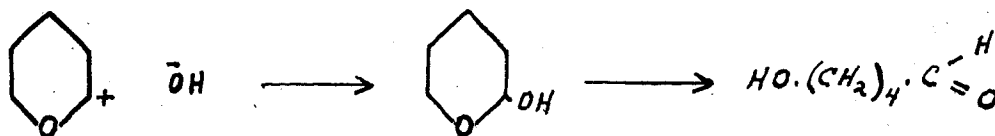


Because of the nature of the ring, the positive charge on the tetrahydropyryl ion would tend to be concentrated on the  $\alpha$ -carbon and combination with the negative groups  $-OH$ ,  $-OR$ , and  $-O.CO.R$  is understandable:

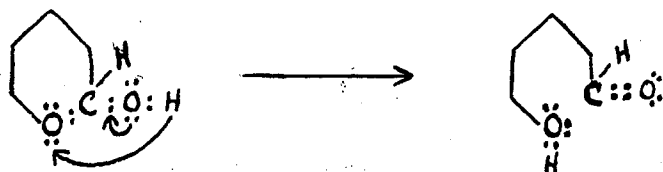


Compounds like  and  would tend to be more stable than , since the negative groups  $-OR$

and  $-O.CO.R$  have much less tendency to lead an independent existence than has the chloride ion. The situation is otherwise with the  $\alpha$ -hydroxyderivative, since the hydroxyl ion resembles the chloride ion in its stability. Here, however, another factor enters the picture. With  $-OH$  in the  $\alpha$ -position the ring tends to open, as has been mentioned, to form an aldehyde, thus preventing the re-ionization of the hydroxy-derivative:



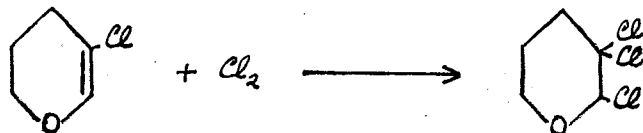
The tendency of  $\alpha$ -hydroxytetrahydropyrans to exist in open chain aldehyde forms is mentioned by Paul (38) and by the Farben chemists (27). Both the simple  $\alpha$ -hydroxy compound and the  $\alpha$ -hydroxy- $\beta$ -halotetrahydropyran show this phenomenon. Apparently there is here a type of tautomerism in which a proton wanders from an oxygen atom in a 1-position to another oxygen atom in a 3-position:  $\begin{array}{c} \ddot{\text{O}} \\ | \\ \text{H} \end{array} - \overset{|}{\text{C}} - \ddot{\text{O}} \quad \text{and as a result}$  electrons are displaced so as to open the ring. The change taking place may be pictured thus:



Paul notes that a 2-hydroxy-3-halotetrahydropyran is less aldehydic in nature than 2-hydroxytetrahydropyran itself and the German chemists claim that a 2-hydroxy-3,3-dihalotetrahydropyran does not exist in the open chain form. Electronegative groups on the  $\beta$ -carbon, as might be expected, inhibit the formation of the carbonyl bond on the  $\alpha$ -carbon.

One other characteristic of the halohydropyrans, to which some study has been given, should be noted. The 3-halodihydropyrans, formed when the dihalotetrahydropyrans are heated, are unusually unreactive compounds as compared with dihydropyran itself. Paul (38) found that 3-bromodihydropyran may remain in contact with hydrogen bromide or with water for weeks and show no evidence of reaction, although dihydropyran itself reacts readily with both reagents in the

cold. On the other hand, it has been found (27) that they do add chlorine or bromine:



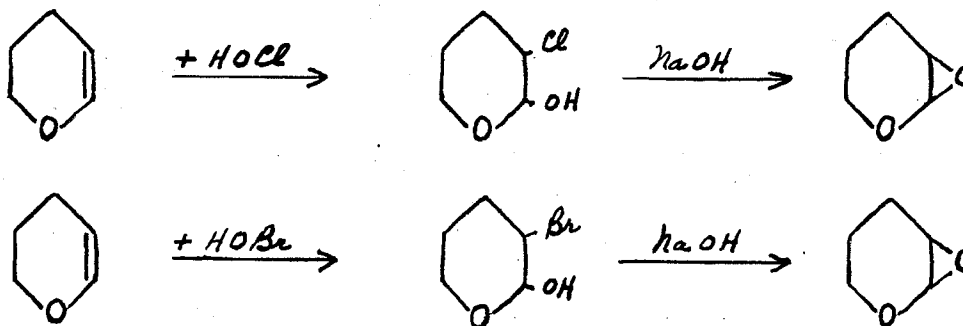
These phenomena can be accounted for, as Paul points out, by the abnormal ionization of the double bond in these compounds:  $\bar{\text{Br}} - \overset{+}{\text{C}} = \overset{+}{\text{C}} - \bar{\text{O}} -$

The bromine atom attached to the  $\beta$ -carbon causes it to have a positive character, just as the oxygen atom attached to the  $\alpha$ -carbon makes it positive. Thus there is no tendency to add an electropositive group to the double bond, although the electronegative halogens can be added.

THE METHODS AND RESULTS OF THIS INVESTIGATION

Purpose of this Work

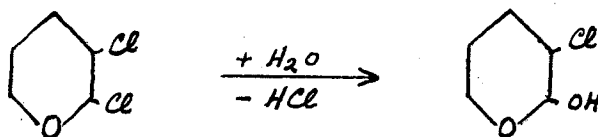
As was explained in the Introduction the original purpose of this investigation was (i) to repeat with dihydropyran the reactions carried out by McRae, Charlesworth, and Alexander (21) with cyclohexene:



and (ii) to use the resulting oxide in condensations with sodio-activated methylene groupings, as was done by these workers, and earlier by Coffey (5), and by Kendall and co-workers (18, 19).

Earlier Preparation of the Chlorohydrin

The chlorohydrin of dihydropyran, 2-hydroxy-3-chloro-tetrahydropyran, has been prepared before. Hawkins and Bennett (15) obtained it as a crystalline solid by hydrolyzing the dichloride:



The more direct method, the addition of hypochlorous acid to dihydropyran, has also been attempted. Paul (41) apparently isolated the chlorohydrin by this method but his product

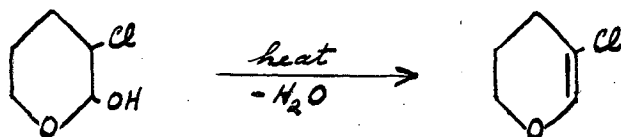
failed to crystallize and the yield was small. Hawkins and Bennett (13) also carried out the addition reaction but apparently made no attempt to purify the crude liquid product obtained. In view of these results, it seemed worthwhile to try again the addition of hypochlorous acid to dihydropyran.

