

THE TETRAHYDROPYRAN-2-OLS

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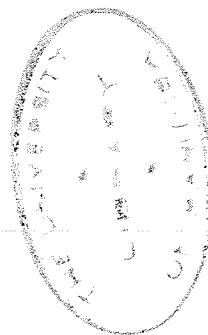
THEIR DERIVATIVES

by

Adam Giesinger

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REACTIONS OF SOME HALOGEN DERIVATIVES OF
TETRAHYDROPYRAN-2-OL

By E. H. CHARLESWORTH AND A. GIESINGER

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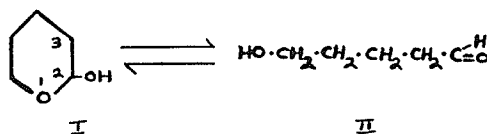
BY E. H. CHARLESWORTH AND A. GIESINGER

ABSTRACT

The 3-halotetrahydropyran-2-ols have been found to readily give derivatives of tetrahydrofurfural in aqueous alcohol under weakly basic or acidic conditions. In strongly alkaline solution tetrahydropyran-2,3-diol and its anhydro-polymers were formed. 3,3-Dichlorotetrahydropyran-2-ol and 2,3,3-trichlorotetrahydropyran have been converted by aqueous alkali to viscous sirups which appear to contain 2-hydroxytetrahydropyran-3-one and its tautomers. On oxidation with permanganate these sirups have yielded succinic acid.

INTRODUCTION

The aldehydic properties of tetrahydropyran-2-ol (I) were explained by Paul (7, 9) on the assumption that it existed in equilibrium with δ -hydroxyvaleric aldehyde (II). Paul's view has since been confirmed by other workers,



particularly Schniepp and Geller (14) and Woods and Sanders (17). The latter authors obtained a crystalline 2,4-dinitrophenylhydrazone.

The 3-halotetrahydropyran-2-ols (IV), readily prepared by the hydrolysis of the corresponding 2,3-dihalides (III) in the presence of mild alkaline reagents, have been reported by Paul (8, 10, 11), by I.G. Farben (5), and by Hawkins and Bennett (1, 2). As these possess some aldehydic properties, it has been assumed that they exist in equilibrium with a δ -hydroxyvaleric aldehyde form (V). Crystalline derivatives, however, are not reported, although Paul (11) did isolate a liquid oxime of tetrahydrofurfural following the hydrolysis of the 2,3-dichloride. Paul (9) found that 3-bromotetrahydropyran-2-ol reacted rapidly with phenylhydrazine, but gave only crystals of phenylhydrazine hydrobromide. This latter reaction suggests that in the presence of an organic base the bromohydrin loses hydrogen bromide more rapidly than it acts as an aldehyde.

In view of their undoubted aldehyde properties, it seemed desirable to prepare crystalline derivatives of these halotetrahydropyrans and thus to determine the nature of the aldehydic substances derived from them. Both the chloro- and bromo-tetrahydropyranol were found to react with substituted phenylhydrazines to yield the same halogen-free derivatives, namely,

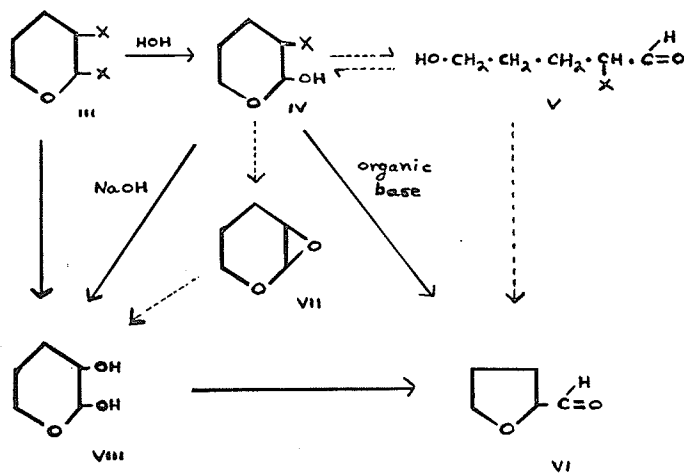
- (i) a 2,4-dinitrophenylhydrazone, m.p. 133-134°;
- (ii) a 2,4-dinitrophenylosazone, m.p. 242°;

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Contribution from the Department of Chemistry, the University of Manitoba, Winnipeg, Man. This paper was read before the XIVth Congress of the International Union of Pure and Applied Chemistry in Zurich.

- (iii) a *p*-nitrophenylhydrazone, m.p. 146°;
- (iv) a *p*-nitrophenylosazone, m.p. 246°;
- (v) a *p*-benzylphenylhydrazone, m.p. 74-75°.

In all cases these derivatives are identical with corresponding products made from an authentic sample of tetrahydrofurfural (VI) prepared by the method of Scheibler, Sotscheck, and Friese (13). Hurd and Edwards (3) obtained the same derivatives from tetrahydrofurfural produced by heating tetrahydropyran-2,3-diol (VIII) under reduced pressure.

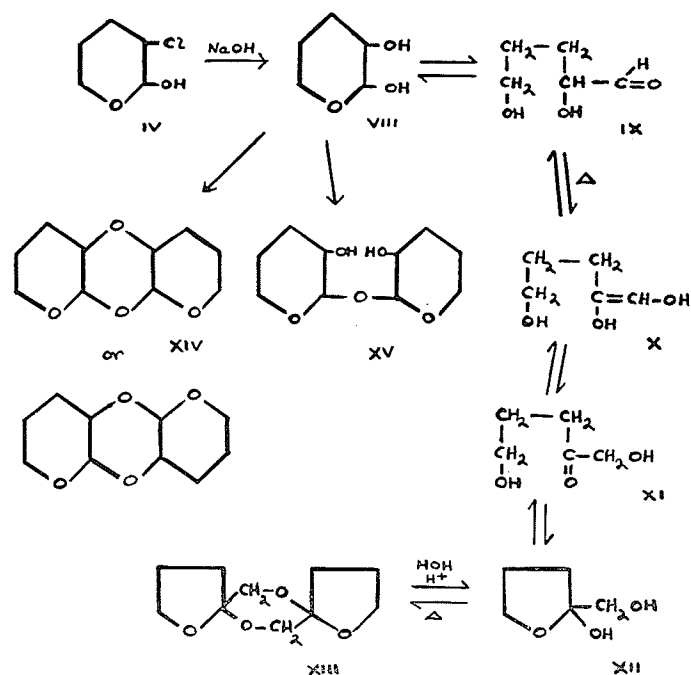


The 3-halotetrahydropyran-2-ols lose hydrogen halide so readily that they can be titrated with aqueous sodium hydroxide. In each case it is possible to isolate a quantitative yield of the sodium halide salt. We had hoped at first to use this method to obtain the oxide (VII). However, in view of the fact that an organic base when extracting hydrogen halide leaves tetrahydrofurfural as a residue, it seemed that the effect of sodium hydroxide might be the same and thus represent a convenient method of preparing tetrahydrofurfural.

The organic product from the reaction proved to be rather elusive. Organic solvents do not extract it in appreciable amounts from the aqueous mixture. Even continuous extraction proved inadequate. The water had to be removed almost completely, either by absorption on drying agents or better by evaporation, before the product could be taken up in organic solvent.

The nature of the product varies somewhat according to the conditions. If the reaction mixture is kept near room temperature throughout the process, a considerable portion of the product is soluble, with some difficulty, in ether. This ether-soluble substance is aldehydic, but it is a higher boiling liquid than tetrahydrofurfural. It gives the same dinitrophenylosazone, m.p. 242°, as tetrahydrofurfural, but not the phenylhydrazone obtainable from that substance. It readily reduces periodic acid to iodate and forms a 3,5-dinitrobenzoate, m.p. 174°. This substance seems to be tetrahydropyran-2,3-diol (VIII), which Hurd and Kelso (4) prepared by hydrogen peroxide oxidation of dihydropyran.

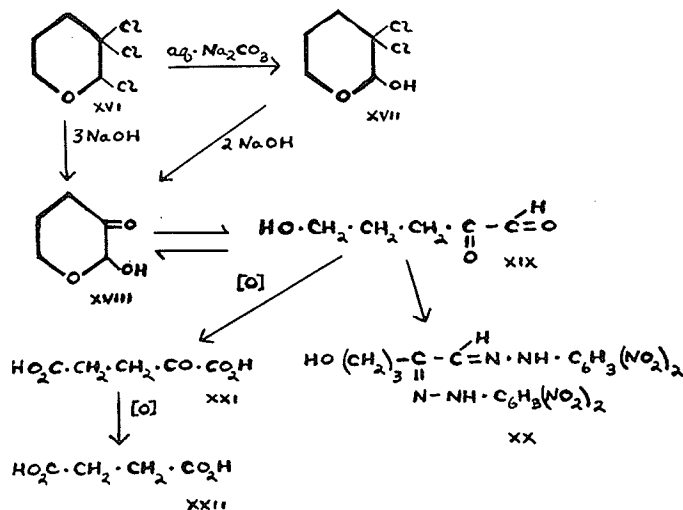
At higher reaction temperatures less of the product is ether-soluble. Small fractions can be extracted with other solvents, but the bulk is soluble only in alcohol and water. Evaporation of the solvent in each case leaves a high boiling sirup which is not easily purified by distillation. In one case a solid, m.p. 190° , precipitated from aqueous solution. In another case a chloroform extract yielded a solid, m.p. $101-102^{\circ}$. The properties of these substances indicate that they are the same $C_{10}H_{16}O_4$ materials as are reported by Hurd and Edwards (3), who obtained them by heating tetrahydropyran-2,3-diol. The lower melting of these two compounds was also obtained by Swadesh and Dunlop (16) from another source. The two groups of workers seem to agree that it has the structure XIII and that it is formed from the diol by the route shown. The structure of the higher melting compound has not been established, but the indications are that it may be XIV. Compound XV has been isolated by Hurd and Kelso (4). Our high boiling sirups are probably mixtures of compounds XIII, XIV, and XV and perhaps more complex structures.



No material was isolated that seemed to be the oxide (VII). If formed at all, it was apparently unstable and hydrolyzed to form the diol (VIII). Other attempts by Paul and Tchelitcheff (12) and by Hurd and Edwards (3) to obtain the oxide have not been too successful.

3,3-Dichlorotetrahydropyran-2-ol (XVII) is mentioned briefly in the literature in a wartime I.G. Farben report (6) and in a German patent (18). We have prepared this substance by warming the 2,3,3-trichloride (XVI) with an equivalent of sodium carbonate solution. It is less aldehydic than the simpler halohydrins discussed earlier, but resembles them in some of its properties. It reduces Fehling's solution when warmed for some time; it

forms the same dinitrophenylosazone, m.p. 242°, but does not form an intermediate hydrazone. When dissolved in warm alcohol, it can be titrated with aqueous sodium hydroxide solution and neutralizes two equivalents of the base. In this reaction the 3,3-dichlorotetrahydropyran-2-ol loses its entire halogen content.



When 2,3,3-trichlorotetrahydropyran (XVI) is warmed and stirred with 3 moles of aqueous sodium hydroxide solution, the organic layer gradually disappears and the alkali is neutralized. A dark red reaction mixture results. The organic product can be isolated by evaporating the water and extracting the residue with alcohol. A quantitative yield of sodium chloride is left behind. On evaporation of the alcohol a viscous dark red halogen-free sirup is left. This material is thought to contain an equilibrium mixture of tetrahydropyranone-3-ol-2 (XVIII) and α -keto- δ -hydroxyvaleric aldehyde (XIX), together with more complex substances. It is aldehydic, reducing Fehling's solution rapidly when warmed. With 2,4-dinitrophenylhydrazine it gives, near room temperature, an almost immediate precipitate of the expected 2,4-dinitrophenylosazone (XX), m.p. 242°. On oxidation with potassium permanganate, both in alkaline and acid solution, succinic acid (XXII) has been obtained. Intermediate compounds such as α -ketoglutaric acid (XXI) have not been isolated as yet from the above oxidations or with milder oxidizing agents.

EXPERIMENTAL

Derivatives of 3-Halotetrahydropyran-2-ols

Both 3-chloro- and 3-bromo-tetrahydropyran-2-ol were prepared by the hydrolysis of the corresponding dihalides with aqueous sodium carbonate solution, following the directions of Hawkins and Bennett (2) for the preparation of 3-chlorotetrahydropyran-2-ol. The methods used for the preparation of the derivatives listed below were essentially those described by Shriner and Fuson (15).

(a) *2,4-Dinitrophenylhydrazones*

The 3-chloro- and 3-bromo-tetrahydropyran-2-ol were treated at room temperature with 2,4-dinitrophenylhydrazine reagent. Voluminous orange-yellow precipitates were formed. Qualitative tests showed no halogen in the products. After repeated crystallization from absolute ethanol both products were obtained as yellow needles which melted at 133–134°C. There was no depression of the melting point when the two products were mixed.

(b) *2,4-Dinitrophenylosazones*

The 3-halotetrahydropyran-2-ols were refluxed with excess 2,4-dinitrophenylhydrazine in aqueous alcohol, in the presence of a few drops of concentrated hydrochloric acid. An orange-red precipitate formed in each case. On recrystallization from acetone or nitromethane orange needles were obtained which in both cases melted at 242°C. The mixed melting point indicated that the products from the two halotetrahydropyrans were the same.

(c) *p-Nitrophenylhydrazones*

The 3-halotetrahydropyrans were warmed for a few minutes with an alcoholic solution of *p*-nitrophenylhydrazine and a trace of acetic acid. The orange-red precipitates were halogen-free. Several recrystallizations from absolute methanol gave the same orange yellow needles which melted at 146°C.

(d) *p-Nitrophenylosazone*

This can be produced by prolonged heating (four hours) with excess *p*-nitrophenylhydrazine and a little concentrated hydrochloric acid. A dark red powder separated on cooling. On recrystallization from methanol it separated as fine dark red crystals which melted at 246°C. with slight decomposition.

(e) *Benzylphenylhydrazone*

The 3-halotetrahydropyran-2-ol in water (1 gm. in 7 ml.) was treated with benzylphenylhydrazine hydrochloride in 95% ethanol (1 gm. in 10 ml.). The mixture was warmed for a few minutes. On cooling a yellowish white precipitate formed. It was recrystallized from methanol in almost colorless needles which melted at 74–75°C.

(f) *Comparison with Tetrahydrofurfural Derivatives*

The derivatives from the halotetrahydropyrans described above were compared with the corresponding derivatives from tetrahydrofurfural, prepared by D. G. Hay in these laboratories by the method of Scheibler, Sotscheck, and Friese (13). Mixed melting points and other tests proved that the above products were identical in all respects with derivatives from tetrahydrofurfural.

Tetrahydropyran-2,3-diol (VIII) and Related Compounds

3-Chlorotetrahydropyran-2-ol (13.6 gm., 0.1 mole) dissolved in water (100 ml.) was treated with sodium hydroxide solution (4 gm. in 100 ml.) and allowed to stand for three to four hours at room temperature. The solution was made just acid with a few drops of dilute hydrochloric acid and allowed to

evaporate at 35–40°C. The residue was extracted with absolute ethanol, leaving behind a quantitative yield of sodium chloride. The alcoholic extract was allowed to evaporate at room temperature. The residue (10 gm.) was extracted several times with ether. Evaporation of the ether gave a high boiling sirup (8 gm.) which is thought to be tetrahydropyran-2,3-diol. Found: C, 51.1; H, 8.07%; Calc. for $C_5H_{10}O_3$: C, 50.9; H, 8.47%.

The same product can be obtained more conveniently in larger quantities by treating crude 2,3-dichlorotetrahydropyran, made by direct chlorination of dihydropyran, with 2 moles of sodium hydroxide and isolating the product as described above.

The product gave the previously described dinitrophenylosazone (m.p. 242°) when refluxed with 2,4-dinitrophenylhydrazine. It reduced periodic acid to iodate and formed a 3,5-dinitrobenzoate, m.p. 174°C.

When the reaction with sodium hydroxide was carried out at 100° on the water bath, very little of the organic product was soluble in ether. The high boiling sirup obtained was probably a mixture of substances of higher molecular weight than the diol. In one trial a chloroform-extracted product solidified. When recrystallized from ethanol it separated in elongated plates which melted at 101–102°C. Found: C, 59.7; H, 8.10%; Calc. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.00%. The melting point and analysis indicates that this is one of the $C_{10}H_{16}O_4$ substances which Hurd and Edwards (3) obtained by heating tetrahydropyran-2,3-diol.

In another trial when excess solid sodium hydroxide was added to the chlorohydrin solution and the mixture left standing, a small quantity of very fine white powder settled out. This melted at 190°C. and could be the other $C_{10}H_{16}O_4$ substance obtained by Hurd and Edwards.

3,3-Dichlorotetrahydropyranol-2 (XVII)

2,3,3-Trichlorotetrahydropyran (9.5 gm.), prepared by the method of Hawkins and Bennett (2), was stirred with sodium carbonate solution (2.6 gm. in 100 ml. of water) at 35–40° for 10 hr. The reaction mixture was then subjected to continuous extraction with ether. After evaporation of the ether a solid recrystallized from aqueous alcohol in plates which melted at 88–89°C. The I.G. Farben chemists (6) reported 90° as the melting point of 3,3-dichlorotetrahydropyran-2-ol.

This product was less aldehydic than the halohydrins, but it did reduce Fehling's solution on warming for some time. When the product was treated at room temperature with 2,4-dinitrophenylhydrazine it did not form a dinitrophenylhydrazone, but when the reaction mixture was heated the previously described 2,4-dinitrophenylosazone (m.p. 242°C.) was precipitated.

When the dichlorotetrahydropyranol was dissolved in warm alcohol, it could be titrated slowly with aqueous sodium hydroxide solution and neutralized two equivalents of the base.

2-Hydroxytetrahydropyran-3-one (XVIII)

2,3,3-Trichlorotetrahydropyran (19 gm., 0.1 mole) was warmed to 35–40°C. so it would remain in the liquid phase, and sodium hydroxide solution (12 gm., 0.3 mole, in 150 ml. of water) was added. The mixture was kept at the

temperature indicated and stirred until the organic layer had disappeared—about 10 hr. The reaction mixture still slightly acid was then allowed to evaporate at just above room temperature. The residue was extracted with absolute ethanol, leaving behind a nearly quantitative yield (16 gm.) of sodium chloride. The alcoholic extract on evaporation gave a very viscous, dark red sirup (10 gm.). No method of purifying it has been found. Its reactions indicated that it was mainly 2-hydroxytetrahydropyran-3-one in equilibrium with an open chain aldehyde form.