#### Preparation of Hypochlorous Acid

Solutions of hypochlorous acid suitable for reaction with ethylenic compounds have been prepared by a number of methods. Fortey (10) passed chlorine into a mixture of ice and water containing freshly precipitated mercuric oxide in suspension. Wohl and Schweitzer (56) passed chlorine into a suspension of sodium bicarbonate in ice-cooled water until the bicarbonate disappeared. Osterberg and Kendall (31) bubbled carbon dioxide through a suspension of bleaching powder in water and filtered off the calcium carbonate formed. Coleman and Johnstone (6) recommend a variation of Fortey's method. None of these, however, claim a hypochlorous acid content of more than 4% for the solutions so prepared. Detoef (7) found monochlorurea solution, acidified with acetic acid, a better source of hypochlorous acid. McRae, Charlesworth, and Alexander (21) recommend Detoef's method, which consistently gave them solutions 10% to 15% in hypochlorous acid. This was the method it was decided to use in this work. It was found to be a very satisfactory source of hypochlorous acid.

Attempted Preparation of the Chlorohydrin  
by the Addition Reaction

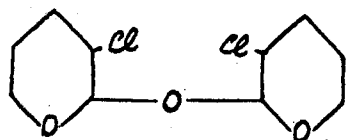
Paul (41) apparently used monochlorurea solution as source of hypochlorous acid in his attempt to prepare the chlorohydrin of dihydropyran by the addition reaction. Unfortunately he gives no experimental details. In this work the reaction was carried out by the procedure used by McRae, Charlesworth, and Alexander (21) with cyclohexene. Since the desired chlorohydrin is a solid, it was hoped that it would crystallize from the ether extract after evaporation of the ether, but it failed to do so after 10 days in the refrigerator. Distillation under reduced pressure failed to give the liquid product obtained by Paul. In fact, decomposition seemed to set in before the temperature he mentions, 123-125°, was reached. The liquid turned a dark brown when heated at this temperature and almost no distillate came over. Even when the temperature was not raised above 100°, there were signs of decomposition. The liquids distilling up to 100° at 20 mm. contained acetic acid and, very probably, 3-chlorodihydropyran. The latter substance, which boils at 141° at 760 mm., is said to be formed (15) when the chlorohydrin is decomposed by heat:



The residue, after the liquids boiling below 100° at 20 mm. had been distilled off, eventually deposited crystals when left in the refrigerator.

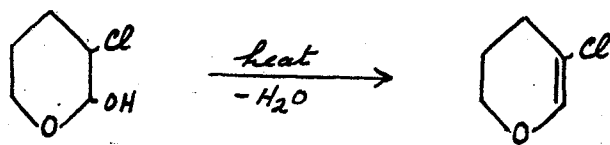


The crystals obtained in this way were not the chlorohydrin. Recrystallized from alcohol, they were found to be white needles melting at 105-108°. Hawkins and Bennett (15) report the melting point of the chlorohydrin to be 64°. A chlorine analysis showed that the product contained 27.78% chlorine, as compared with a calculated 25.97% for the chlorohydrin. The melting point and chlorine analysis indicate that the product is the dichloroditetrahydropyryl ether:



This substance melts at 108°, according to Paul (41), and has a chlorine content of 27.79%.

The formation of this ether from the chlorohydrin, under the conditions used here, is not an improbable reaction. Hawkins and Bennett (15) report that the chlorohydrin, when heated, loses water to form 3-chlorodihydropyran:



Elsewhere (16) they report that 3-chlorodihydropyran readily reacts with the chlorohydrin to form the dichloroditetrahydropyryl ether:



There seems, therefore, no reason to doubt that the chlorohydrin is actually formed first in the reaction carried

out here. The high temperature of the distillation, however, in the attempt to isolate it, causes it to go over into the ditetrahydropyryl ether. There are, obviously, two possible methods that offer hope of isolating the chlorohydrin from this reaction: (i) to distil at a lower temperature by further reducing the pressure, or (ii) to bring about crystallization from the ether extract. It is the writer's intention to make further efforts in this direction.

#### Preparation of Hypobromous Acid

When the addition of hypochlorous acid to dihydropyran provided the difficulties noted, it was decided to attempt instead the addition of hypobromous acid. This reaction has apparently not as yet been attempted. To carry it out, it was necessary to find a convenient source of hypobromous acid.

McRae, Charlesworth, and Alexander (21), in their work with cyclohexene, obtained hypobromous acid from monobrom-urea solution. After the difficulties encountered in attempting to isolate the chlorohydrin from the monochlorurea reaction, however, it was thought best to try another method. A literature search revealed that at least two other methods have been used successfully. Mokiewsky (24) prepared hypobromous acid, for reaction with ethylenic compounds, by adding bromine to an aqueous suspension of mercuric oxide and treating the resulting solution with a slight excess of potassium sulfide to precipitate the mercury. Read and

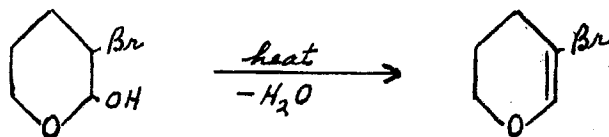
collaborators discovered a more expeditious method. They found that many olefines react with dilute solutions of bromine in water to give good yields of the bromohydrins. The method was first used by Pope and Read (43) to prepare the bromohydrin of indene. Read and Williams (48) used it to prepare ethylene bromohydrin. Read and Reid (47) list an impressive number of ethylenic compounds for which the method was successful. These workers found also that, in spite of the instability of hypobromous acid, the yields were often better at temperatures as high as 90° than at 0° or room temperature. This method seemed worth a trial with dihydropyran.

Attempted Preparation of the Bromohydrin  
by the Addition Reaction

Since dihydropyran is a volatile liquid, it was decided to carry out the addition reaction at room temperature, as Read and Reid (47) did for amylene. The dihydropyran was emulsified with water, using a mechanical stirrer, and bromine was added gradually in the form of 7% bromine in 10% potassium bromide solution. Extraction with ether and the usual treatment gave a yellow liquid which failed to deposit crystals on standing some days in the refrigerator. Distillation at 20 mm. gave a colorless distillate which separated into two layers, one of which proved to be water. Above 120°, although the boiling in the flask was still vigorous, the distillation was very slow and the liquid gradually turned black. When the

distillation was stopped, at about 125°, the residue solidified. The solid is a tar-like material, from which it has not been found possible to isolate any crystals. The distillate, dried to remove the water, was redistilled at 20 mm. and collected in two fractions: a colorless fraction under 100° and a yellowish fraction 100-125°. Both of these again had a water layer, both eventually turned a dark brown, and neither deposited crystals.

The phenomena observed in the distillation are most easily interpreted by assuming that the bromohydrin is formed in the reaction and that it decomposes when heated, like the chlorohydrin:



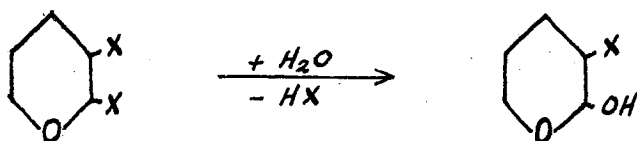
This would account for the water in the distillate. The 3-bromodihydropyran is said to boil at 63° at 22 mm. (35) and is probably present in the distillate. The distillate turning brown and the tar-like residue are probably due to polymerization reactions, which have been noted elsewhere as a property of 3-bromodihydropyran. The Farben chemists (27) report that they heated 2,3-dibromotetrahydropyran in an attempt to obtain 3-bromodihydropyran, a reaction which is reported by Paul (35), but obtained only dark brown tar-like material.