It reduced Fehling's solution rapidly when warmed. With 2,4-dinitrophenylhydrazine it gave an almost immediate precipitate of the expected 2,4-dinitrophenylosazone (m.p. 242°), previously described.

The crude red sirup was treated at room temperature for several days with an alkaline solution of potassium permanganate. The manganese dioxide was filtered off and the filtrate acidified with dilute sulphuric acid. Further decolorization of the permanganate now occurred. When this acid oxidation was complete the excess permanganate was destroyed with a little sodium bisulphite, the solution evaporated to dryness, and the residue extracted with ether. On evaporation of the ether a solid acid (m.p. 186°) was left. This was identified as succinic acid by the preparation of the *p*-bromophenacyl ester (m.p. 210–211°) and the *p*-nitrobenzyl ester (m.p. 87–88°). Mixed melting points of these derivatives with samples prepared from an authentic specimen of succinic acid showed no depression.

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ABSTRACT

In this investigation various halogen derivatives of dihydropyran were prepared, by methods described by earlier workers. Those having halogen in the 2-position were hydrolyzed to obtain the corresponding tetrahydropyran-2-ols. The aldehyde properties of these substances were studied and crystalline derivatives prepared. In the case of the 3-halotetrahydropyran-2-ols these derivatives showed that the presumed aldehyde forms were not stable, that in the presence of phenylhydrazines, in weakly basic or in acid solution, they lost hydrogen halide to go over into tetrahydrofurfural.

Tetrahydropyran-2-ols with one or two halogen atoms at the 3-position were found to neutralize readily an alkali solution. The resulting organic product had the halogens replaced by hydroxyls. Tetrahydropyran-2,3-diol and 2-hydroxytetrahydropyran-3-one were obtained by such reactions. These were shown to be aldehydic substances and a number of their derivatives were prepared.

The easily hydrolyzable 2-halotetrahydropyrans were found to react readily also with sodium methyrate to produce 2-methoxytetrahydropyrans. These could be hydrolyzed by dilute acid to form the corresponding tetrahydropyran-2-ols.

A reaction between dihydropyran and formaldehyde, suggested by the work of Beets and others on certain dienes, was also attempted. It was found to go readily but the isolation of pure products has not as yet been accomplished.

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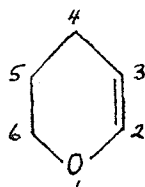
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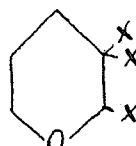
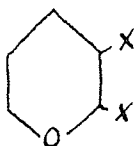
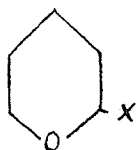
INTRODUCTION

Dihydropyran, the substance first prepared by Paul (39) in 1933, was the starting material for the reactions of this investigation. It has the structure:



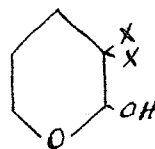
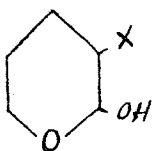
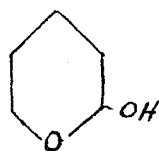
It and the ring compounds obtainable from it are named in a variety of ways in the chemical literature. In this work the substance will be called simply dihydropyran and the corresponding saturated ring tetrahydropyran. The ring positions will be numbered as shown.

Paul and others (23, 36, 38, 42, 45, 48, 69) have prepared halotetrahydropyrans of the types:

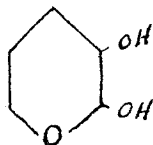


They found that the halogen atom in the 2-position is readily exchanged for hydroxy and alkoxy groups.

Dihydropyran itself and its 2-halogen derivatives have been hydrolyzed (23, 36, 41, 44, 45, 69) to give tetrahydropyran-2-ols such as the following:

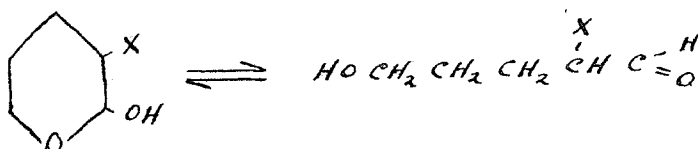
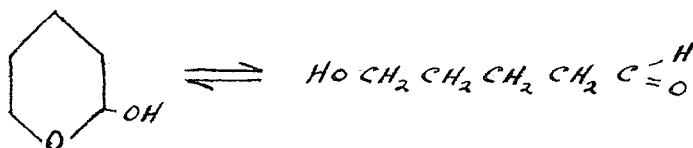


Tetrahydropyran-2,3-diol, prepared (27).



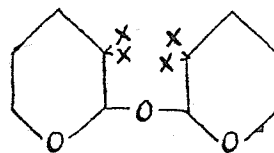
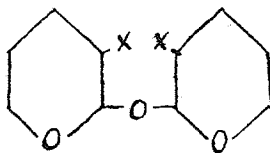
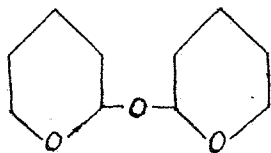
, has also been

Some of these substances have been found (27, 36, 45, 48) to have aldehyde properties, said to be due to an open-chain aldehyde in equilibrium with the ring form:

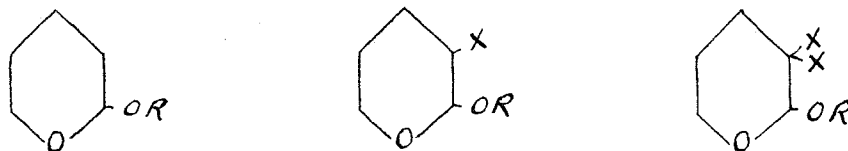


Paul (45) found also that 3-bromotetrahydropyran-2-ol readily neutralized an equivalent of an alkali solution. He seems to have made no effort, however, to isolate an organic product from the neutralization.

Ditetrahydropyranyl ethers of the types

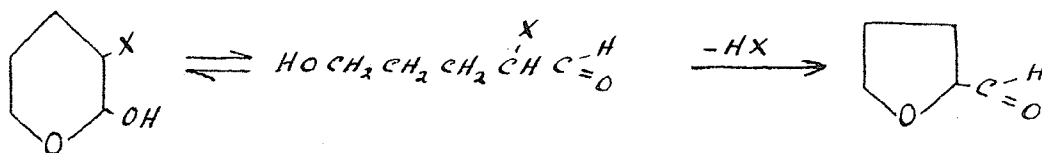


were obtained as by-products when the 2-hydroxy derivatives were prepared. A number of alkyl tetrahydropyranyl ethers of the types

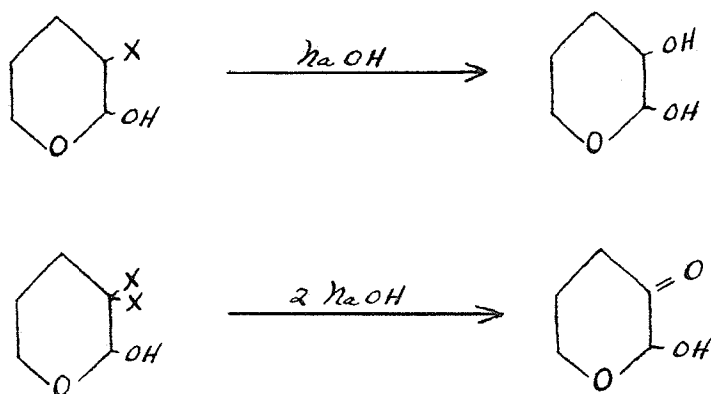


have also been prepared (31, 41, 44, 52, 66, 68).

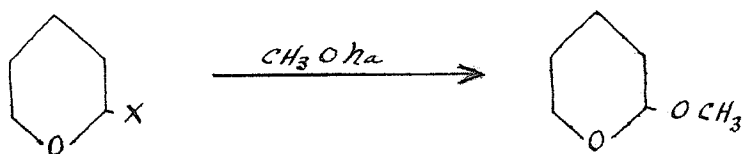
In this investigation various halogen derivatives of dihydropyran were prepared, by methods described by earlier workers. Those having halogen in the 2-position were hydrolyzed to obtain the corresponding tetrahydropyran-2-ols. The aldehyde properties of these substances were studied and crystalline derivatives prepared. In the case of the 3-halotetrahydropyran-2-ols these derivatives showed that the presumed aldehyde forms were not stable, that in the presence of phenylhydrazines, in weakly basic or in acid solution, they lost hydrogen halide to go over into tetrahydrofurfural:



Tetrahydropyran-2-ols with one or two halogen atoms at the 3-position were found to neutralize readily an alkali solution. The resulting organic product had the halogens replaced by hydroxyls:



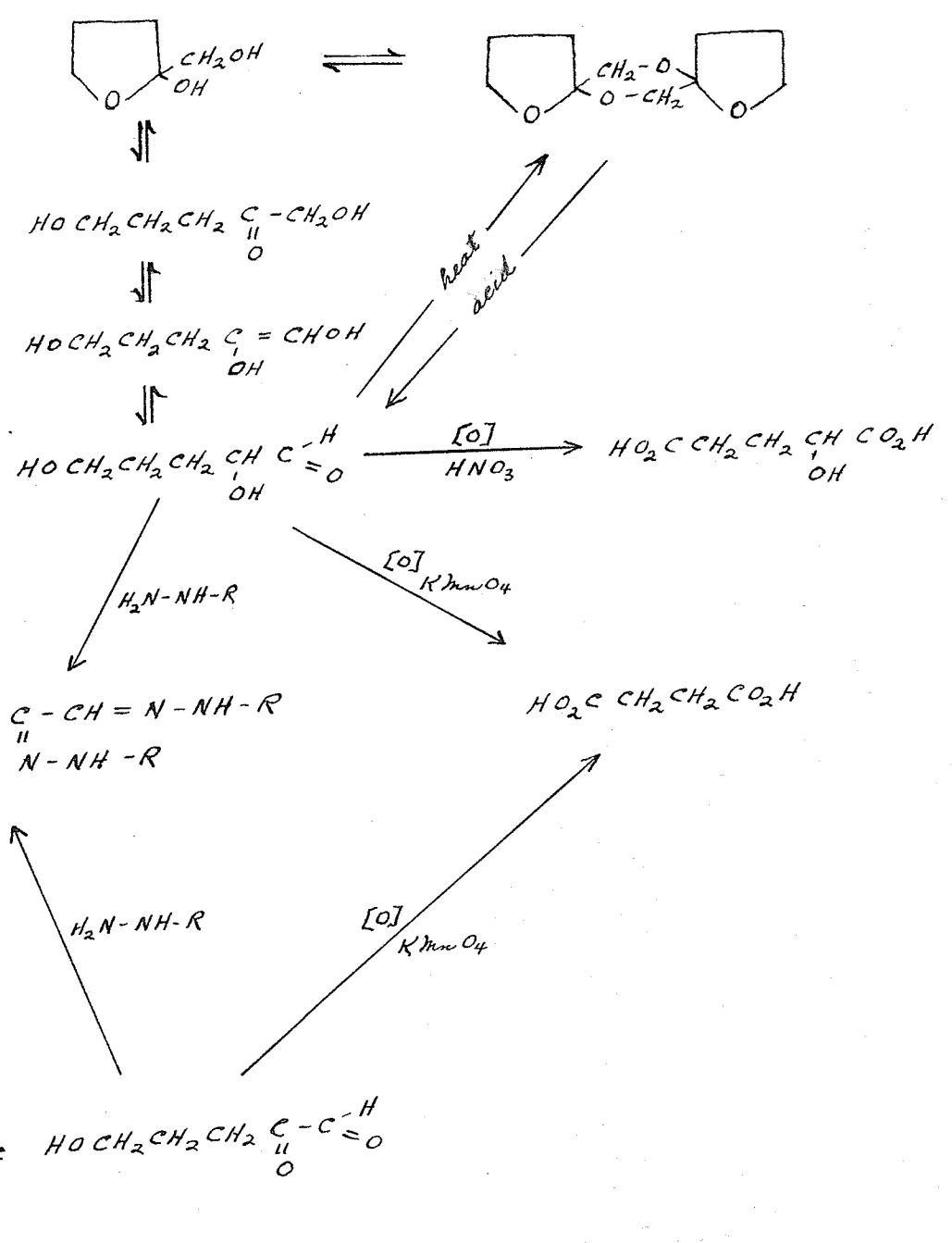
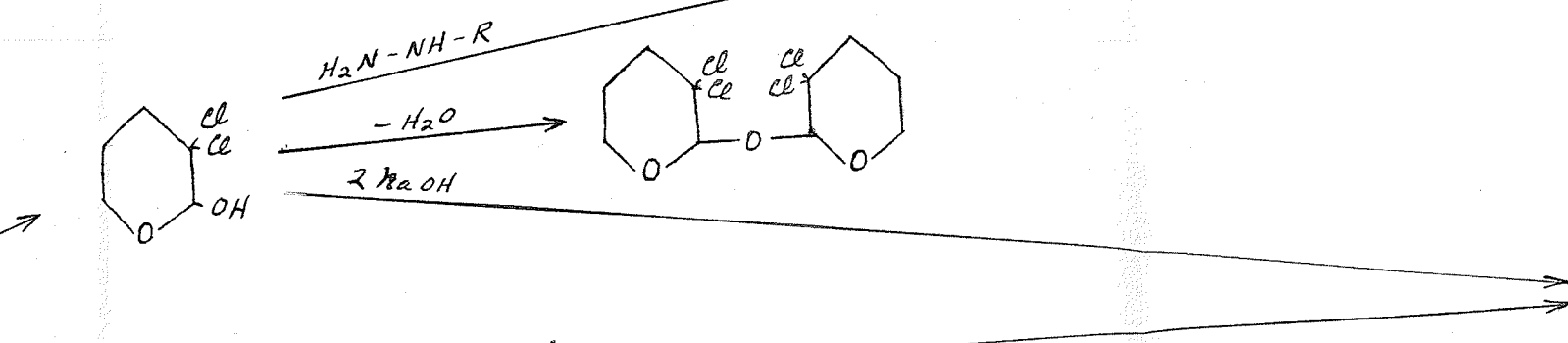
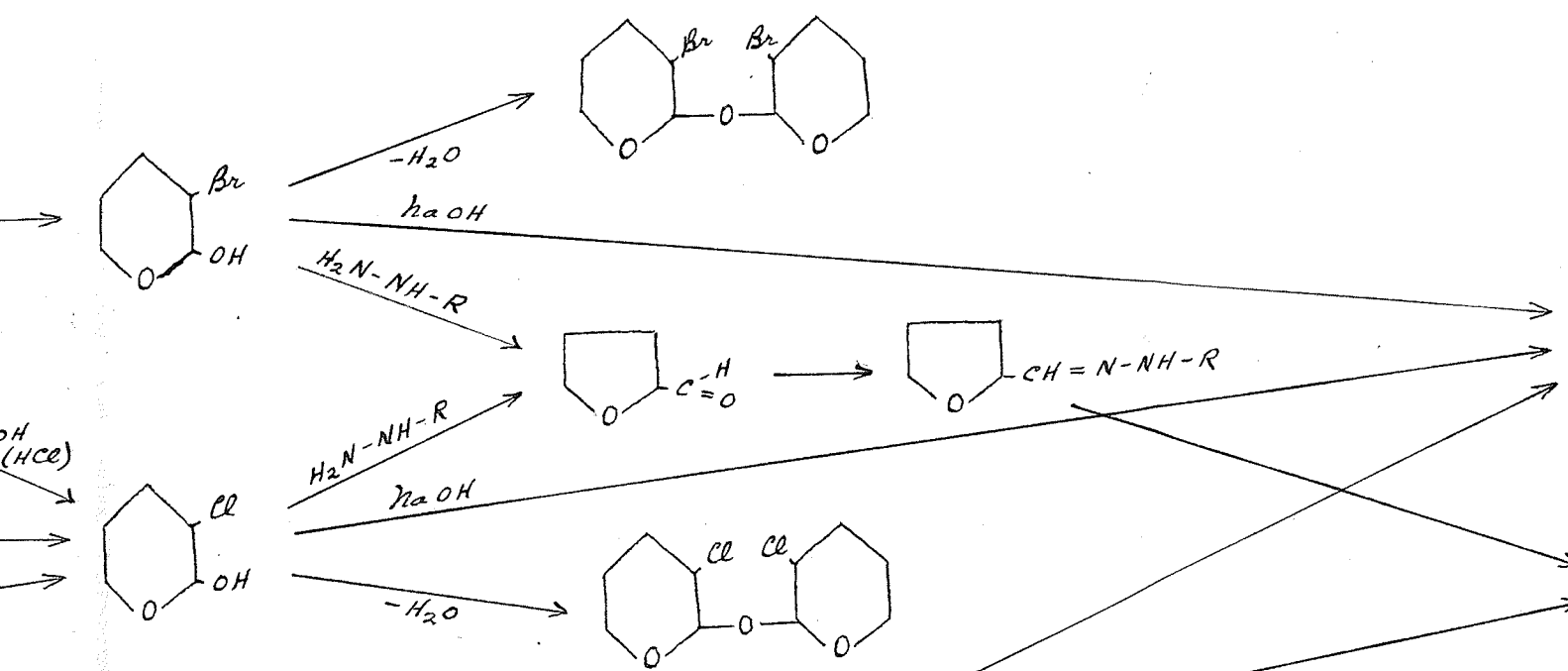
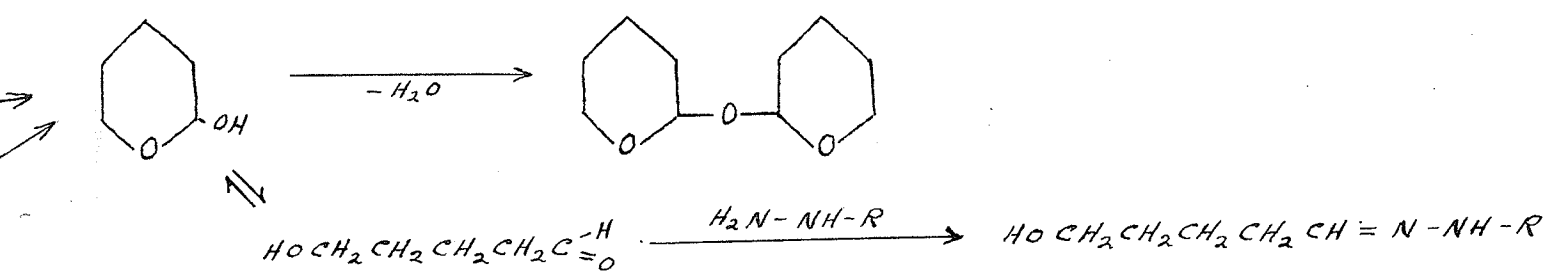
The 2-halotetrahydropyrans were found to react readily with sodium methyrate to give 2-methoxytetrahydropyrans:

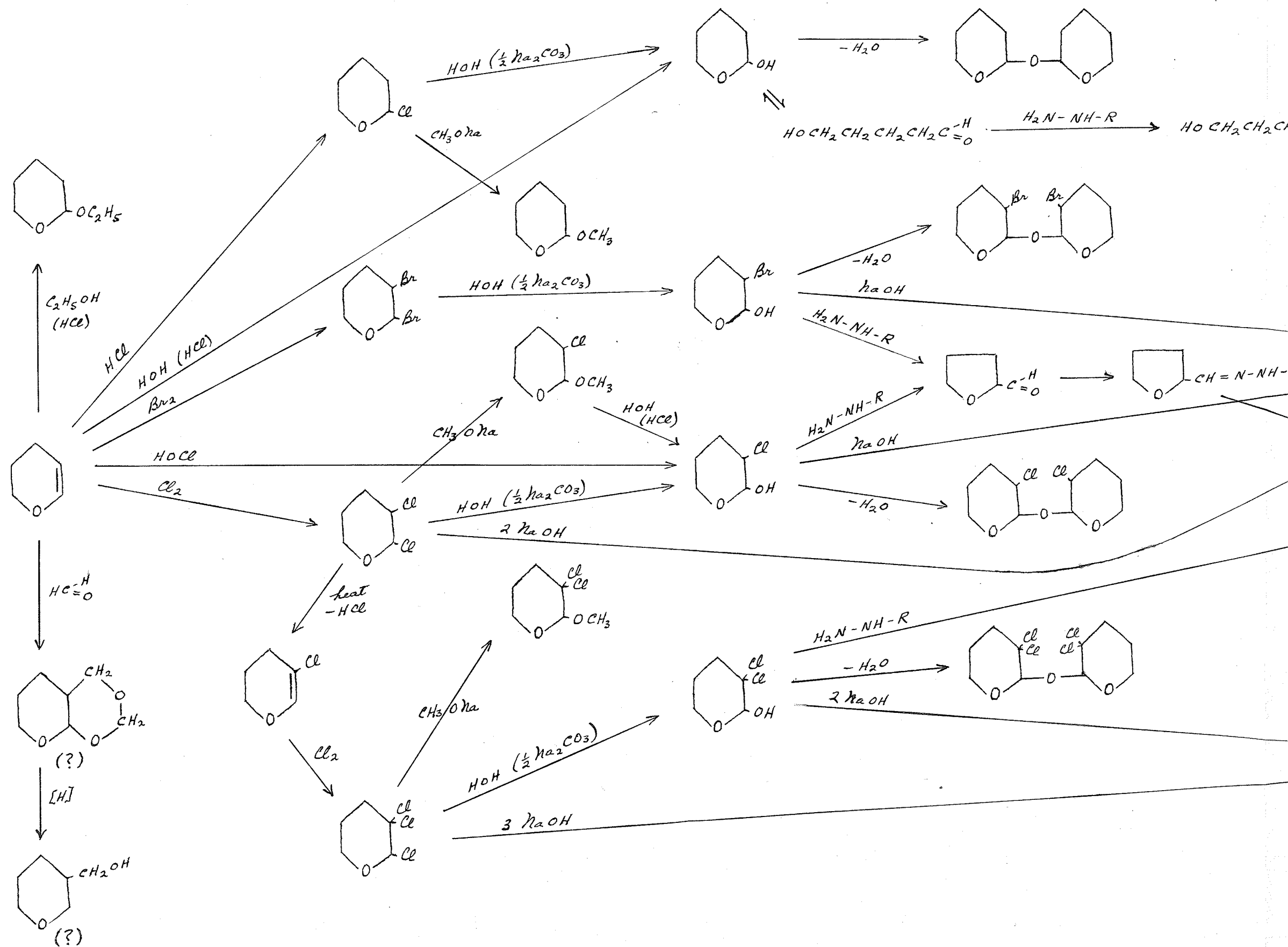


A reaction between dihydropyran and formaldehyde, suggested by the work of Beets and others (4, 5, 6, 7, 13, 15) on certain dienes, was also attempted. It was found to go readily but the isolation of pure products has not as yet been accomplished.

All the reactions studied during the course of this investigation are summarized on the flow-sheet following.

Part of this work has been published in the Canadian Journal of Chemistry, March 1956. A reprint is attached.

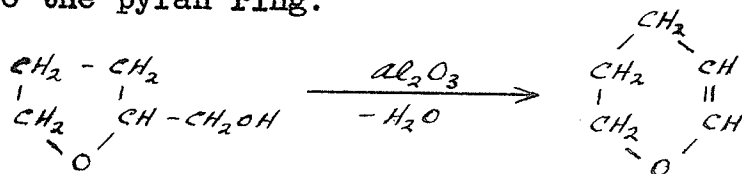




LITERATURE REVIEW

Dihdropyran and its Reactions

Dihdropyran can be prepared by passing the vapor of tetrahydrofurfuryl alcohol over heated alumina, the method originally used by Paul (40). The alcohol loses water and a methylenic transposition enlarges the furan ring to the pyran ring:

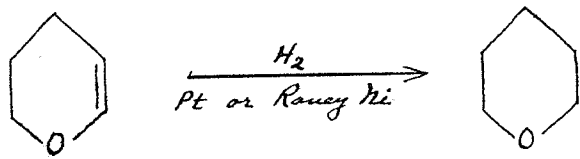
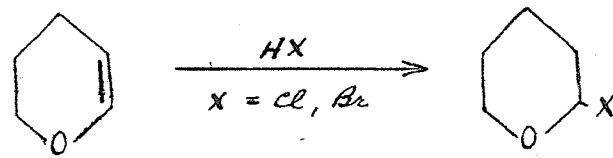
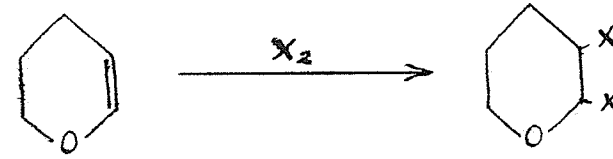
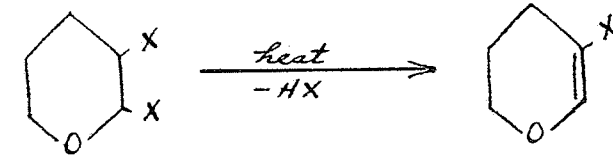
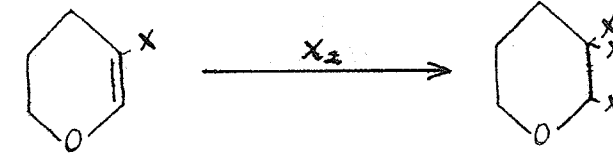
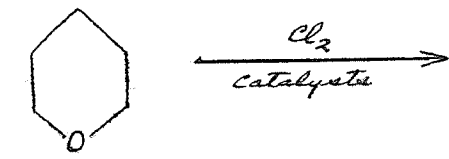


The substance is now commercially available.

It is a mobile colorless liquid which boils at 86° at normal pressure. It is only slightly soluble in water but soluble in most organic solvents. It is very reactive, showing 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 are useful reagents in syntheses.

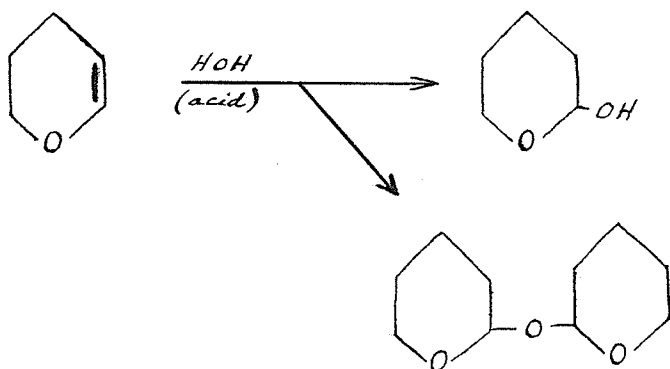
The literature on the reactions of dihydropyran and its derivatives is becoming voluminous. The most recent review of the field is one by Jones and Taylor (32) in 1950. A number of new reactions have

been studied since then. The following list gives a picture of the chemistry of dihydropyran and its more immediate derivatives:

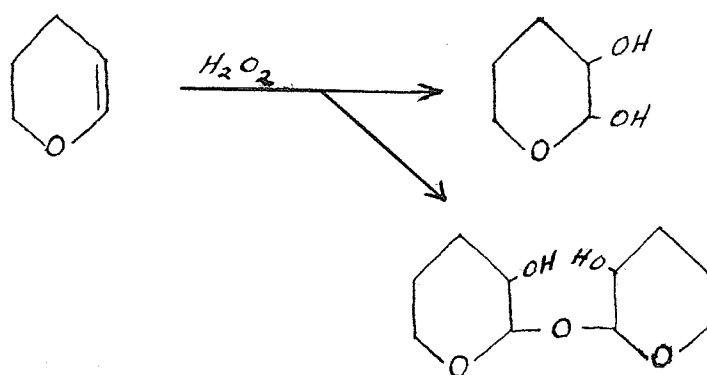
<u>Reaction</u>	<u>References</u>
 <chem>C1=CCCCC1.O>>C1CCCCC1</chem>	(2), (40)
 <chem>C1=CCCCC1.HX>>C1CCC(CC1)X</chem>	(38), (42), (45)
 <chem>C1=CCCCC1.X2>>C1CCC(CC1)X2</chem>	(23), (36), (42) (45), (48)
 <chem>C1CCC(CC1)X2>>C1=CCCCC1</chem>	(23), (36), (42) (45), (48)
 <chem>C1CCC(CC1)X.X2>>C1CCC(CC1)X2</chem>	(23), (36), (69)
 <chem>C1CCCCC1.Cl2>>C1C(Cl)C(Cl)C(Cl)C1</chem>	several trichloro and tetrachloro substitution products (23)

Reaction

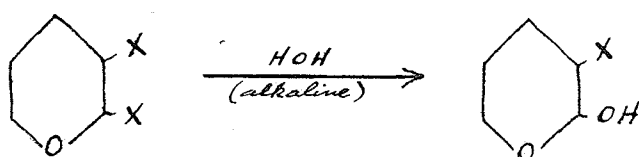
References



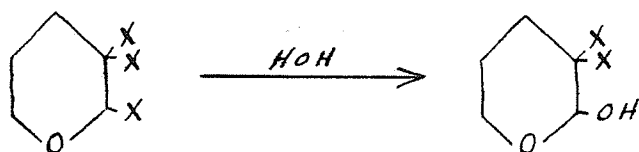
(41), (44), (65)



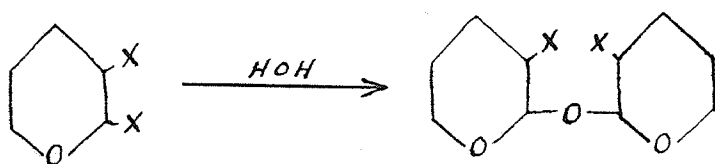
(27)



(23), (36), (45),
(48)



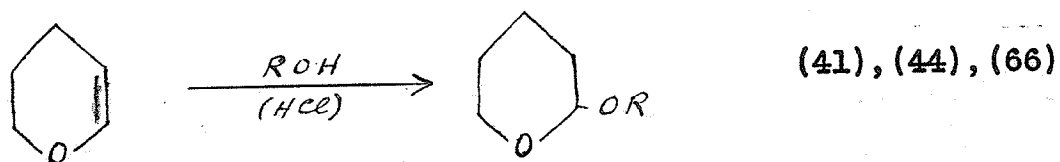
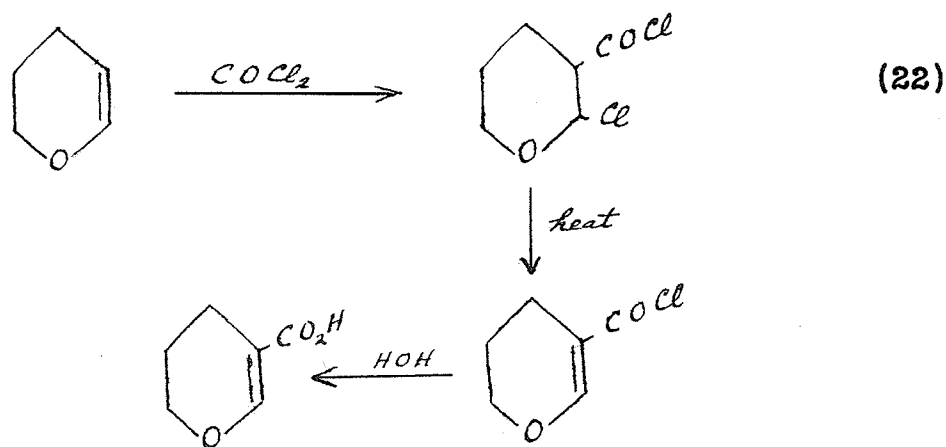
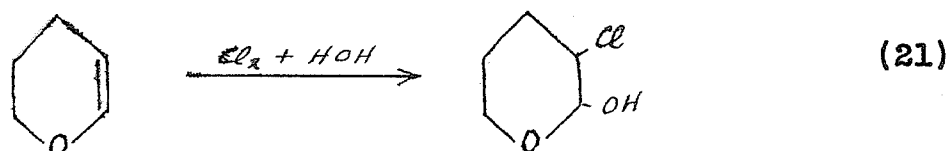
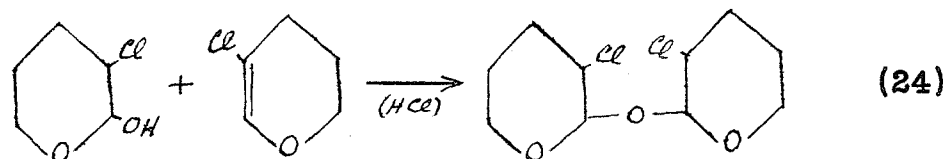
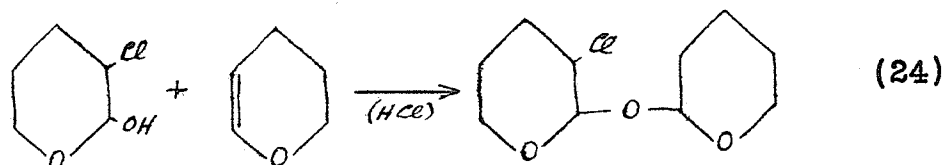
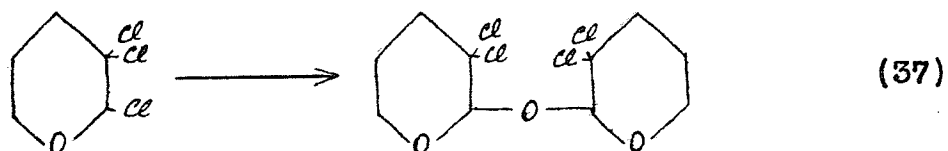
(36), (54), (55),
(69)



(38), (42),
(45), (48)

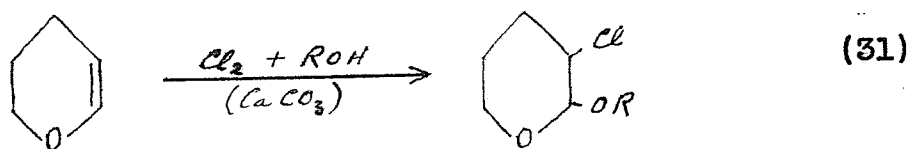
Reaction

References

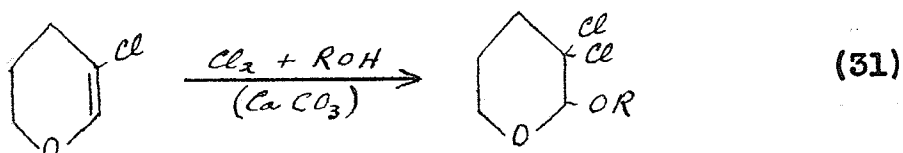


Reaction

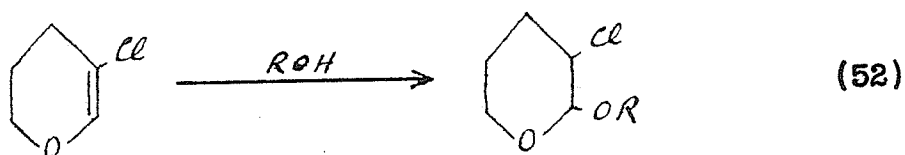
References



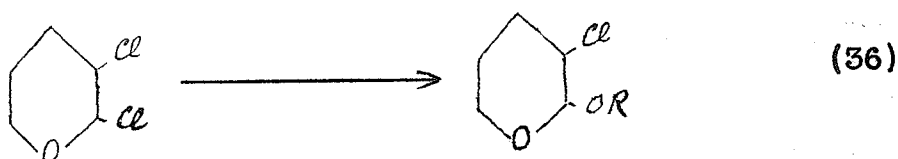
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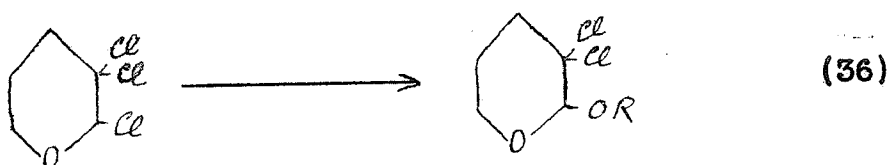
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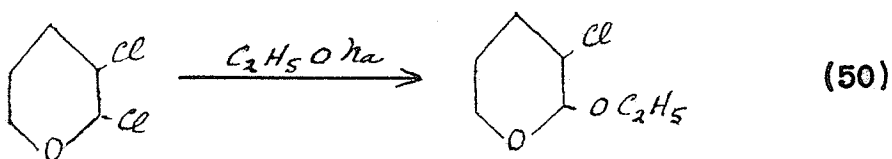
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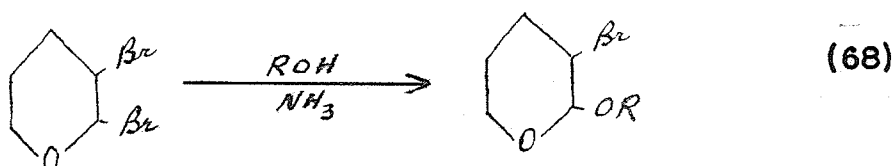
(36)



(36)



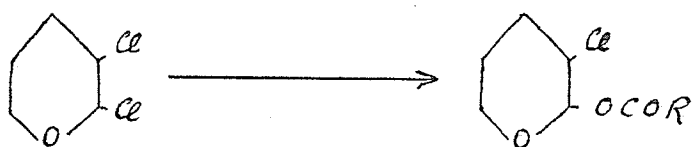
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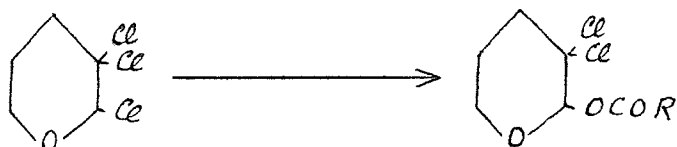
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Reaction

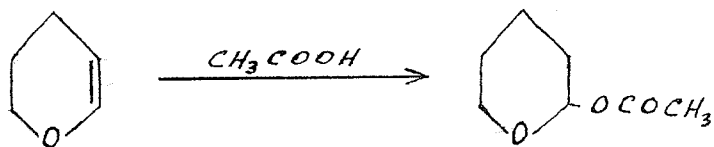
References



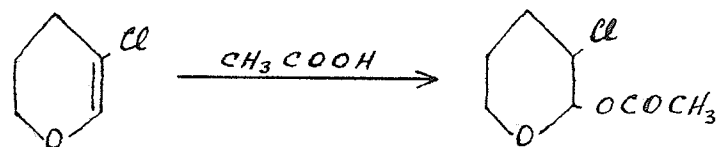
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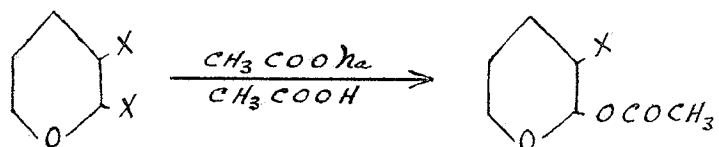
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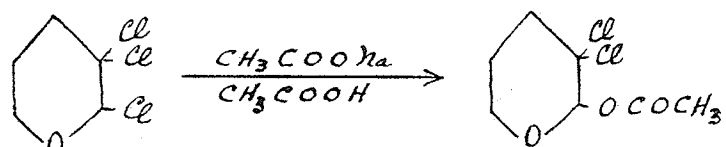
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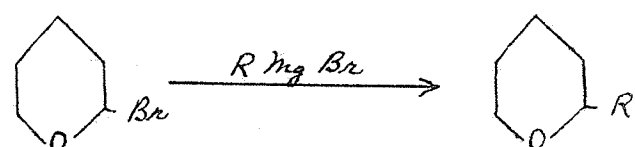
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(9)



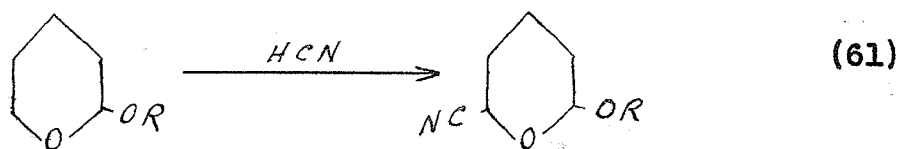
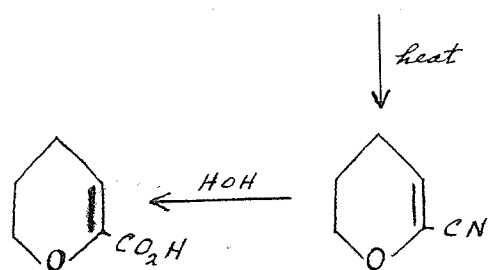
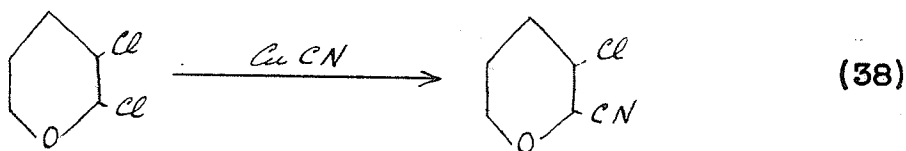
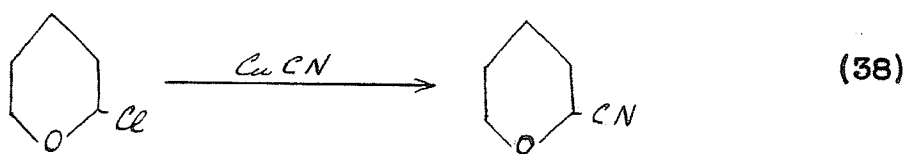
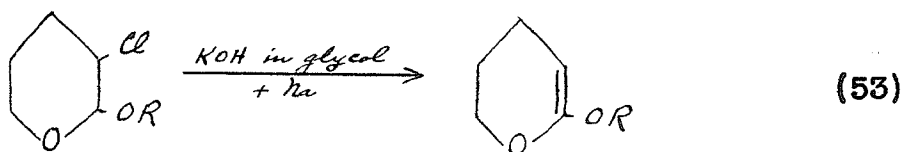
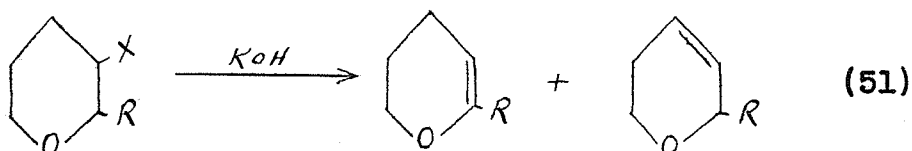
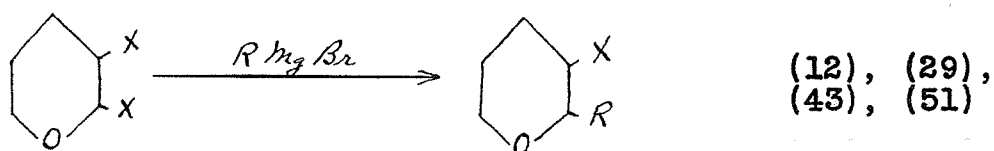
(9)



(43)

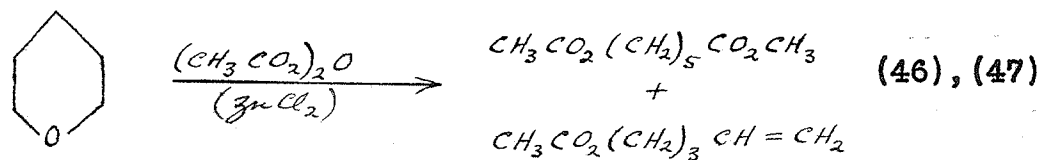
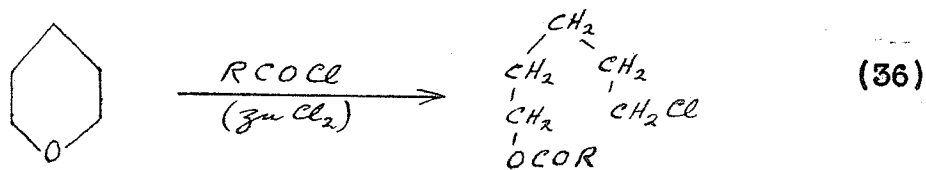
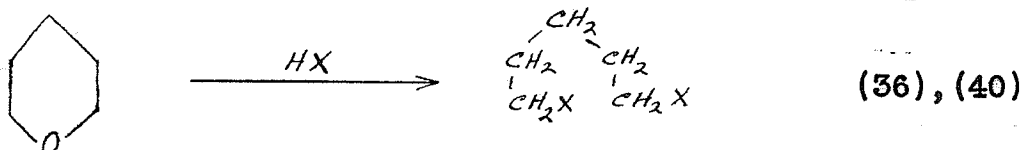
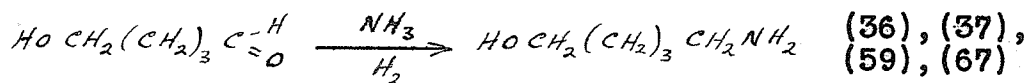
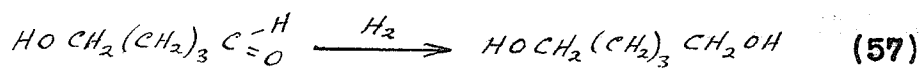
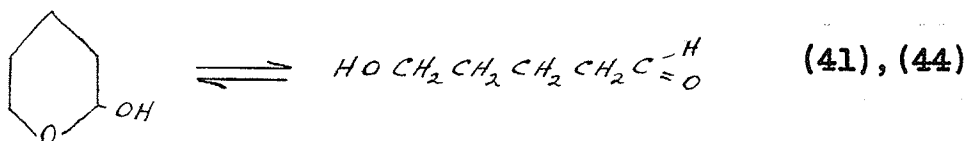
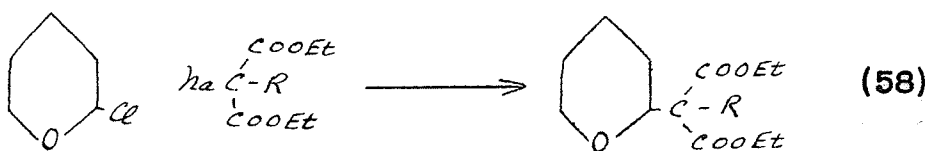
Reaction

References



Reaction

References

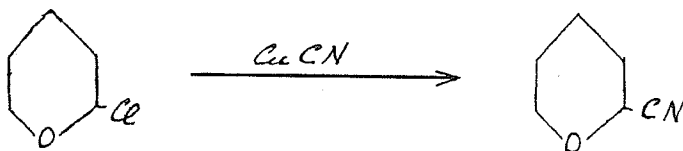


2-Chlorotetrahydropyran

The chemists of I.G. Farben (38) made this compound by passing dry hydrogen chloride gas into dihydropyran:



The product distilled at 42° at 11 mm. It was used to prepare 2-cyanotetrahydropyran:



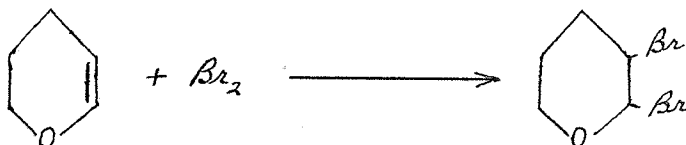
Schudel and Rice (58) used it in malonic ester condensations:



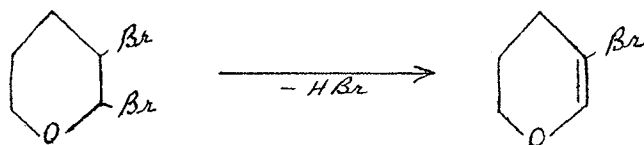
for R = H, Et, Ph, PrMeCH, iso-Pr, Bu, iso-Bu, and others.

2,3-Dibromotetrahydropyran

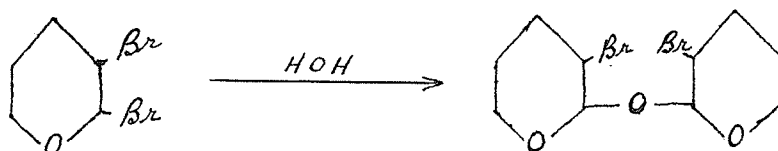
Paul (42, 45) added dry bromine to dihydropyran in ether or carbon tetrachloride solution at -15°. A vigorous reaction took place and a dibromide boiling at 96-98° at 9 mm. was distilled off.



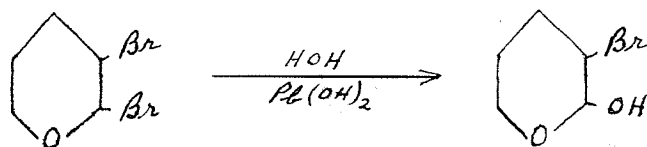
The product, a colorless liquid which fumed in air, could not be purified by distillation. Rectified slowly through a long column it decomposed to give 3-bromo-dihydropyran, a liquid boiling at 63° at 22 mm.



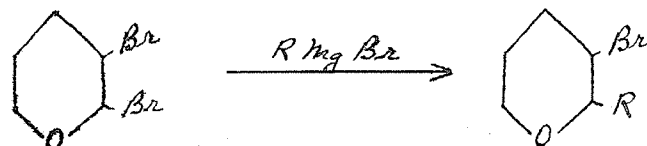
When the dibromide was left in contact with water for some time at room temperature, it formed a symmetrical ether:



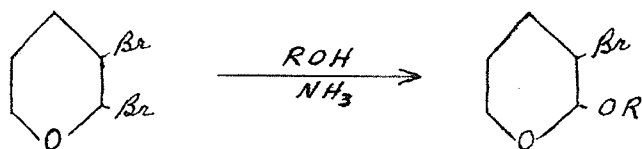
In the presence of an alkaline reagent, the hydrolysis gave the bromohydrin:



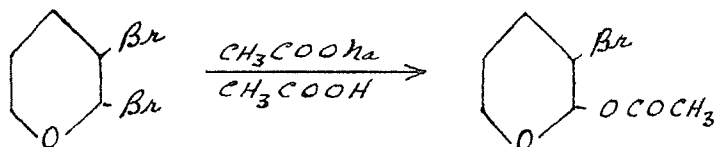
Paul (43) also used the dibromide with Grignard reagents to prepare 2-ethyl-3-bromo- and 2-phenyl-3-bromotetrahydropyran:



Woods and Sanders (68) treated the dibromide with anhydrous alcohols in liquid ammonia and isolated 2-alkoxy-3-bromotetrahydropyrans:



Bremner and Jones (9) treated it with anhydrous sodium acetate and acetic acid in acetic anhydride solution and isolated 2-acetoxy-3-bromotetrahydropyran:

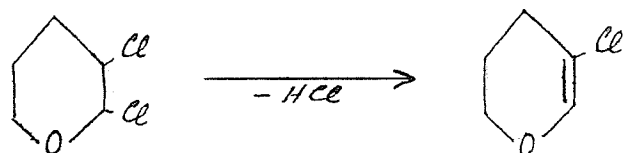


2,3-Dichlorotetrahydropyran

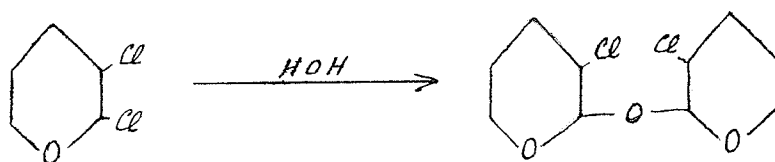
The preparation of this substance has been described by Paul (48) and by Hawkins and Bennett (23). Chlorine passed into dihydropyran at 0° was found to add rapidly to the double bond:



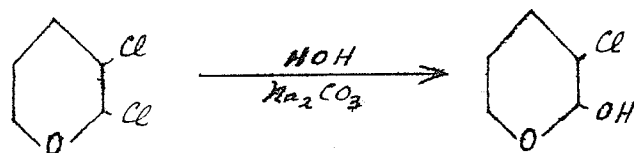
The product distilled at 89-90° at 20 mm. (74° at 11 mm.). It was a colorless, viscous liquid, which fumed in air. When distilled at normal pressure it lost hydrogen chloride to form 3-chlorodihydropyran:



Left in contact with water at room temperature it was converted (48) to the ditetrahydropyranyl ether:

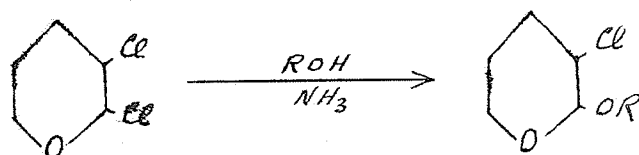


Hydrolysis in the presence of sodium or calcium carbonate (23) yielded the chlorohydrin:

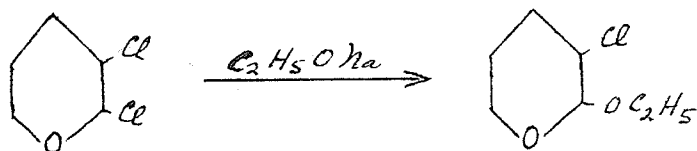


The I.G. Farben chemists (36) found that the Cl-atom in the 2-position was readily exchanged for -OR and -OCOR, but they reported no details.

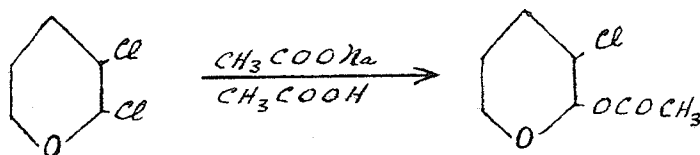
Woods and Sanders (68) prepared 2-alkoxy-3-chlorotetrahydropyrans by treating the dichloride with anhydrous alcohols in liquid ammonia:



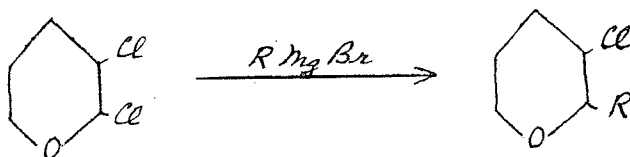
Quennehen and Normant (50) obtained 2-ethoxy-3-chlorotetrahydropyran by treating the dichloride with sodium ethylate:



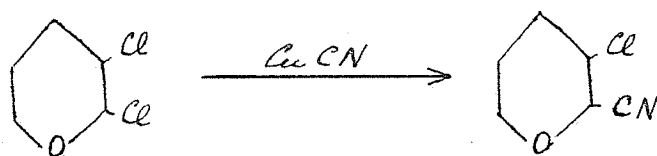
Bremner and Jones (9) prepared 2-acetoxy-3-chlorotetrahydropyran by treating the dichloride dissolved in acetic anhydride with anhydrous sodium acetate and acetic acid:



Riobe (51), Jacobson (29), and Crombie and Harper (12) used the dichloride in Grignard reactions to prepare 2-alkyl-3-chlorotetrahydropyrans:

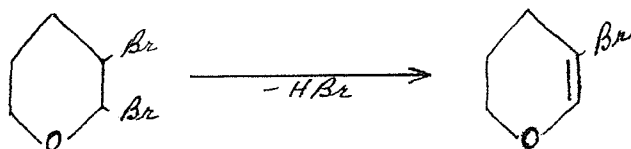


The I.G. Farben chemists (38) treated it with cuprous cyanide to prepare the 2-cyano-derivative:



3-Bromodihydropyran

Paul (42, 45) obtained this substance by slow distillation of the dibromide at atmospheric pressure through a long column:

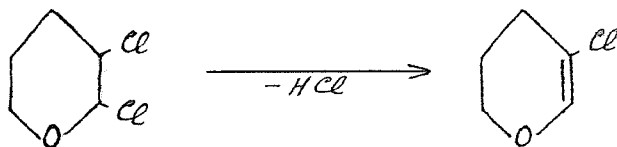


It distilled at 63° at 22 mm. Its olefinic activity was found to be much less than that of dihydropyran.