The important fact that emerges from these experiments on the addition of hypochlorous and hypobromous acids to

dihydropyran is that both the chlorohydrin and the bromohydrin are unstable to heat. They can not be distilled from a solution, except perhaps at very low pressures. Subsequent experience with these substances in the course of this work gives further confirmation of this. It is, however, probably possible so to modify the methods used here for the addition reactions as to make the isolation of the addition products a possibility.

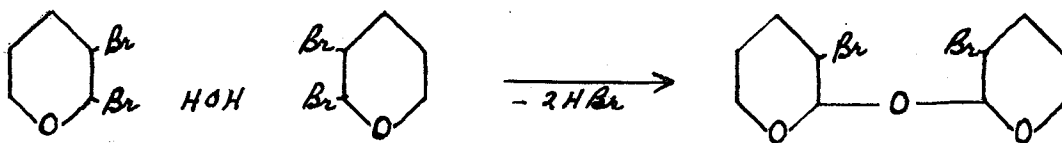
#### Hydrolysis of the Dihalides

Both the chlorohydrin and the bromohydrin of dihydropyran have been prepared (15, 38) by the hydrolysis of the dihalides:

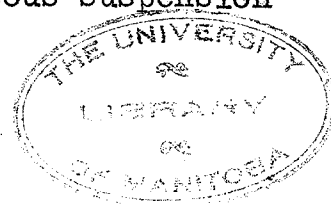


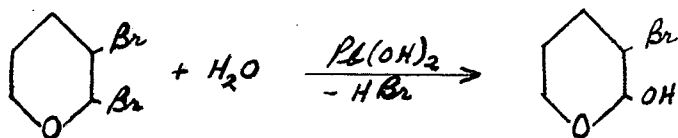
The halohydrins, however, are not invariably the products of this hydrolysis reaction. The nature of the product depends upon the conditions under which the reaction is carried out.

Paul (38) studied the hydrolysis of the dibromide. He found that when it was simply left in contact with water at room temperature the product formed was the dibromoditetrahydropyryl ether:

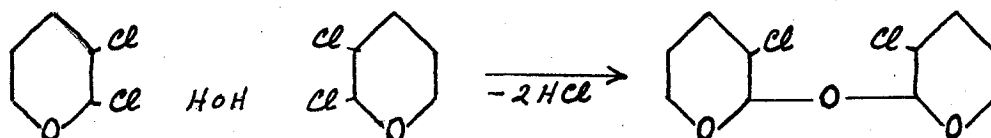


On the other hand, when the dibromide was added gradually, apparently also at room temperature, to an aqueous suspension of lead hydroxide, the bromohydrin was formed:

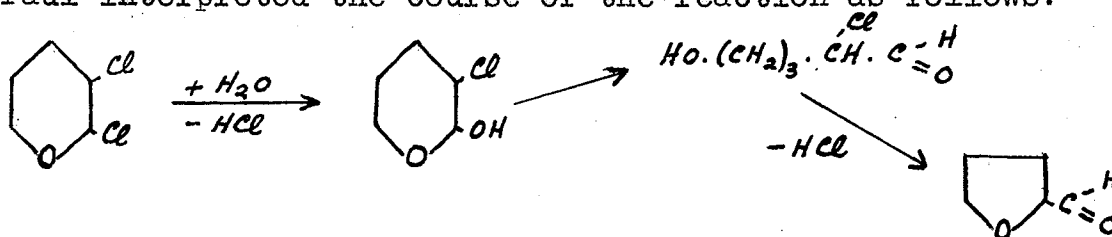




Later, Paul (41) attempted to repeat the same reactions with the dichloride. Leaving it in contact with water at room temperature produced, as with the dibromide, a ditetrahydropyryl ether:



Hydrolysis with heat or in the presence of an alkaline reagent, however, gave a different result than with the dibromide. He found that the reaction was rapid and that an aldehydic solution was formed. Treatment of this solution with hydroxylamine gave the oxime of tetrahydrofurfural. Paul interpreted the course of the reaction as follows:



Hawkins and Bennett (15), on the other hand, did isolate the chlorohydrin from the hydrolysis of the dichloride in the presence of alkaline reagents. They agitated the dichloride with sodium carbonate solution or with an aqueous suspension of calcium carbonate and apparently had no difficulty in extracting and crystallizing the chlorohydrin.

### Preparation of the Halohydrins

After the failure to isolate the halohydrins from the addition reactions, it was decided to try to prepare them by the hydrolysis of the dihalides. A modification of one of the procedures used by Hawkins and Bennett (15) was employed and it gave both the chlorohydrin and the bromohydrin without difficulty.

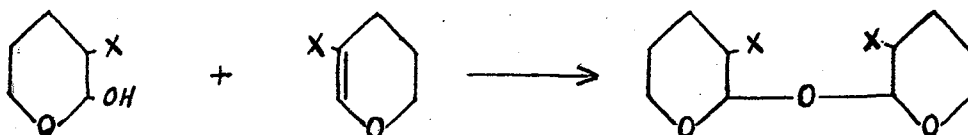
The dihalides were prepared by adding chlorine or bromine slowly to dihydropyran, kept cooled to 0°, without a solvent. The crude dihalide was then added gradually to a solution of sodium carbonate in water, also cooled to 0°, and stirred mechanically. The halohydrins crystallized out of the reaction mixture when it was left standing in the refrigerator. A further quantity was obtained by extracting the liquid with ether.

The halohydrins obtained in this way contain some impurities, probably the dihaloditetrahydropyryl ethers, but after two or three recrystallizations from anhydrous ether the products were found to have the reported melting points. Chlorine and bromine analyses confirmed that they were the expected substances.

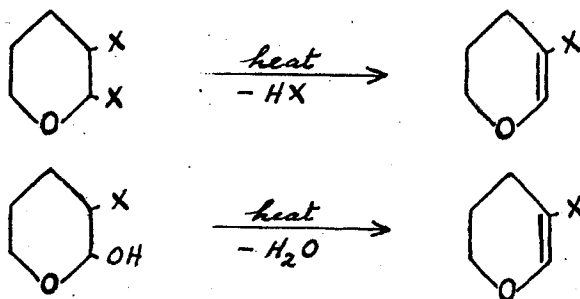
### The Dihaloditetrahydropyryl Ethers

These ethers have been mentioned a number of times. Paul (38, 41) obtained them by leaving the dihalides in contact with water at room temperature for some time. The work of Hawkins and Bennett (15, 16) indicates that

these substances are probably formed by the following reaction:



Both the dihalides and the halohydrins tend to decompose to form the 3-halodihydropyrans:



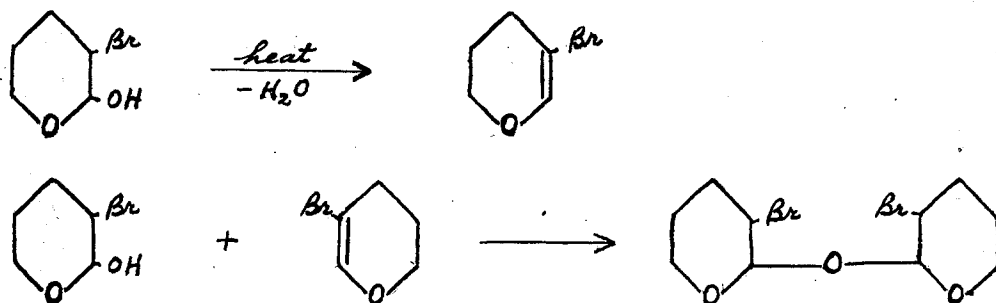
Therefore, unless these two decomposition reactions are prevented by keeping the temperature at or near 0° during the preparation of the dihalide and the hydrolysis reaction, the halohydrin formed in the hydrolysis will tend to go over into the ditetrahydropyryl ether more or less. The presence of acid has been found to promote the formation of the ether. If the halohydrin is the desired product, the acid formed in the hydrolysis must, therefore, be neutralized by an alkaline reagent.

In this work the dichloroditetrahydropyryl ether was obtained (see page 37) in the attempt to isolate the chlorohydrin from the addition of hypochlorous acid to dihydropyran. It will be seen that the conditions there were favorable for the formation of the ether.

The dibromoditetrahydropyryl ether was obtained from a



sample of the bromohydrin in a manner which illustrates how readily the bromohydrin goes over into the ether. Crystals of the bromohydrin were left for some days on a watch glass, at times exposed to sunlight, to dry. They dried at first, then became moister again for no apparent reason. The pasty mass that resulted was filtered with suction, part of it recrystallized from ethyl ether and the melting point determined. The melting point had jumped from 75°, that of the original sample, to 105°. This melting point, and a bromine analysis later, indicated that the bromohydrin had changed to the ether. The reaction probably took place in the following steps:



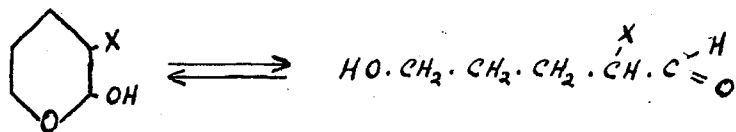
### Properties of the Halohydrins

The chlorohydrin and bromohydrin of dihydropyran are both low-melting crystalline solids, the former melting at 64° and the latter at 79°. They are soluble in water, alcohol, and ether.

Their tendency to decompose when heated and to change to the ditetrahydropyryl ethers has been discussed.

Both of these substances have aldehyde properties: their water solutions reduce Fehling's solution and

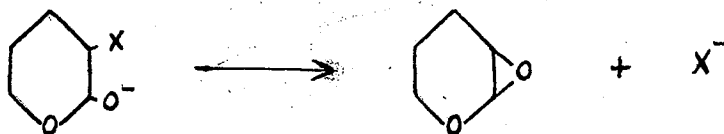
ammoniacal silver nitrate. This is explained by assuming that they exist in equilibrium with aldehyde forms:



Their water solutions can also be titrated with sodium hydroxide and neutralize it nearly quantitatively. This suggests that the halohydrins tend to act as acids:

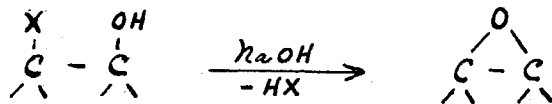


There is no evidence as yet that the negative ion tends to go over into an ethylenic oxide:

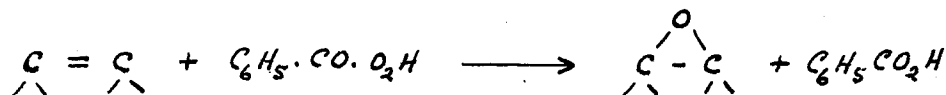


### Methods of Preparing Ethylenic Oxides

Ethylenic oxides have been prepared by two general methods: (i) treating a halohydrin with sodium or potassium hydroxide:



(ii) perbenzoic acid oxidation of an olefine:



Procedures using the first method are described by Brunel (3), who prepared cyclohexene oxide by treating the iodohydrin in ethereal solution with powdered potassium hydroxide, and

more recently by Osterberg (30), who prepared the same oxide by stirring the chlorohydrin with a water solution of sodium hydroxide. The perbenzoic acid oxidation method seems to have been used first by Prileschajew (45). Procedures using it are described also by Godchot and Bedos (11), Nametkin and Brussoff (25), and Hibbert and Burt (17). Essentially the method consists in treating the olefine with an ether or chloroform solution of perbenzoic acid at 0° or room temperature.

#### Attempted Preparation of the Oxide of Dihydropyran

Paul (42) attempted to prepare the oxide of dihydropyran by perbenzoic acid oxidation of dihydropyran but did not succeed in isolating such an oxide.

In this work an attempt was made to prepare the oxide by the method of Osterberg (30), also without success.

Very probably the oxide, if it exists at all, is a somewhat unstable substance. One would expect it to be unstable to heat, as are the dichloride and the chlorohydrin, and therefore, unless it is a solid at ordinary temperature, it would be difficult to isolate. Only distillation at very low pressure offers any hope.

## EXPERIMENTAL DETAILS

### Preparation of Monochlorurea Solution

This solution, to be used as a source of hypochlorous acid, was prepared by the method of Detoef (7), as described by McRae, Charlesworth, and Alexander (21).

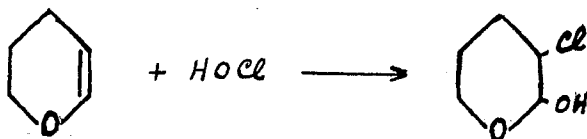
Urea (120 grams, 2 moles), precipitated chalk (80 grams, excess), and water (100 ml.) were placed in a liter flask and cooled in an ice-water mixture. Chlorine gas was passed in until the weight had increased by 71 grams (1 mole). The solution was then diluted to 400 ml. with water and the excess calcium carbonate filtered off.

This solution, when acidified with glacial acetic acid, produces hypochlorous acid. The potential hypochlorous acid content can be estimated by titrating the iodine which it frees from potassium iodide with standard thiosulfate solution, using starch as indicator.

For a typical run, 1 ml. of the solution added to 10 ml. of 2M potassium iodide solution and 25 ml. of water, acidified with acetic acid, and titrated with 0.110 N sodium thiosulfate solution, required 48.5 ml. of the thiosulfate. This indicated a potential hypochlorous acid content of 12.7%.

When left standing, even in the refrigerator, the solution deteriorates. One sample went from 12% down to 10% overnight. It should, therefore, be used as soon as possible after preparation.

Attempted Preparation of 2-hydroxy-3-chlorotetrahydropyran  
by Addition of Hypochlorous Acid to Dihydropyran



This reaction was attempted by the method used for cyclohexene by Detoef (7), as modified by McRae, Charlesworth, and Alexander (21).