The I.G. Farben chemists (36) were not able to isolate this substance by simple distillation of the dibromide. They found that hydrogen bromide was lost rapidly but the product resinified.

3-Chlorodihydropyran

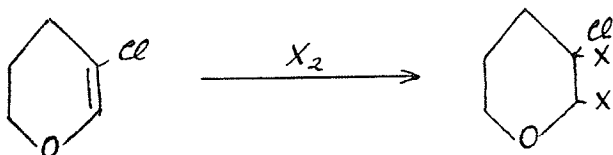
This substance has been reported by Paul (48), by Hawkins and Bennett (23) and by the I.G. Farben chemists (36, 37). It was obtained by slow distillation of the dichloride at atmospheric pressure:



It was found to be a stable, colorless liquid, which boiled at 141° at 760 mm. According to the I.G. Farben chemists (37), after standing for some time it became

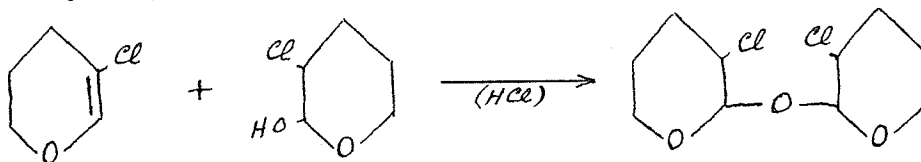
acid in reaction due to impurities which they were not able to remove.

Although it is not an active olefinic compound, the I.G. Farben chemists (36) found that it added either chlorine or bromine in exothermic reactions to form trihalides:

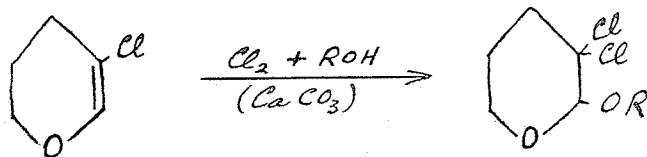


A number of other addition reactions have also been reported.

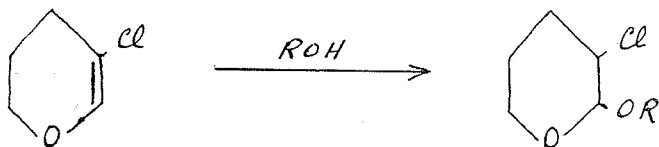
Hawkins and Bennett (24) found that in the presence of a trace of hydrogen chloride 3-chlorodihydropyran would add 3-chlorotetrahydropyran-2-ol to form the ditetrahydropyranyl ether:



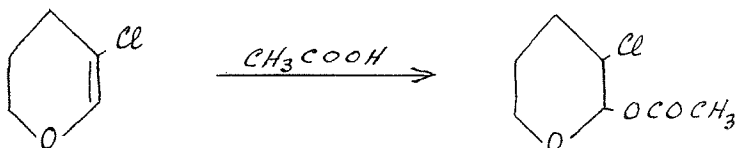
Jones and Bremner (31) treated it with chlorine and alcohols in the presence of calcium carbonate and produced 2-alkoxy-3,3-dichlorotetrahydropyrans:



Riobe (52) prepared 2-alkoxy-3-chlorotetrahydropyrans by treating 3-chlorodihydropyran with the calculated quantity of the alcohol:

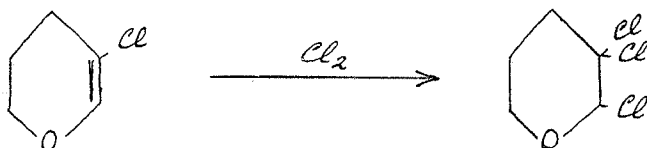


Bremner and Jones (10) treated it with acetic acid and isolated 2-acetoxy-3-chlorotetrahydropyran:



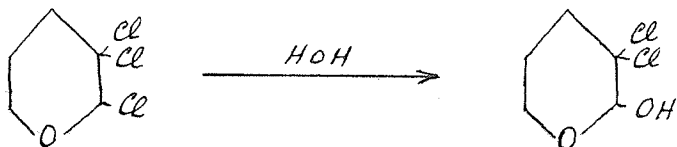
2,3,3-Trichlorotetrahydropyran

This substance was prepared by Hawkins and Bennett (23) and by the I.G. Farben chemists (36) by passing chlorine into 3-chlorodihydropyran:

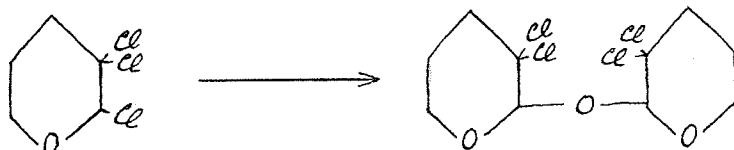


The product distilled at 86° at 8 mm. (92-94° at 15 mm.) and set to a solid melting at 31-32°.

The I.G. Farben chemists (36) obtained from it the 2-hydroxy derivative on mere shaking with water:

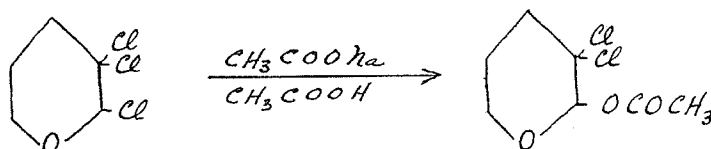


They also prepared (37) the corresponding ditetrahydropyranyl ether:



As in the case of the dichloride, they reported (36) that the Cl-atom in the 2-position is readily exchanged for -OR and for -OCOR but gave no details.

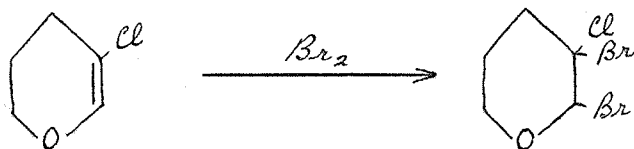
Bremner and Jones (9) treated the trichloride with anhydrous sodium acetate and acetic acid and produced 2-acetoxy-3,3-dichlorotetrahydropyran:



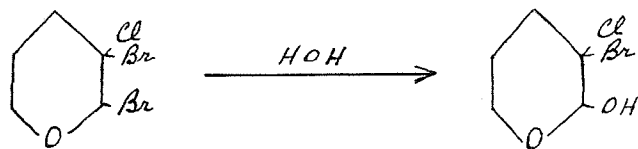
Riobe (55) isolated a liquid isomer of the trichloride which hydrolyzed to give the same 2-hydroxy derivative as the trichloride prepared by the earlier workers.

2,3-Dibromo-3-chlorotetrahydropyran

The I.G. Farben chemists (36) prepared this substance by adding bromine to 3-chlorodihydropyran:



The product was distilled at 125-127° at 20 mm. It formed a 2-hydroxy derivative on shaking with water:

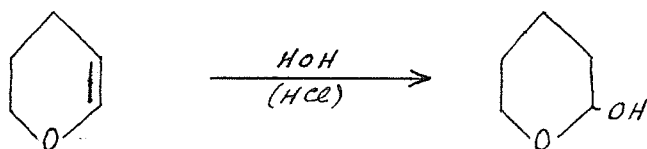


The Tetrahydropyran-2-ols

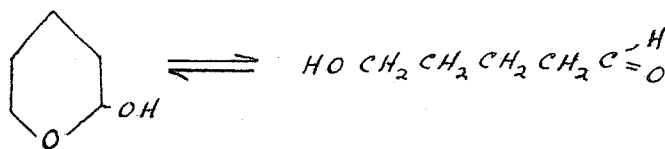
A number of the reactions of these substances have been given special study in the present work. Their known properties, as described in the literature, are summarized in the following paragraphs.

Tetrahydropyran-2-ol

This substance was first prepared by Paul (41, 44) by treating dihydropyran with a very dilute hydrochloric acid solution:

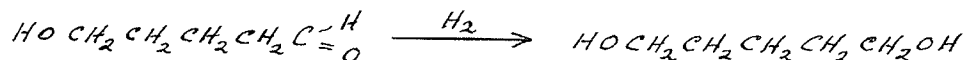


The product distilled at 80-81° at 16 mm. It had aldehyde properties, giving Schiff's, Fehling's, and Tollens' tests. Paul ascribed these properties to an equilibrium with an open-chain aldehyde form:

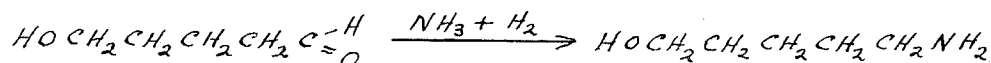


He prepared an oxime, m.p. 92-93°. Woods and Sanders (67) and Wilson (63) prepared a 2,4-dinitrophenylhydrazone, the former giving m.p. 109°, the latter m.p. 112-113°.

By catalytic hydrogenation, Schniepp and Geller (57) converted it to 1,5-pentanediol:



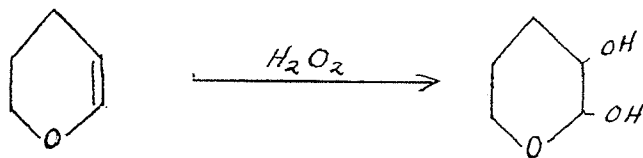
By treatment with liquid ammonia and hydrogen, Woods and Sanders (67) prepared an aminoalcohol:



The I.G. Farben chemists (36, 37) had carried out the latter reaction also with amines.

Tetrahydropyran-2,3-diol

Hurd and Kelso (27) prepared this substance by hydroxylation of dihydropyran, using hydrogen peroxide in tert. butyl alcohol, with osmium tetroxide as catalyst:



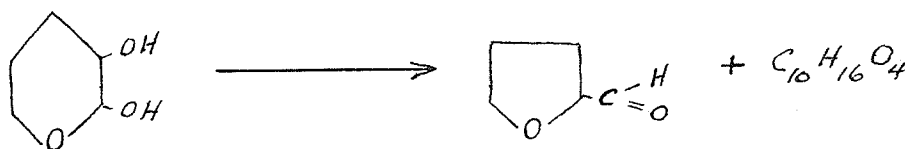
The product was a high-boiling liquid, which decomposed when attempts were made to distil it, even at low pressures. It was found to be soluble in water and in

organic solvents. It reduced Benedict's solution at 90°. It gave a 3,5-dinitrobenzoate, m.p. 174-175°, and a 2,4-dinitrophenylosazone, m.p. 242°.

Hurd and Edwards (26) prepared a 2,4-dinitrophenylhydrazone, m.p. 132-133°.

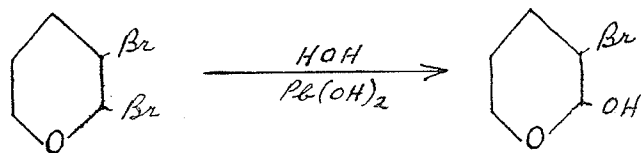
Hurd and Edwards (26) also subjected the diol to heat under reduced pressure. At 150° and 1 mm. pressure it lost water and yielded tetrahydrofurfural and two crystalline isomers, m.p. 103° and 190°, of formula

$C_{10}H_{16}O_4$:



3-Bromotetrahydropyran-2-ol

This substance was first prepared by Paul (45) by treating crude 2,3-dibromotetrahydropyran with water containing suspended lead hydroxide:

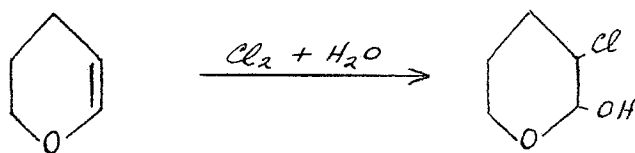


He isolated the product as a crystalline solid, m.p. 79-80°. He found that it reduced Fehling's solution when hot and ammoniacal silver nitrate, but did not affect Schiff's reagent. He attempted, without success,

to prepare a phenylhydrazone. With phenylhydrazine in ether, it gave him crystals of phenylhydrazine hydrobromide. He concluded that it lost hydrogen bromide more readily than it acted as an aldehyde. Titration with sodium hydroxide showed that it neutralized an alkali like a monobasic acid.

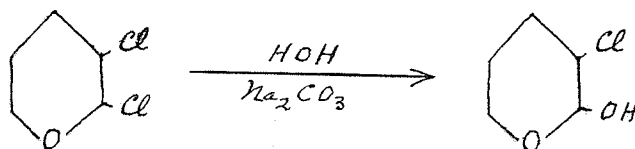
3-Chlorotetrahydropyran-2-ol

Hawkins and Bennett (21) obtained this substance by passing chlorine into dihydropyran kept suspended in water by stirring:

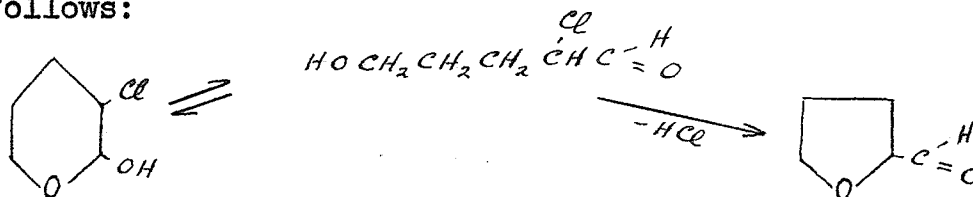


The product distilled at $95-100^\circ$ at 2 mm. and set to crystals melting at 64° . It did not reduce bromine water in the cold, nor Schiff's reagent, nor ammoniacal silver nitrate, but reduced hot Fehling's solution.

Hawkins and Bennett (23) also prepared this chlorohydrin by adding 2,3-dichlorotetrahydropyran to water containing dissolved sodium carbonate or suspended calcium carbonate:

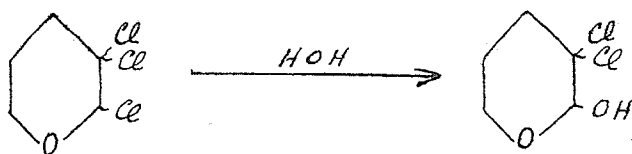


Paul (48), in attempting to prepare the substance by alkaline hydrolysis of the dichloride, obtained an aldehydic solution from which he prepared the oxime of tetrahydrofurfural. He explained the reaction as follows:



3,3-Dichlorotetrahydropyran-2-ol

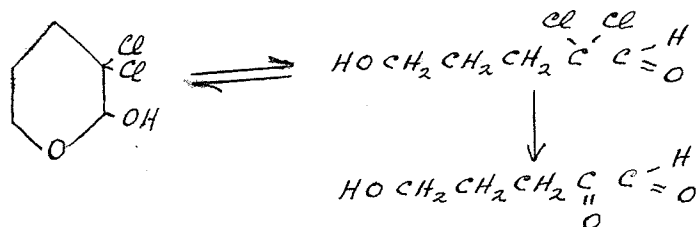
The I.G. Farben chemists (36) obtained this substance by shaking the trichloride with water:



The product distilled at 122-124° at 15 mm. and set to crystals of m.p. 90°. It was found to be insoluble in water and not aldehydic.

Riobe (54, 55) found that it crystallized as a hemihydrate of melting point 85.5°, according to one report, or 83.5°, according to the other report. He found also that in aqueous solution it was quite aldehydic, reducing Schiff's reagent and ammoniacal silver nitrate and giving crystalline derivatives characteristic of aldehydes. He isolated a bis-semi-

carbazone melting at 258° and a bis-2,4-dinitrophenylhydrazone melting at 121°, according to one report, or 216°, according to the other report. From analyses he concluded that these were derivatives of 5-hydroxy-2-ketovaleric aldehyde formed as follows:

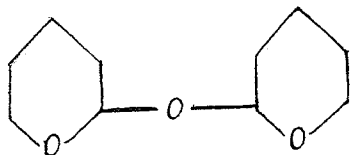


Ether Derivatives of the Tetrahydropyran-2-ols

Ditetrahydropyranyl Ethers

These are usually by-products whenever the tetrahydropyran-2-ols are prepared. The following have been reported in the literature:

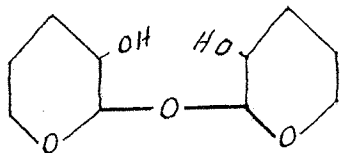
(a)



This substance was obtained as a by-product when Paul (44) prepared tetrahydropyran-2-ol.

It is a liquid boiling at 106-110° at 12 mm. Paul found that it was easily hydrolyzed by dilute acids to form tetrahydropyran-2-ol.

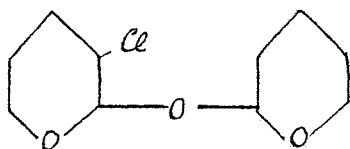
(b)



Hurd and Kelso (27) obtained this ether as a by-product in their preparation of tetrahydropyran-2,3-diol. It was

found to be a crystalline solid melting at 142-143° and soluble in water. It formed a 3,5-dinitrobenzoate, m.p. 245-246°. Warming it with dilute hydrochloric acid at 70° converted it to tetrahydropyran-2,3-diol.