Monochlorurea solution (265 ml. containing  $\frac{1}{2}$  mole potential hypochlorous acid), dihydropyran (46 grams, excess), glacial acetic acid (25 ml.), ice (200 grams), and water (200 grams) were placed in a 2-liter flask with a mechanical stirrer and kept cooled in an ice-water mixture. After two hours, titration of a sample showed that all the hypochlorous acid had been used up and the reaction was over.

Difficulties were encountered in attempts to isolate the product of the reaction. Several procedures were tried:

(i) Following the method of McRae and co-workers, the reaction mixture was steam distilled, the distillate saturated with salt and extracted with ether. The ether extract was dried over sodium sulfate and the ether distilled off. The residue, a pale yellow liquid, was left in the refrigerator with the hope that the chlorohydrin would crystallize. No crystals had formed after ten days. Distillation of the liquid at 20 mm. on the water bath produced first a colorless distillate, mainly acetic acid and probably unused dihydro-~~pyran~~ pyran, and, as the temperature rose toward 100°, signs of decomposition. The heating was continued on an oil bath with

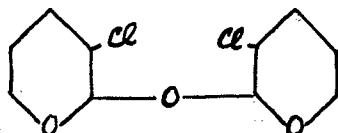
the hope that the chlorohydrin would be obtained as a liquid boiling at 123-125° at 19 mm., as Paul (41) had obtained it. There was vigorous boiling in the distillation flask but only very slow distillation. The residue in the flask gradually turned black. The distillate, a small quantity of a brown liquid, deposited crystals when left in the refrigerator for two days. Recrystallized from alcohol, these had a melting point of 105-106°, as compared with a reported melting point of 64° for the chlorohydrin.

(ii) It was thought that the steam distillation may have decomposed the chlorohydrin and therefore in the next trial this was eliminated. The reaction mixture was saturated with salt and extracted with ether directly. Again the liquid left after evaporation of the ether failed to deposit crystals. It was distilled as before at 20 mm. with similar results. Again the liquid mentioned by Paul was not obtained. The distillate from 100° up was a brown liquid which gave the same crystals as before.

(iii) In a third trial the distillation at the higher temperatures, which probably decomposes the chlorohydrin, was eliminated. The reaction mixture was saturated with salt and extracted with ether. After evaporation of the ether, only the low-boiling fraction, mainly acetic acid and probably unused dihydropyran, which came over under 70° at 20 mm., was distilled off. The residue, when left in the refrigerator, deposited crystals. These, recrystallized from alcohol, were

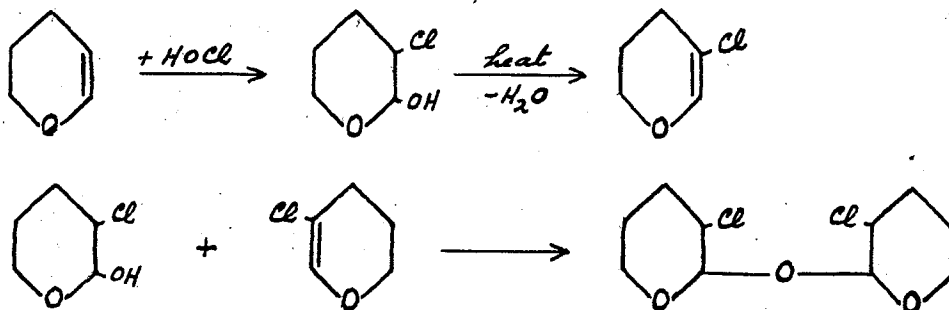
white needles melting at 105-108°, indicating that the product was the same as before and not the chlorohydrin. The yield of this product was 10 grams.

The melting point, and a chlorine analysis, indicate that the product is the dichloroditetrahydropyryl ether:



Paul (41) gives the melting point of this substance as 108°, the Farben chemists (28) give 106°, and Hawkins and Bennett (16) 105-107°.

The course of the reaction, leading to the formation of this product, is probably as follows:



This has been discussed earlier (page 37). The low yield of the ether, about 15%, indicates that not all the chlorohydrin was converted to the ether. Probably some of the 3-chlorodihydropyran, which boils at 141° at 760 mm., distilled off directly with the low-boiling fraction at 20 mm., instead of combining with the chlorohydrin to form the ether.

A chlorine analysis here and subsequent halogen analyses were carried out by the semi-micro method of

Sucharda and Bobranski (51). In this method the sample is submitted to combustion in the presence of a platinum catalyst and the chloride formed is absorbed in barium carbonate. The barium carbonate is then titrated with standard silver nitrate solution using a weight-burette.

Chlorine analysis of the presumed dichloroditetrahydro-  
pyryl ether : 18.34 mg. of sample gave sufficient  
chloride to react with 2.740 grams of standard silver  
nitrate solution (1.000 g. = 1.860 mg. chloride).

$$\text{Percentage chlorine} = \frac{2.740 \times 1.860 \times 100}{18.34} = 27.78\%$$

Calculated for the dichloroditetrahydropyryl

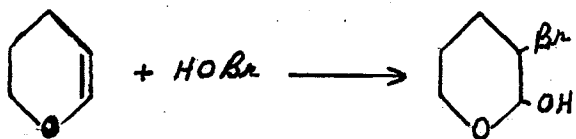
ether,  $C_{10}H_{16}O_3Cl_2$ , 27.79% chlorine.

Calculated for the chlorohydrin,

$C_5H_9O_2Cl$ , 25.97% chlorine.



Attempted Preparation of 2-hydroxy-3-bromotetrahydropyran  
by Addition of Hypobromous Acid to Dihydropyran



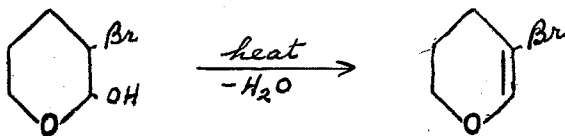
This reaction was attempted by the method used by Read and Reid (47) to prepare the bromohydrin of amylene.

Dihydropyran (42 grams,  $\frac{1}{2}$  mole) was stirred mechanically with 1 liter of water while bromine was added gradually in the form of 7% bromine in 10% potassium bromide solution until the color of the bromine persisted. The reaction mixture was extracted with ether and the extract dried over sodium sulfate. The residue after the evaporation of the ether was a yellow oil with a pleasant odor. This was left in the refrigerator for some days with the hope that the bromohydrin would crystallize but no crystals appeared. The liquid was then distilled at 20-22 mm. Up to 120° the distillate was colorless and separated into two layers. One of the layers proved to be water, indicating that decomposition was taking place in which water was a product. Above 120°, although vigorous boiling continued in the flask, little distillate came over and the liquid in the flask thickened and turned darker in color. Distillation was stopped at 125°.

The residue in the distillation flask was a tar-like material, from which it has not been found possible to isolate crystals. The distillate, dried over sodium sulfate

to remove the water present, also failed to deposit crystals on standing for some days. It was redistilled at 20 mm. and collected in two fractions: I, up to 100°, colorless; II, 100-125°, yellowish. Both had water layers, like the original distillate. Left in the refrigerator, neither formed crystals. Eventually both turned a dark brown.

As has been mentioned elsewhere (page 40), the phenomena observed in the distillation here can be interpreted most easily by assuming that the bromohydrin is formed in the reaction and is decomposed during the distillation as follows:



The 3-bromodihydropyran formed, which boils at 63° at 22 mm., will be present in the distillate, along with the water formed in the decomposition of the bromohydrin. The 3-bromodihydropyran is known to have a tendency to polymerize, which accounts for the tar-like residue and for the distillate turning brown.

Preparation of 2,3-Dichlorotetrahydropyran

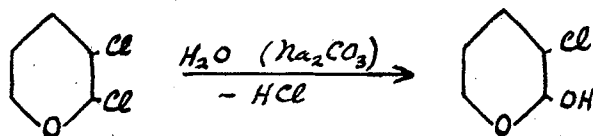


Paul (41) carried out this reaction by passing chlorine into dihydropyran dissolved in anhydrous ether or carbon tetrachloride cooled to  $-10^{\circ}$ . Hawkins and Bennett (15) cooled only to  $0^{\circ}$  and did the reaction both with and without a solvent. In this work, because the dichloride was to be used to prepare the chlorohydrin which is somewhat unstable to heat, it was thought best not to use a solvent which would have to be distilled off later.

Dihydropyran (84 grams, 1 mole) was cooled to  $0^{\circ}$  and chlorine was passed in until the weight had increased by 71 grams (1 mole of chlorine). The stream of chlorine must not be too rapid. If the reaction is hurried, the heat of reaction brings some decomposition, indicated by evolution of hydrogen chloride. The operation takes three to four hours.

The product is a heavy yellow liquid which fumes in moist air. It should be kept in the refrigerator until used. It was used in the crude form for the preparation of the chlorohydrin.

Preparation of 2-hydroxy-3-chlorotetrahydropyran  
by Hydrolysis of 2,3-dichlorotetrahydropyran



Paul (41) did not succeed in isolating the chlorohydrin from the hydrolysis of the dichloride in the presence of an alkaline reagent. Hawkins and Bennett (15), however, prepared the chlorohydrin successfully by this method. They mixed the crude dichloride with an aqueous suspension of calcium carbonate or with sodium carbonate solution and stirred the mixture, at room temperature or with cooling, until the bulk of the oil had disappeared. As is to be expected, they obtained better yields when they cooled the reaction mixture. They found the reaction more rapid with sodium carbonate solution.

In this work the method using sodium carbonate solution was adopted but instead of mixing the reactants the crude dichloride was added gradually in small portions to the carbonate solution. It was found that this gave better yields. The reaction mixture was also kept cooled to 0° throughout the progress of the reaction.

Sodium carbonate (53 grams,  $\frac{1}{2}$  mole) dissolved in water (200 ml.) was stirred mechanically while cooling to 0° in an ice-water mixture. The crude dichloride (155 grams, 1 mole) was added gradually over a period of two to three hours. The stirring was continued for an hour after the addition

of the dichloride had been completed. After the reaction was over, indicated by no more evolution of carbon dioxide, there was a heavy yellow oil below the water layer. Left in the refrigerator, the bulk of the oil solidified. It was filtered with suction. The aqueous filtrate, still containing oil droplets, was extracted with ether and the extract dried over sodium sulfate. Evaporation of the ether gave a liquid which, when cooled in the refrigerator for some days, deposited more crystals.

The total yield of the reaction was 80 grams, about 60% of the theoretical, calculated on the basis of the original dihydropyran.

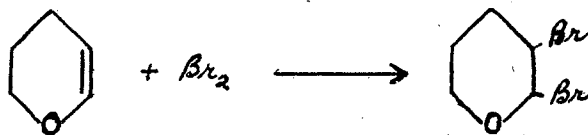
The crude crystals melted at 47-51°. Recrystallized three times from anhydrous ether, they melted at 64°, the reported melting point of the chlorohydrin.

Chlorine analysis: 32.46 mg. of sample were found to contain sufficient chlorine to react with 4.671 grams of standard silver nitrate solution (1.000 g. = 1.798 mg. chloride).

$$\begin{array}{l} \text{Percentage} \\ \text{chlorine} \end{array} = \frac{4.671 \times 1.798 \times 100}{32.46} = 25.87\%.$$

Calculated for the chlorohydrin,  $C_5H_9O_2Cl$ , 25.97%.

Preparation of 2,3-Dibromotetrahydropyran



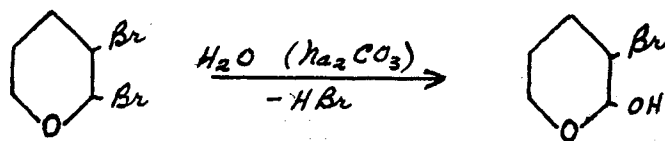
Paul (35, 38) carried out this reaction by adding bromine gradually to dihydropyran dissolved in carbon tetrachloride or anhydrous ether and cooled to  $-15^{\circ}$ .

In this work no solvent was used and the reaction was carried out at  $0^{\circ}$ . Possibly the lower temperature used by Paul would increase the eventual yield of the bromohydrin.

Dihydropyran (84 grams, 1 mole) was stirred in a large flask cooled to  $0^{\circ}$  while the calculated quantity of bromine (160 grams, 1 mole) was dropped in slowly over a period of about three hours. The reaction was more vigorous than with chlorine and some hydrogen bromide was evolved.

The product was a heavy yellow liquid which was used in the crude form for the preparation of the bromohydrin.

Preparation of 2-hydroxy-3-bromotetrahydropyran  
by Hydrolysis of 2,3-dibromotetrahydropyran



Paul (38) used lead hydroxide to neutralize the hydrogen bromide liberated in the hydrolysis. In this work it was found more convenient to use sodium carbonate solution as in the hydrolysis of the dichloride.

The crude dibromide (244 grams, 1 mole) was added gradually over a period of two to three hours to sodium carbonate (53 grams,  $\frac{1}{2}$  mole) dissolved in water (300 ml.) which was stirred mechanically and cooled to 0°.

When the reaction was over, there was a dark yellow oil below the water layer. The mixture was placed in the refrigerator, where the oil had crystallized after two days. The crystals were filtered off and the filtrate extracted with ether. This extract, dried over sodium sulfate and the ether evaporated, gave a further crop of crystals.

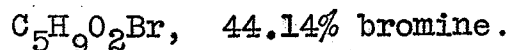
The yield of the crude crystals was 75 grams, 42% on the basis of the original dihydropyran. The crude crystals melted at 50-60°. Recrystallized several times from anhydrous ether, they melted at 79°, the reported melting point of the bromohydrin.