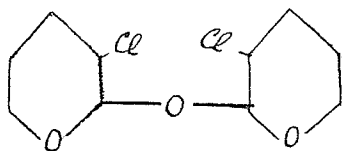
(c)



This substance was prepared by Hawkins and Bennett (24) by dissolving 3-chlorotetrahydropyran-2-ol in

dihydropyran and saturating the solution with hydrogen chloride gas. The product boiled at 115-121° at 2.5 mm.

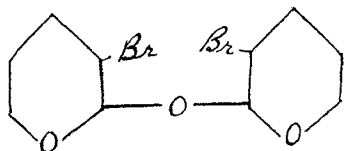
(d)



Paul (48) obtained this substance when he left 2,3-dichlorotetrahydropyran in contact with water

for some time. It was found to be a solid of m.p. 108°. Hawkins and Bennett (24) made it by dissolving 3-chlorotetrahydropyran-2-ol in 3-chlorodihydropyran and saturating the solution with hydrogen chloride gas. They found that it resisted hydrolysis by hot water and did not react with alcoholic potash, nor with sodium ethoxide, nor with the sodio-derivative of diethyl malonate.

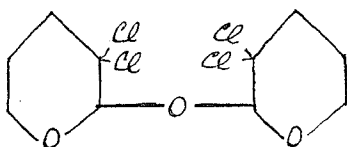
(e)



Paul (42) obtained this substance by leaving 2,3-dibromotetrahydropyran in contact with water for

some time. It was found to be a solid melting at 110° , which was hydrolyzed only slowly by dilute acids.

(f)

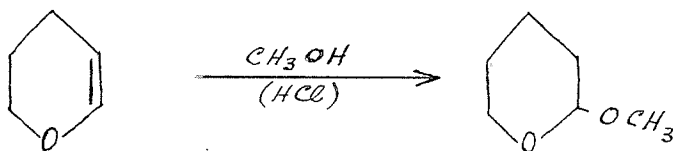


This substance was reported by the I.G. Farben chemists (37) as a product of the basic hydrolysis of

2,3,3-trichlorotetrahydropyran. It was obtained as a solid melting at $136-137^{\circ}$.

Alkyl Tetrahydropyranyl Ethers

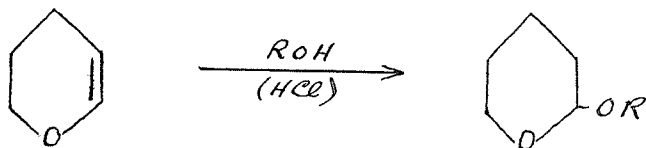
Paul (41, 44) prepared the first of these, 2-methoxytetrahydropyran, by the addition of methanol to dihydropyran, in the presence of a trace of hydrogen chloride:



The product distilled at $128-129^{\circ}$ at atmospheric pressure. It was found to be easily hydrolyzed by dilute acids at ordinary temperatures.

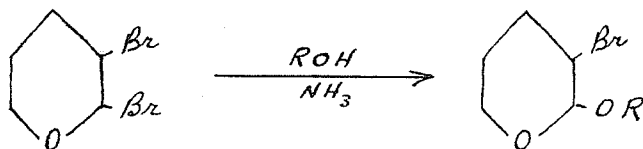
In recent years a number of other similar ethers have been prepared by a variety of methods.

Woods and Kramer (66) used Paul's method to prepare a series of ethers like Paul's:

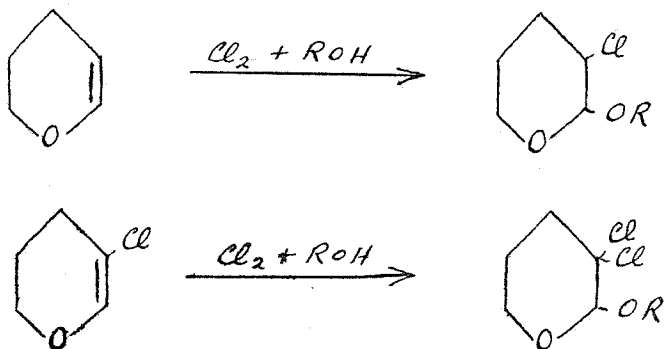


The series included methyl, ethyl, n-propyl, n-butyl, allyl, phenyl, benzyl, and furfuryl tetrahydropyranyl ethers.

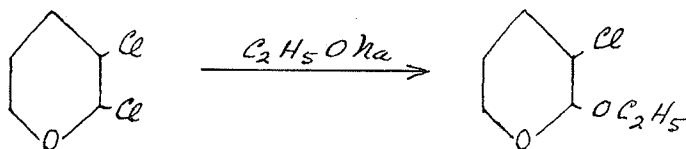
Woods and Sanders (68) prepared 2-alkoxy-3-bromo-tetrahydropyrans by treating 2,3-dibromotetrahydropyran with anhydrous alcohols in liquid ammonia:



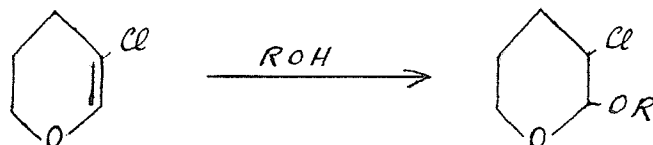
Jones and Bremner (31) prepared 2-alkoxy-3-chloro- and 2-alkoxy-3,3-dichlorotetrahydropyrans by treating dihydropyran and 3-chlorodihydropyran, respectively, with chlorine and anhydrous alcohol in the presence of basic reagents:



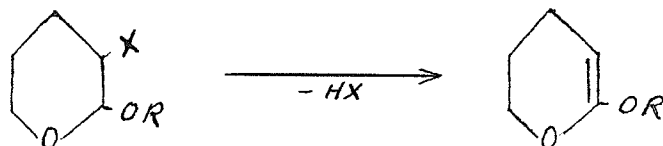
Quennehen and Normant (50) treated 2,3-dichlorotetrahydropyran with sodium ethylate to obtain 2-ethoxy-3-chlorotetrahydropyran:



Riobe (52) prepared a series of 2-alkoxy-3-chlorotetrahydropyrans by treating 3-chlorodihydropyran with the calculated quantity of alcohol:



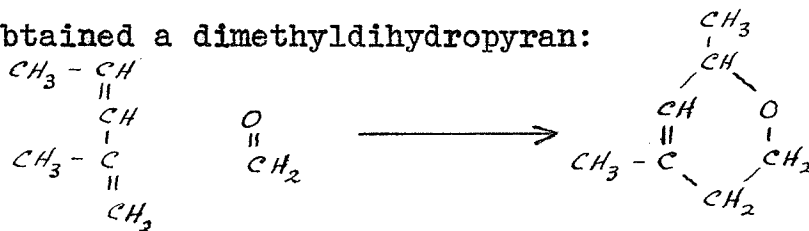
Woods and Sanders (68) and Riobe (53) have succeeded in removing hydrogen halide from 2-alkoxy-3-halotetrahydropyrans, by treatment with strong alkalis in absolute alcohols, to obtain 2-alkoxydihydropyrans:



The Reaction of Olefines with Formaldehyde

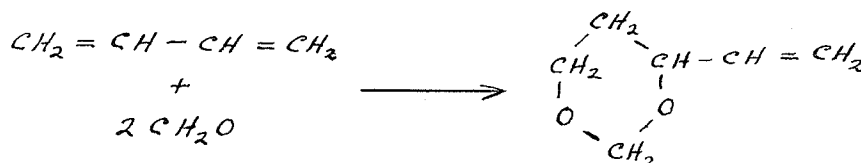
Formaldehyde reacts readily with certain dienes having a conjugated system of double bonds, particularly in the presence of acid catalysts. This reaction has been studied in recent years by a number of workers.

Gresham and Steadman (20) heated 2-methylpenta-
diene-1,3 with paraformaldehyde, without a catalyst,
and obtained a dimethyldihydropyran:

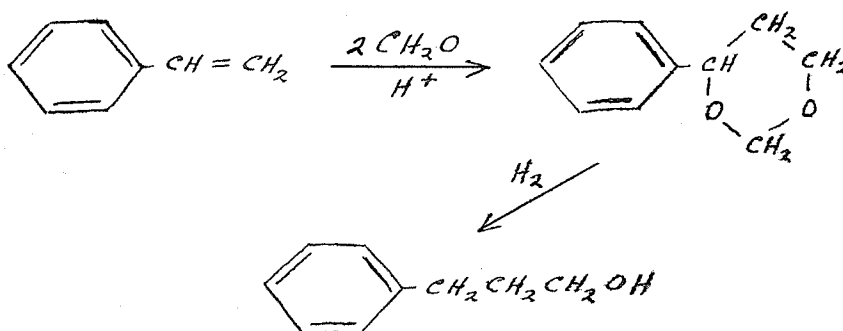


Butadiene and piperylene were found not to react with
formaldehyde under the same conditions.

Dermer, Kohn and Nelson (13), on the other hand,
treated butadiene with paraformaldehyde in the presence
of sulfuric acid and isolated 4-vinyl-m-dioxan:

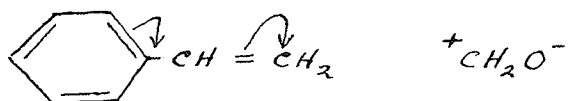
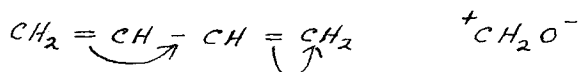


Beets and co-workers (4, 6, 7, 15) found that the
acid-catalyzed reaction goes readily with certain aryl-
alkenes, such as styrene, 1,2-dihydronaphthalene, and
indene. The products are m-dioxans which when hydrogenated
yield arylaliphatic alcohols. Thus with styrene:

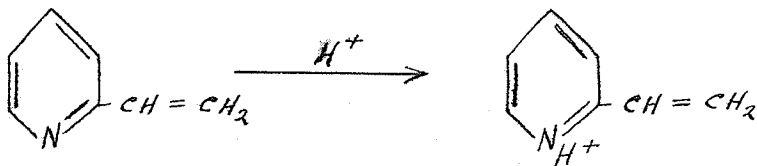


They found (5), however, that 2-vinylpyridine, β -bromostyrene and α -bromostyrene did not show this reaction.

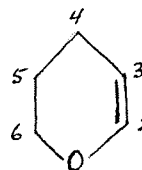
Beets and Drukker (5) attempted to explain why reaction takes place in some cases and not in others. They suggested that formaldehyde acts as an electrophilic reagent and attacks the diene molecule at a carbon atom which is somewhat negative. In some of the conjugated dienes one of the terminal carbon atoms becomes negative as a result of an electron shift produced by the approach of the formaldehyde molecule:



In other cases the formation of a negative centre at such a carbon atom is inhibited by some structural feature of the molecule. Thus in 2-vinylpyridine the positive nitrogen atom prevents the electron shift which would make the terminal carbon atom negative.

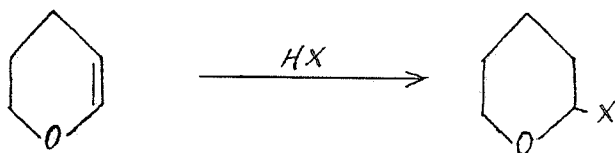


From theoretical considerations dihydropyran would be expected to have a negative carbon at the 3-position.



This has been shown to be the case.

Paul (42) and others (38) found, for instance, that dry hydrogen halide adds to the double bond as follows:

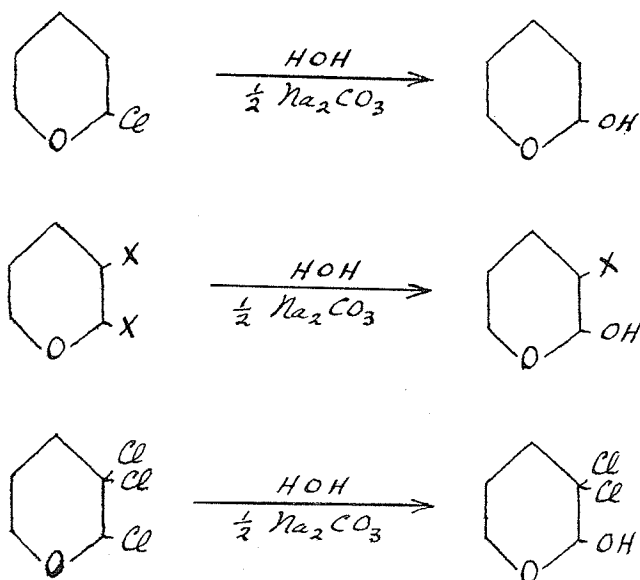


Other reactions confirm this tendency for positive ions to go to the 3-position. One would expect, therefore, that dihydropyran should be attacked by formaldehyde at the 3-position in much the same way as are conjugated dienes at a negative terminal carbon atom. In view of this it was decided to undertake an investigation of the reaction between dihydropyran and formaldehyde.

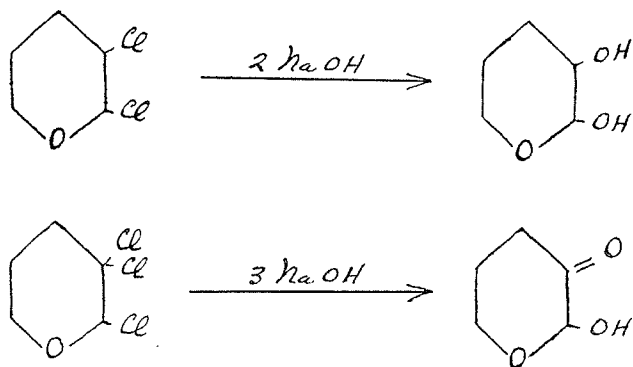
DISCUSSION OF RESULTS

Preparation of the Tetrahydropyran-2-ols

The methods used by earlier workers for preparing the tetrahydropyran-2-ols have been described (pages 24-28). In this investigation these substances were obtained by hydrolysis of the 2-halotetrahydropyrans, in the presence of a half mole proportion of sodium carbonate. This method, used by Hawkins and Bennett (23) to prepare 3-chlorotetrahydropyran-2-ol, was found to be generally applicable. It was very rapid with 2-chlorotetrahydropyran, slower with the 2,3-dihalides, and still slower with the 2,3,3-trichloride. In each case the halogen atom in the 2-position was replaced by hydroxyl:



When a larger proportion of sodium carbonate was used, or better sodium hydroxide, and more time was given, the halogen atoms in the 3-position were also substituted by hydroxyls:



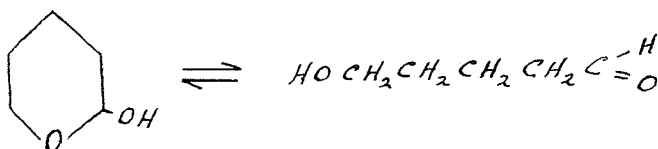
These two reactions will be discussed later under another heading (pages 44-50).

Aldehyde Properties of the Tetrahydropyran-2-ols

All the tetrahydropyran-2-ols have been reported to be more or less aldehydic.

Tetrahydropyran-2-ol

Paul (41, 44) found that tetrahydropyran-2-ol itself gave Schiff's, Fehling's, and Tollens' tests for aldehydes. He explained its aldehydic nature by postulating an equilibrium with δ -hydroxyvaleric aldehyde:

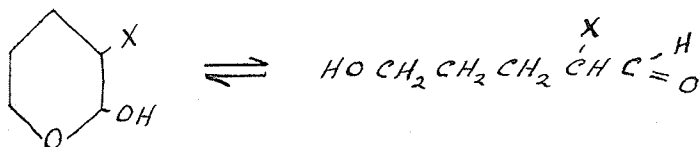


His view has since been confirmed by other workers, particularly by Schniepp and Geller (57) and Woods and Sanders (67). Paul (44) prepared a crystalline oxime and Woods and Sanders (67) and Wilson (63) prepared a 2,4-dinitrophenylhydrazone.

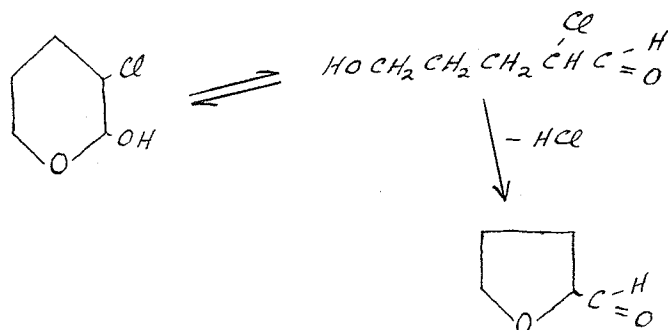
The 3-Halotetrahydropyran-2-ols

The 3-halotetrahydropyran-2-ols have also been found to be somewhat aldehydic. Paul (45) noted that 3-bromotetrahydropyran-2-ol reduced Fehling's solution when hot and ammoniacal silver nitrate but did not affect Schiff's reagent. Hawkins and Bennett (21) found that 3-chlorotetrahydropyran-2-ol also reduced hot Fehling's solution but did not affect Schiff's reagent nor ammoniacal silver nitrate.

Because of these aldehyde properties it has been assumed (36, 48) that the 3-halotetrahydropyran-2-ols also exist in equilibrium with a δ -hydroxyvaleric aldehyde form:



No crystalline derivatives of these postulated aldehyde forms have been reported. Paul (45) found that 3-bromotetrahydropyran-2-ol reacted rapidly with phenylhydrazine, but he succeeded in isolating only phenylhydrazine hydrobromide. In attempting to prepare 3-chlorotetrahydropyran-2-ol by alkaline hydrolysis of the 2,3-dichloride, Paul (48) obtained an aldehydic solution from which he made the liquid oxime of tetrahydrofurfural. He explained this reaction as follows:



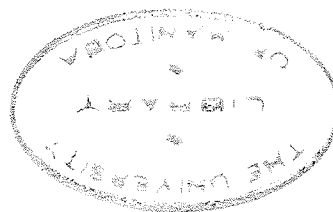
In view of their undoubted aldehyde properties, it seemed desirable to prepare crystalline derivatives of these halotetrahydropyrans and thus to determine the nature of the aldehydic substances derived from them. This has been accomplished. Both the chloro- and the bromotetrahydropyranol were found to react with substituted phenylhydrazines to give crystalline products. All of these products were found to be halogen-free. Moreover, with each of the phenylhydrazines the same phenylhydrazone was formed under the same conditions whether the chloro- or the bromo-

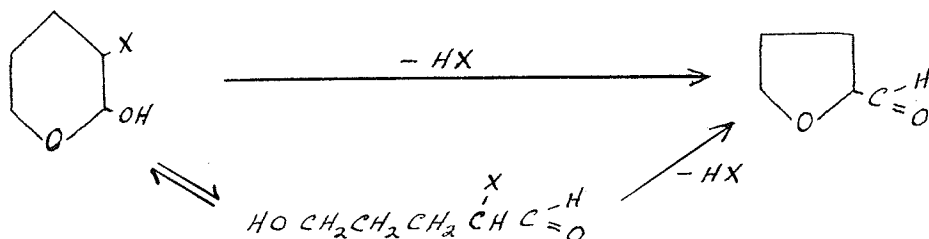
compound was used as the starting material. The following derivatives were thus obtained:

- (i) a 2,4-dinitrophenylhydrazone, m.p. 133-134°;
- (ii) a 2,4-dinitrophenylosazone, m.p. 242°;
- (iii) a p-nitrophenylhydrazone, m.p. 146°;
- (iv) a p-nitrophenylosazone, m.p. 246°;
- (v) a p-benzylphenylhydrazone, m.p. 74-75°.

In view of Paul's suggestion (48) that the chlorotetrahydropyranol tends to go over into tetrahydrofurfural, these derivatives were compared with corresponding products obtained from an authentic sample of tetrahydrofurfural prepared by the method of Scheibler, Sotscheck, and Friese (56). All were found to be identical with the tetrahydrofurfural derivatives. Except for the p-nitrophenylosazone, all these substances had been previously prepared by Hurd and Edwards (26) from tetrahydrofurfural obtained by heating tetrahydropyran-2,3-diol under reduced pressure.

Thus one can conclude that the 3-halotetrahydropyran-2-ols, in the presence of phenylhydrazines, lose hydrogen halide to go over into tetrahydrofurfural:

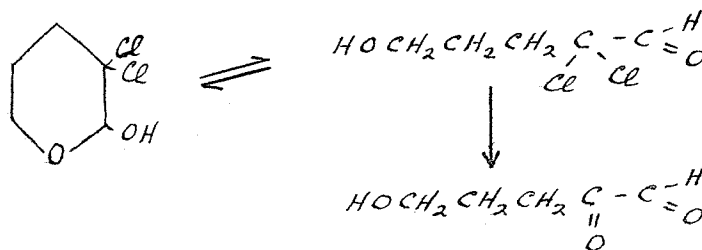




The postulated δ -hydroxyvaleric aldehyde forms may or may not be intermediates in this reaction.

3,3-Dichlorotetrahydropyran-2-ol

3,3-Dichlorotetrahydropyran-2-ol has been reported by the I.G. Farben chemists (36) to exist only in the cyclic form. Presumably this means that they detected no aldehyde properties. Riobe (54, 55), however, has found this substance quite aldehydic. It gave the usual tests for aldehydes with Schiff's reagent and ammoniacal silver nitrate. He obtained from it a crystalline bis-semicarbazone melting at 258° and a bis-2,4-dinitrophenylhydrazone melting at 121° , according to one report, or 216° , according to the other report. From analyses he concluded that these substances were derivatives of 5-hydroxy-2-ketovaleric aldehyde formed from the open chain form of the dichlorotetrahydropyranol:



The work here showed that the dichlorotetrahydro-pyranol does have some aldehyde properties, but not to the extent described by Riobe. It did not affect Schiff's reagent and ammoniacal silver nitrate but reduced Fehling's solution when warmed for some time. It gave crystalline derivatives with semicarbazide and with 2,4-dinitrophenylhydrazine. With the latter reagent it gave the orange-colored 2,4-dinitrophenylosazone, m.p. 242° , obtained also from the simpler halohydrins and from tetrahydrofurfural. With semicarbazide hydrochloride it gave a white solid whose melting point depended upon the temperature at which it was immersed in the melting point bath. When immersed at room temperature and heated rapidly it melted at 215° , with decomposition. When immersed at 210° , it melted at 225° , with decomposition. Three recrystallizations from water failed to change this melting point.

Apparently this kind of phenomenon has been observed with other semicarbazones. Campbell (11) has written "The melting points of many semicarbazones are dependent on the rate of heating, and frequently are not sharp."

Although the melting points reported by Riobe are not the same as those found here, there is little doubt that the same substances were prepared in each case. Their preparation here from other starting materials,

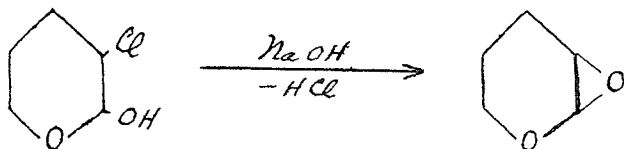
which suggest the structure they must have, has shown that they are derivatives of 5-hydroxy-2-ketovaleric aldehyde, as Riobe has suggested. This will be more evident later in this discussion (pages 51-54).

It is uncertain, however, whether there is a dichloro-hydroxyvaleric aldehyde in equilibrium with the ring structure of the dichlorotetrahydropyranol.

Reactions of the Halotetrahydropyran-2-ols
with Sodium Hydroxide

Paul (45) had found that 3-bromotetrahydropyran-2-ol could be titrated with sodium hydroxide and neutralized it like a monobasic acid. Apparently he made no effort to isolate an organic product from the reaction.

In the present work it was found that 3-chloro-tetrahydropyran-2-ol behaves similarly. A quantitative yield of sodium chloride could be isolated from the reaction. It was hoped at first that the organic product might be the oxide:

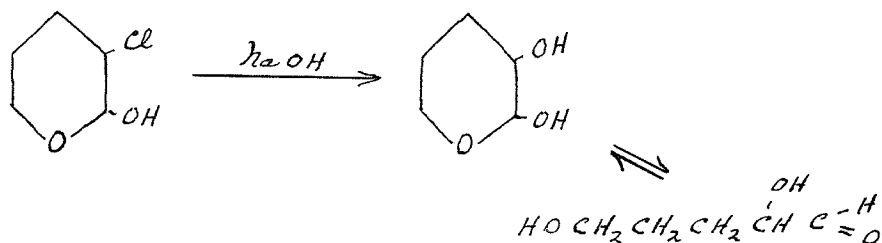


However, in view of the fact that an organic base when extracting hydrogen halide leaves tetrahydrofurfural

as residue, it seemed that the effect of sodium hydroxide might be the same and thus represent a convenient method of preparing tetrahydrofurfural.

The organic product from the reaction proved to be rather elusive. Organic solvents did not extract it in appreciable amounts from the aqueous mixture. Even continuous extraction proved inadequate. The water had to be removed almost completely, either by absorption on drying agents or better by evaporation, before the product could be taken up in organic solvent.

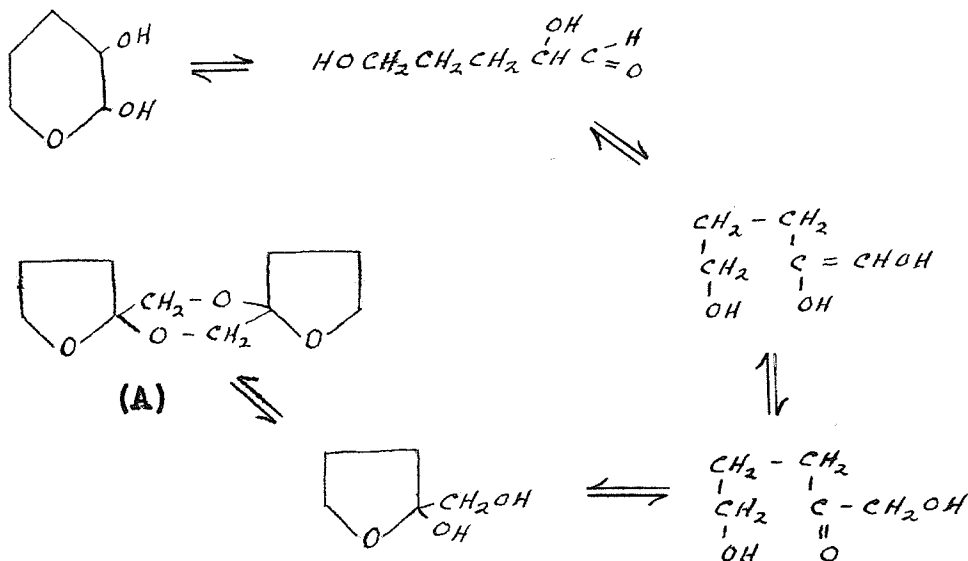
The nature of the product varied somewhat according to the conditions. When the reaction mixture was kept near room temperature throughout the process, a considerable portion of the product was soluble, with some difficulty, in ether. This ether-soluble substance was aldehydic, but was a higher boiling liquid than tetrahydrofurfural. It gave the same dinitrophenyl-osazone, m.p. 242° , but not the dinitrophenylhydrazone obtainable from that substance. It also gave a semi-carbazone, which proved to be identical with that obtained from 3,3-dichlorotetrahydropyran-2-ol (page 43). It readily reduced periodic acid to iodate and formed a 3,5-dinitrobenzoate, m.p. 174° . These properties suggested that the product was tetrahydropyran-2,3-diol, in equilibrium with a valeric aldehyde form:



This substance had been previously prepared by Hurd and Kelso (27) who made it by hydrogen peroxide oxidation of dihydropyran and obtained from it a dinitrophenyl-osazone, m.p. 242° , and a dinitrobenzoate, m.p. 174° .

When the reaction between the chlorotetrahydro-pyranol and sodium hydroxide was carried out at higher temperatures, less of the product was ether-soluble. Small fractions could be extracted with other solvents, but the bulk was soluble only in alcohol and water. Evaporation of the solvent in each case left a high boiling sirup which could not be purified by distillation. In one case a solid, m.p. 190° , precipitated from aqueous solution. In another case a chloroform extract yielded a solid, m.p. $101-102^\circ$. The properties of these substances indicated that they were the same $\text{C}_{10}\text{H}_{16}\text{O}_4$ materials as were reported by Hurd and Edwards (26), who obtained them by heating tetrahydro-pyran-2,3-diol. The lower melting of these two compounds was also obtained by Swadesh and Dunlop (62) from another source. The two groups of workers seemed

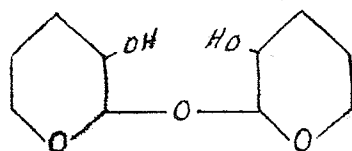
to agree that it has the structure (A) and that it was formed from the diol by the following route:



The structure of the higher melting compound has not been established. The indications are that it may be one of the following:

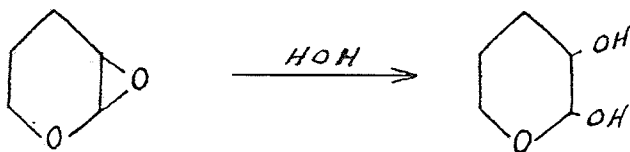


Hurd and Kelso (27) also isolated an ether of the structure:



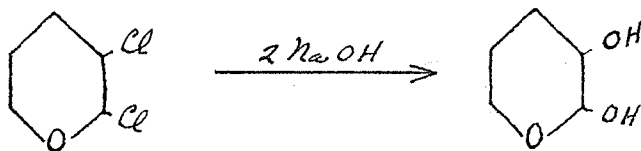
Our high boiling sirups were probably mixtures of a number of these compounds, and perhaps more complex structures.

No material was isolated that seemed to be the oxide. If formed at all, it was apparently unstable and hydrolyzed to form the diol:



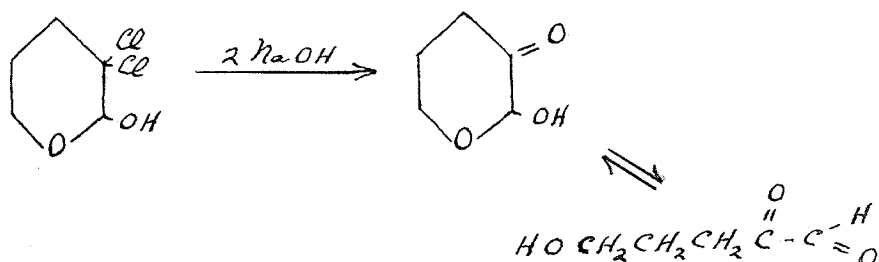
Other attempts by Paul and Tchelitcheff (49) and by Hurd and Edwards (26) to obtain the oxide have not been too successful.

Tetrahydropyran-2,3-diol has been prepared also by treating 2,3-dichlorotetrahydropyran with two mole proportions of sodium hydroxide, without isolating the intermediate chlorohydrin:

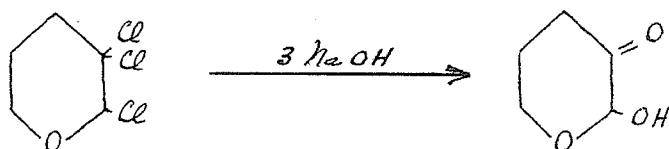


This was less laborious and gave a better overall yield.

3,3-Dichlorotetrahydropyran-2-ol, when dissolved in warm alcohol, could also be titrated with aqueous sodium hydroxide solution and neutralized two equivalents of the alkali. In this reaction it lost its entire halogen content. The product is thought to be 2-hydroxytetrahydropyran-3-one, in equilibrium with an open chain valeric aldehyde form:



The same product was obtained more expeditiously by treating 2,3,3-trichlorotetrahydropyran directly with three mole proportions of aqueous sodium hydroxide solution:

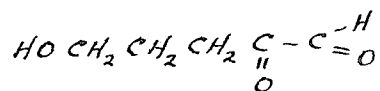


The reaction was slower than in the case of the dichloride. The mixture had to be warmed and stirred for several hours before the reaction was complete. Then evaporation of the water and extraction of the residue with absolute ethanol left a quantitative yield of sodium chloride. On evaporation of the alcoholic extract there remained a very viscous dark red halogen-free sirup, which could not be purified by distillation. It was used in the crude form for the preparation of derivatives.

One hope for the purification of this new substance is chromatographic adsorption. A serious difficulty in the application of this technique is the fact that the

material is practically insoluble in most organic solvents. A trial run using aluminum oxide as adsorbent showed that the substance is readily adsorbed from its solution in ethanol. No method was found, however, of recovering it from the adsorbent.

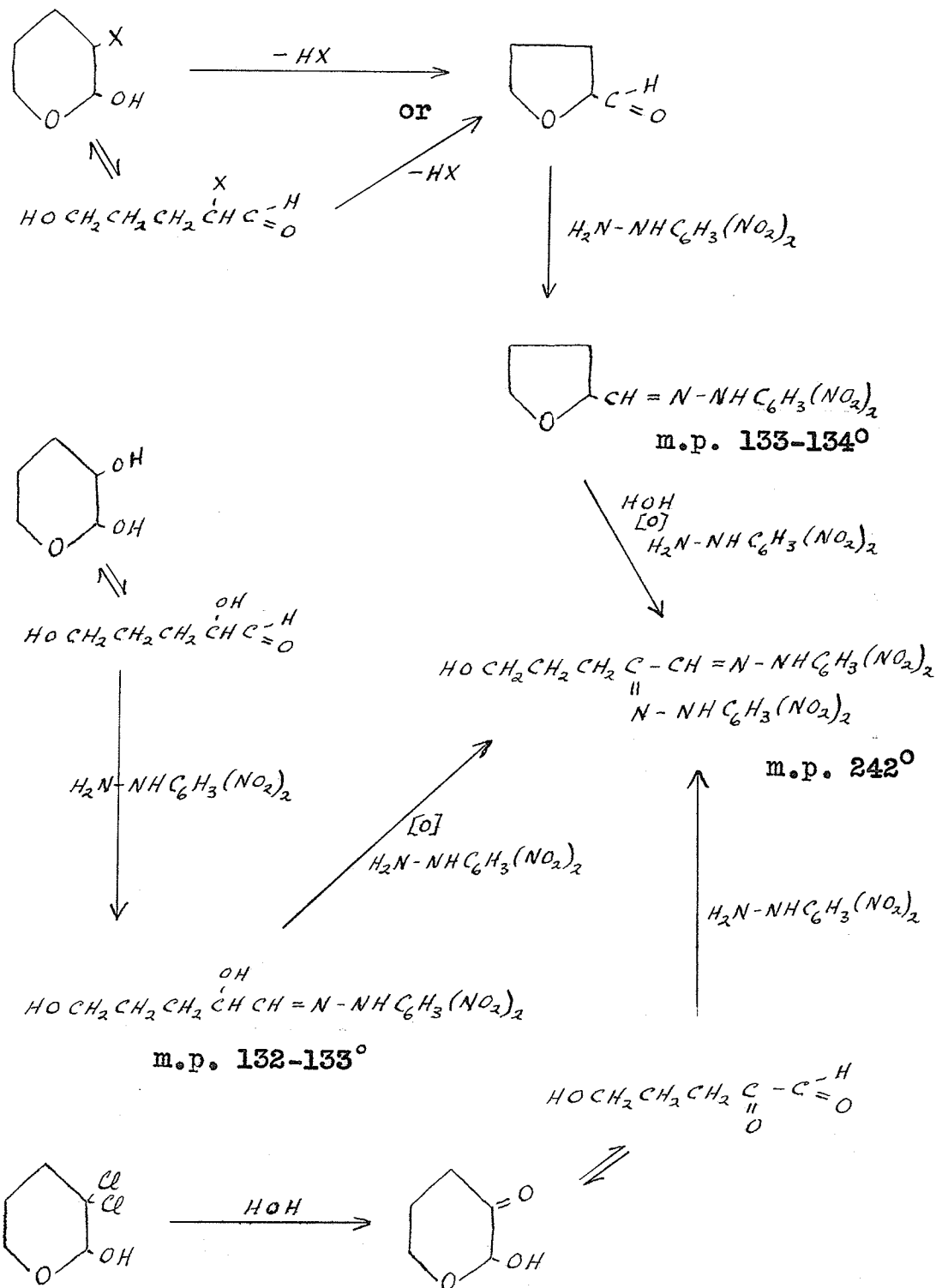
The presumed 2-hydroxytetrahydropyran-3-one was found to be very soluble in water and alcohol but insoluble in other common organic solvents. Its solution was strongly aldehydic, reducing Fehling's solution rapidly when warmed. With 2,4-dinitrophenylhydrazine it gave, near room temperature, an almost immediate precipitate of a 2,4-dinitrophenylosazone, m.p. 242°, of known structure (26, 27). Similarly, with p-nitrophenylhydrazine it gave a p-nitrophenylosazone, m.p. 246°, previously prepared in this work from tetrahydrofurfural and the halotetrahydropyrans. It also gave a disemicarbazone which had been obtained from 3,3-dichlorotetrahydropyran-2-ol and from tetrahydropyran-2,3-diol. The structures of these substances are obvious from the sources from which they have been obtained. They suggest an aldehyde of the structure



which is the open chain form of 2-hydroxytetrahydropyran-3-one. This will be apparent from the following sections.