Bromine analysis: 35.00 mg. of sample gave sufficient bromide to react with 3.874 grams of standard silver nitrate

solution (1.000 g. = 4.053 mg. bromide)

$$\text{Percentage bromine} = \frac{3.874 \times 4.053 \times 100}{35.00} = 44.86\%$$

Calculated for the bromohydrin,

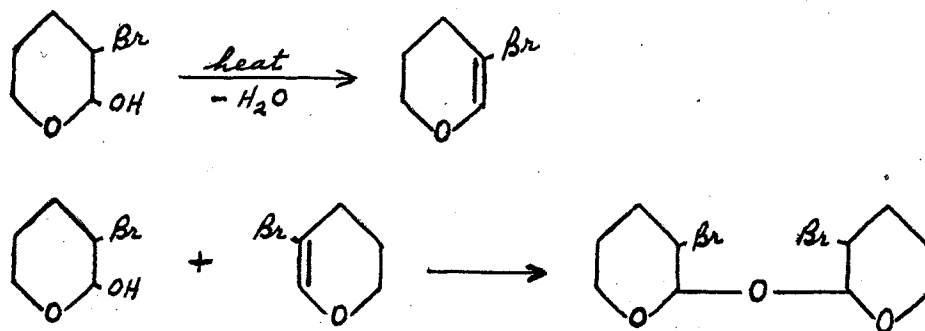


Formation of the Dibromoditetrahydropyryl Ether

from the Bromohydrin, 2-hydroxy-3-bromotetrahydropyran

A sample of the bromohydrin (65 grams) was left on a watch glass to dry, at times exposed to the heat of the summer sun. After some days it was found to have become pasty. On filtering with suction and recrystallizing from ether, it was found that the melting point had jumped from 75°, that of the original sample, to 105°.

The work of Hawkins and Bennett (15, 16) on the chlorohydrin indicates that the heat of the sun had brought about the following reactions:



Paul (35) reports the melting point of this dibromoditetrahydropyryl ether to be 110°. On further recrystallization the product gave this melting point.

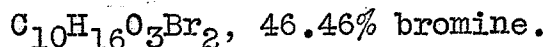
Bromine analysis: 20.39 mg. of sample gave sufficient



bromide to react with 2.351 grams of standard silver nitrate solution (1.000 g. = 4.053 mg. bromide).

$$\text{Percentage bromine} = \frac{2.351 \times 4.053 \times 100}{20.39} = 46.72\%$$

Calculated for the dibromoditetrahydropyryl ether,

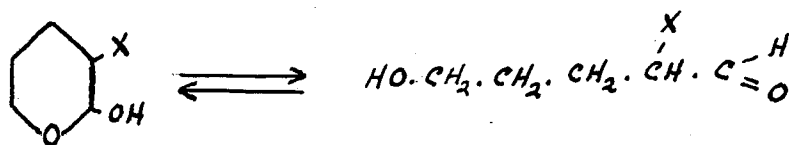


### Aldehydic Properties of the Halohydrins

Paul (38) found that the bromohydrin reduced Fehling's solution when heated and also ammoniacal silver nitrate.

In this work it was found that both the chlorohydrin and the bromohydrin show these aldehyde reactions. Neither, however, gives Schiff's test.

The reducing properties of these halohydrins are thought to be due to an equilibrium of the cyclic form with an aldehyde form:



An attempt to prepare a crystalline oxime of the chlorohydrin failed. No further attempts to prepare crystalline aldehyde derivatives were made.

Paul (38) treated the bromohydrin with phenylhydrazine in ether solution and isolated crystals of the hydrobromide of phenylhydrazine, in place of the expected phenylhydrazone. Apparently with this reagent the substance acts as a bromohydrin rather than as an aldehyde.

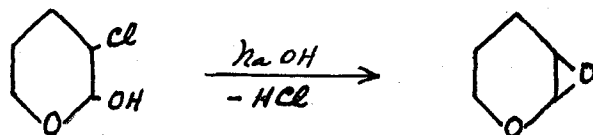
### Acid Reaction of the Halohydrins

Paul (38) titrated the bromohydrin of dihydropyran with sodium hydroxide solution and found that it neutralized it almost quantitatively. He found, however, that it tended to take a slight excess of sodium hydroxide.

In this work the same reaction was attempted for the chlorohydrin, with similar results.

A recrystallized sample of the chlorohydrin (0.3646 grams) was dissolved in water and diluted to 100 ml. The equivalent quantity of sodium hydroxide (0.1069 grams) was similarly dissolved and diluted to 100 ml. Titration of 25 ml. of the chlorohydrin solution, using phenolphthalein as indicator, required 29 ml. of the alkali solution.

### Attempted Preparation of the Oxide of Dihydropyran



This reaction was attempted by the method which Osterberg (30) used to prepare cyclohexene oxide.

The chlorohydrin (17 grams, 1/8 mole) was added to a solution of sodium hydroxide (5 grams, 1/8 mole) in water (100 ml.). The mixture was stirred mechanically at room temperature for two hours. No oil separated from the solution. The reaction mixture was extracted with

ether and the extract dried over sodium sulfate. Evaporation of the ether left a small residue of liquid, which failed to deposit crystals and showed no constancy in boiling point. It is probably a mixture of decomposition products.

Concentration of the residual water solution brought crystallization of sodium chloride, indicating that hydrogen chloride had been lost by the chlorohydrin during the reaction.

It is very probable that the oxide of dihydropyran, if it exists at all, is an unstable substance. One would expect it to be unstable to heat, as are the dichloride and the chlorohydrin, and hence difficult to isolate.

CONCLUSIONS

1. Hypochlorous and hypobromous acids probably add directly to the double bond of dihydropyran but the isolation of the resulting halohydrins is complicated by the fact that these substances are somewhat unstable to heat.
2. Both the chlorohydrin and the bromohydrin of dihydropyran can be easily prepared by the hydrolysis of the dihalides in the presence of an alkaline reagent.
3. The halohydrins tend to decompose when heated to form 3-halodihydropyrans. These substances react readily with the halohydrins themselves to form dihaloditetrahydropyryl ethers. These ethers are more easily isolated than the halohydrins.
4. Both the chlorohydrin and the bromohydrin show some aldehyde reactions and therefore probably exist in equilibrium with open-chain aldehyde forms.
5. Both of these halohydrins also tend to act as acids. They neutralize sodium hydroxide almost quantitatively.
6. The oxide of dihydropyran, if it exists, is probably unstable to heat and hence difficult to isolate.

SUGGESTIONS FOR FURTHER WORK

Isolation of the Halohydrins from the Addition Reactions

Since this investigation has provided some evidence that hypochlorous and hypobromous acids add to the double bond of dihydropyran, probably further attempts should be made to isolate the halohydrins produced. The fact that they are solids at ordinary temperature should make it possible to obtain them as crystals from an ether extract of the reaction mixture, as they are actually obtained when prepared from the dihalides. If cooling in the refrigerator produces no results, more drastic cooling with solid carbon dioxide might be effective. High vacuum distillation, which has not been tried, obviously also offers some hope of successful isolation of these halohydrins.

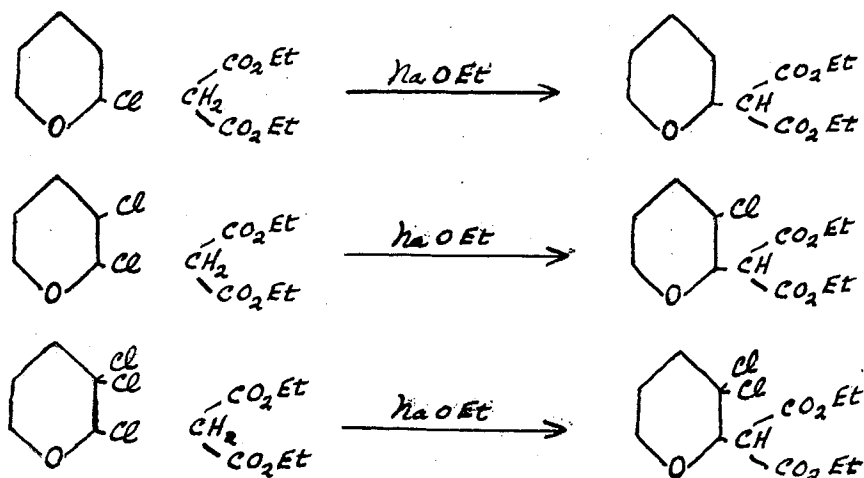
Further Attempts to Prepare the Oxide

Whether the oxide of dihydropyran can be prepared or not has not been exhaustively investigated. Perbenzoic acid oxidation of dihydropyran was attempted by Paul and Tchelitcheff (42) but they did not succeed in isolating an oxide. Here one attempt was made by the method of Osterberg (30), also without success. The method used by Brunel (3), treating a halohydrin in a non-aqueous solvent with a solid alkali, might well be tried. There is a possibility that the oxide may be more stable in the absence of water.

Condensations with Sodio-activated Methylene Compounds


When this work was begun, it was planned to use the oxide of dihydropyran in condensations with activated methylene compounds, as earlier workers (see pages 1-2) had used cyclohexene oxide. Because of the elusive character of dihydropyran oxide, there is not too much hope that such a plan can be realized. Condensations with the halohydrins themselves might be attempted but in these the dihydropyran ring is likely to open so that derivatives like those made from cyclohexene oxide would probably not be obtained.

A study of the chemistry of dihydropyran indicates that the various types of  $\alpha$ -halogen derivatives offer a more promising point of attack on this problem. These substances should condense readily with malonic ester, acetoacetic ester, and similar compounds, as follows:

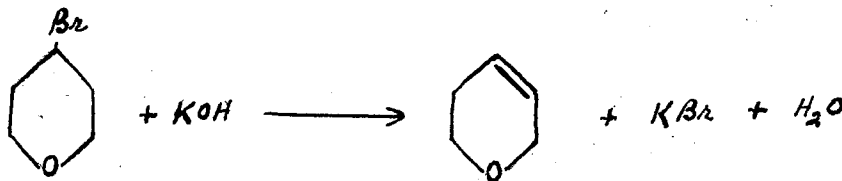


From the condensation products a wide variety of other substances should be obtainable. These reactions, therefore, offer an extensive field of work.

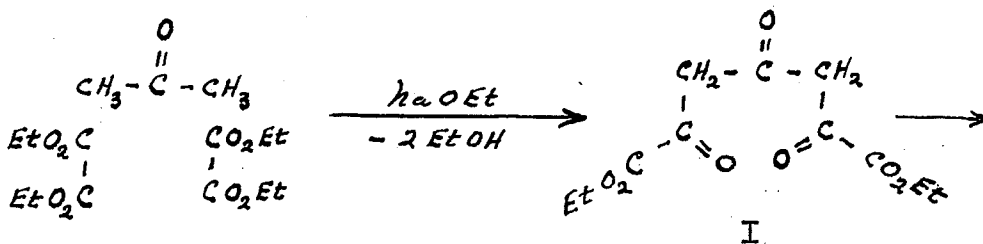
Possible Work on the New Dihydropyran

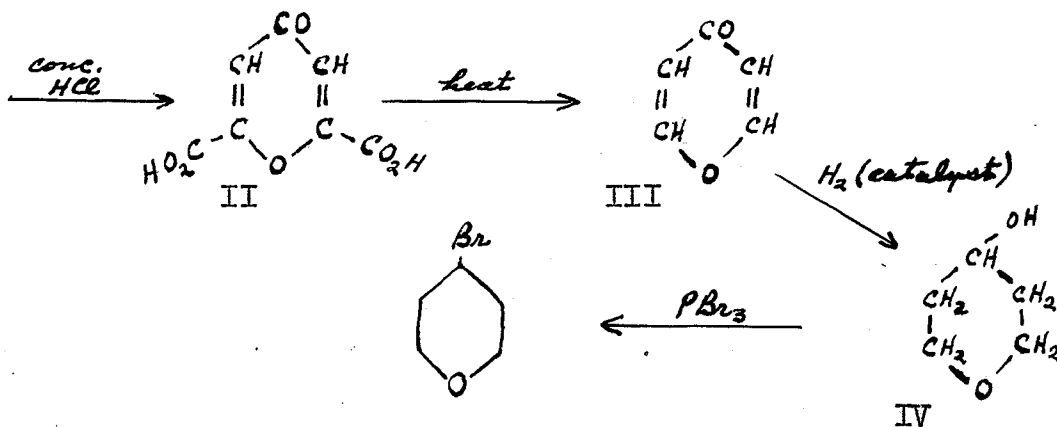
The more recently discovered dihydropyran, , first reported by Paul and Tchelitcheff (42) in 1947, is much more likely to show reactions like those of cyclohexene than the older dihydropyran investigated here. A stable oxide of this new compound has been prepared by perbenzoic acid oxidation. Therefore, if the new dihydropyran were available, it is very probable that the reactions carried out with cyclohexene by Coffey (5), Kendall and co-workers (18, 19), and McRae, Charlesworth, and Alexander (21) could be repeated.

Paul and Tchelitcheff prepared the new substance by a slow distillation of 4-bromotetrahydropyran with potassium hydroxide in glycol:



They do not explain how they obtained the 4-bromotetrahydropyran, which is not a readily available compound. A literature search indicates that it can be prepared by the following series of reactions:





Acetone condensed with 2 moles of ethyl oxalate, in the presence of sodium ethylate, gives an ester (I), which can be hydrolyzed with concentrated hydrochloric acid to form chelidonic acid (II). These reactions are described by Riegel and Zwilgmeyer (49). Willstatter and Pummerer (54) used chelidonic acid to make  $\gamma$ -pyrone (III). Prelog and co-workers (44) submitted  $\gamma$ -pyrone to catalytic hydrogenation and obtained tetrahydropyranol-4 (IV), from which they made 4-bromotetrahydropyran by treatment with phosphorus bromide. It would be interesting to attempt the preparation of the new dihydropyran using this series of reactions.

Apart from the report by Paul and Tchelitcheff (42), the new compound has not as yet been mentioned in the chemical literature. These men carried out a few reactions only. Many other possible ones remain to be tried.

It is the writer's intention to do further research on the dihydropyrans and their derivatives along the lines suggested in the concluding section of this thesis.



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