2,4-Dinitrophenylhydrazones of Tetrahydrofurfural
and of the 3-Substituted Tetrahydropyran-2-ols

Tetrahydrofurfural forms a 2,4-dinitrophenylhydrazone of m.p. 133-134°, which on heating with excess reagent goes over into a 2,4-dinitrophenylosazone of m.p. 242°. The 3-halotetrahydropyran-2-ols, probably via tetrahydrofurfural, yield the same products. Tetrahydropyran-2,3-diol, according to Hurd and Edwards (26), forms a different 2,4-dinitrophenylhydrazone, m.p. 132-133°, not prepared here, but the same 2,4-dinitrophenylosazone. 3,3-Dichlorotetrahydropyran-2-ol and our presumed 2-hydroxytetrahydropyran-3-one give the same dinitrophenylosazone without an intermediate hydrazone. The latter compound forms the osazone particularly readily. The structures of these substances must be those pictured on the following page.

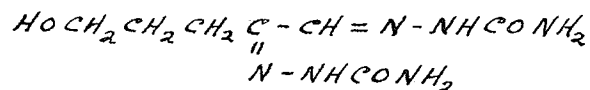


p-Nitrophenylhydrazones

Tetrahydrofurfural forms a p-nitrophenylhydrazone, m.p. 146°, which with excess reagent goes over into a p-nitrophenylosazone, m.p. 246°. The 3-halotetrahydropyran-2-ols give the same two derivatives. The osazone obtained here, like the 2,4-dinitrophenylosazone, m.p. 242°, must be a derivative of 2-keto-5-hydroxyvaleric aldehyde, the aldehyde form of 2-hydroxytetrahydropyran-3-one. Our new substance, presumed to be 2-hydroxytetrahydropyran-3-one, was found to give this derivative readily, a confirmation of the structure assigned to it.

Disemicarbazones

The presumed 2-hydroxytetrahydropyran-3-one gave readily a white crystalline semicarbazone which melted in the range 215-225°, the melting point depending on the temperature at which it was immersed. Analysis for nitrogen indicated that this was the expected disemicarbazone:

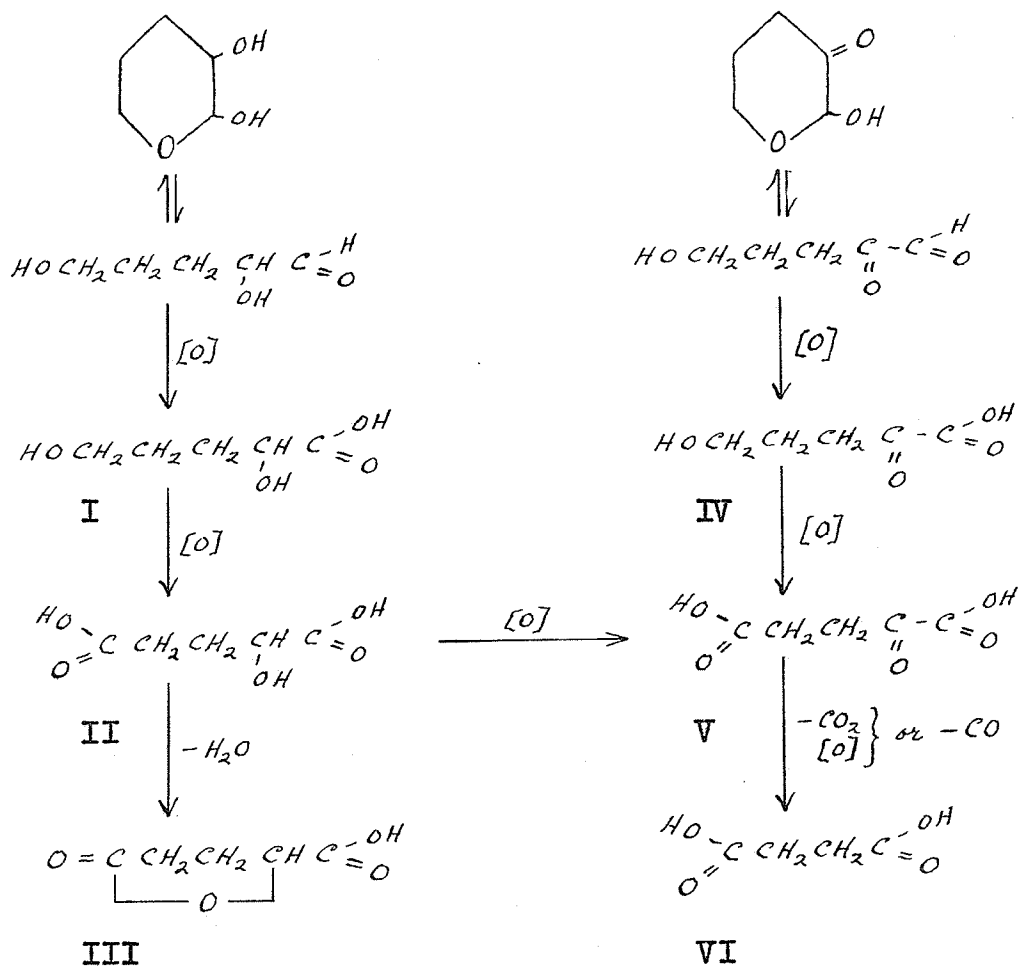


The same derivative was obtained, on longer heating of the reaction mixtures, from both tetrahydropyran-2,3-diol and 3,3-dichlorotetrahydropyran-2-ol. Undoubtedly, if time had permitted, the same substance could have been prepared from tetrahydrofurfural and the 3-halotetrahydropyran-2-ols.

McElvain (34) has listed a semicarbazone of tetrahydrofurfural of m.p. 166° but has not given the literature source. Presumably this is the mono-semicarbazone, which might be expected to go over into the disemicarbazone prepared here, just as the dinitrophenylhydrazine goes over into the osazone.

Oxidation Products from Tetrahydropyran-2,3-diol
and 2-Hydroxytetrahydropyran-3-one

Tetrahydropyran-2,3-diol and 2-hydroxytetrahydropyran-3-one might be expected to give a series of oxidation products such as the following:



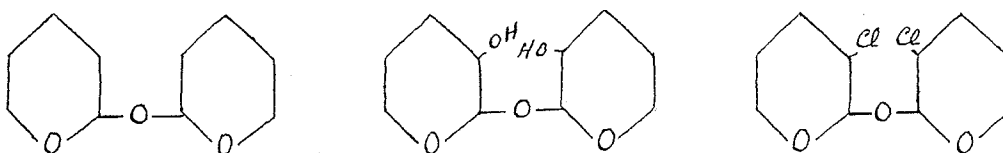
Substance II, α -hydroxyglutaric acid, and substance III, the corresponding lactonic acid, have been prepared by Ingold (28) by hydrolysis of α -bromoglutaric acid. Substance V, α -ketoglutaric acid, has been prepared by several methods (8, 18, 28, 64) and a number of its derivatives are known.

Permanganate oxidation, either alkaline or acid, of either tetrahydropyran-2,3-diol or 2-hydroxytetrahydropyran-3-one was found to yield substance VI, succinic acid. Apparently permanganate is too drastic a reagent to make possible the isolation of an intermediate product. The reaction indicates that α -ketoglutaric acid decarboxylates, or decarbonylates, readily.

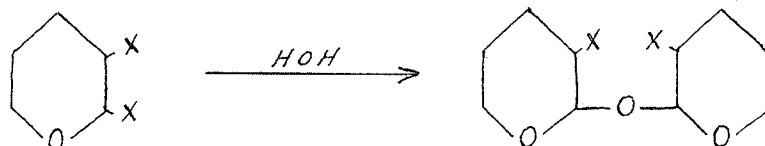
By nitric acid oxidation of tetrahydropyran-2,3-diol there was isolated a white crystalline product of m.p. 98° , which seems to be substance II, α -hydroxyglutaric acid. Ingold (28) found the melting point of this substance to be $98-100^{\circ}$, with decomposition. By the same process it was hoped to obtain α -ketoglutaric acid from 2-hydroxytetrahydropyran-3-one but none of this product was isolated. Instead there was obtained a high melting organic solid whose nature has not as yet been determined.

Ditetrahydropyranyl Ether Derivatives
of the Tetrahydropyran-2-ols

Ditetrahydropyranyl ethers have usually been isolated as by-products in the preparation of tetrahydropyran-2-ols. This was the case in Paul's preparation of tetrahydropyran-2-ol (44), Hurd and Kelso's preparation of tetrahydropyran-2,3-diol (27), and Hawkins and Bennett's preparation of 3-chlorotetrahydropyran-2-ol (23). They isolated, respectively, the ethers:



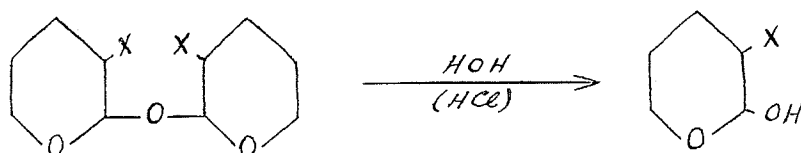
Paul (42, 48) found that such ethers were formed when the 2,3-dihalotetrahydropyrans were left in contact with water for some time at room temperature:



According to Hawkins and Bennett (24) the formation of these ethers is catalyzed by the presence of hydrogen halide. On the other hand, heating the ethers with dilute acids is said (27, 44) to re-convert them to the corresponding tetrahydropyran-2-ols, apparently with some difficulty in the case of the halogenated ethers (42). The halogen atoms in the halogenated ethers are firmly

held. Hawkins and Bennett (24) found that they resisted the action of alcoholic potash, sodium ethylate, and the sodio-derivative of malonic ester.

In the present work no particular effort was made to prepare these ethers but a number of them were obtained as by-products in the preparation of the tetrahydropyran-2-ols. Higher temperature seems to promote the formation of the ethers at the expense of the yields of the tetrahydropyran-2-ols. A sample of 3-chlorotetrahydropyran-2-ol refluxed for an hour on the oil bath, for example, was converted almost completely to the corresponding ether. 3-Bromotetrahydropyran-2-ol seemed to go over into the ether even more readily. The halogenated ethers were found to be very stable compounds. Refluxing them with alkali for days had little or no effect on them. Refluxing them with dilute acid eventually converted them to the halotetrahydropyrans:



2-Alkoxytetrahydropyrans

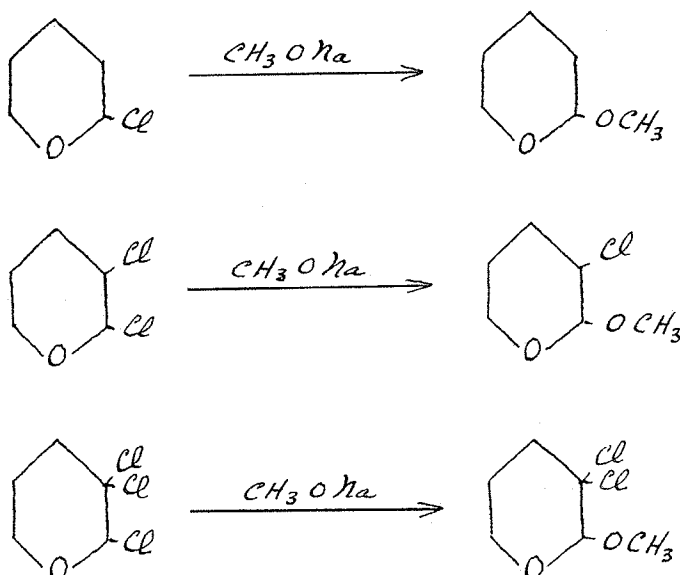
At one stage in this work it was intended to investigate malonic ester condensations with 2-chloro-

tetrahydropyrans. A series of such reactions had been carried out by Schudel and Rice (58) using 2-chlorotetrahydropyran with various substituted malonic esters and sodium hydride as condensing agent. In the work here, trial runs were made with both 2-chlorotetrahydropyran and 2,3-dichlorotetrahydropyran and malonic ester, using sodium and absolute ethanol as condensing agent. The results were disappointing. The bulk of the product consisted of more volatile liquids than the expected high boiling tetrahydropyranyl malonic esters. It was suspected that these more volatile products might include 2-ethoxytetrahydropyrans formed by a reaction competitive with the malonic ester condensation, the mere substitution of the ethoxy group for chlorine. This led to an investigation of methods of preparing 2-alkoxytetrahydropyrans.

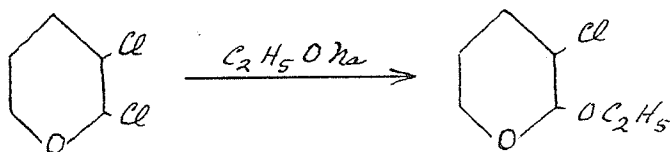
2-Ethoxytetrahydropyran was prepared by treating dihydropyran with absolute ethanol in the presence of a trace of hydrogen chloride gas, the method Paul (44) had used to prepare 2-methoxytetrahydropyran. Subsequently it was discovered that Woods and Kramer (66) had prepared the same substance by the same method. Comparison with one of the fractions from the malonic ester condensation with 2-chlorotetrahydropyran

indicated that 2-ethoxytetrahydropyran was one of the products. This meant that the 2-chlorotetrahydropyrans must react very readily with sodium alkoxides.

This was confirmed by treating each of the three 2-chlorotetrahydropyrans with sodium methyrate. All reacted rapidly to form the expected 2-methoxytetrahydropyrans:

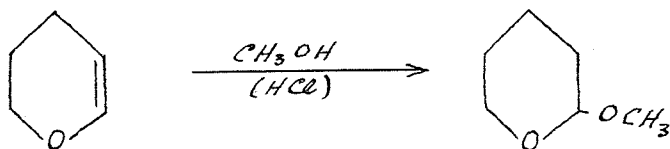


A similar reaction had been previously carried out by Quennehen and Normant (50), who treated 2,3-dichlorotetrahydropyran with sodium ethylate to obtain 2-ethoxy-3-chlorotetrahydropyran:

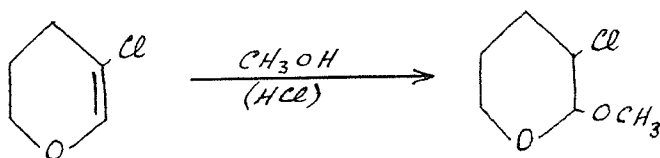


The 2-methoxytetrahydropyrans prepared here had all been previously prepared by other methods.

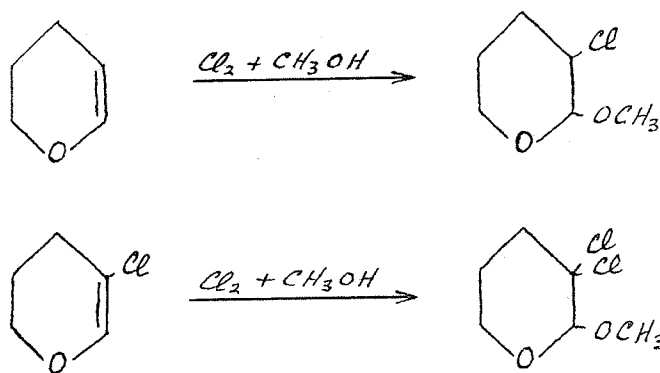
Paul (41, 44) produced 2-methoxytetrahydropyran by treating dihydropyran with methanol in the presence of hydrogen chloride:



Riobe (52) obtained 2-methoxy-3-chlorotetrahydropyran by treating 3-chlorodihydropyran with the calculated quantity of methanol in the presence of hydrogen chloride:

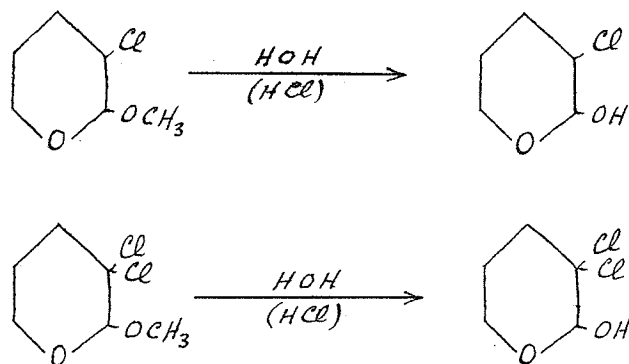


Jones and Bremner (31) made both 2-methoxy-3-chlorotetrahydropyran and 2-methoxy-3,3-dichlorotetrahydropyran by treating dihydropyran and 3-chlorodihydropyran, respectively, with chlorine and methanol:



Comparison of the boiling points and refractive indices of the substances prepared here with those

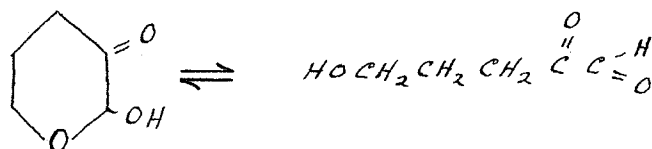
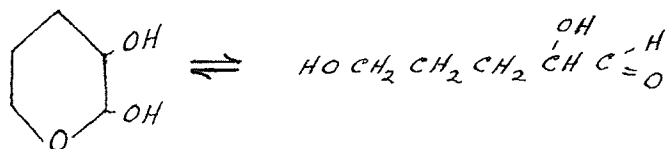
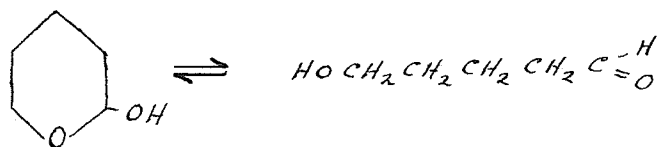
of the substances prepared by these workers indicated that they were the same. Analysis for chlorine confirmed this conclusion for 2-methoxy-3-chlorotetrahydropyran. In the case of 2-methoxy-3,3-dichlorotetrahydropyran the chlorine analysis was high, indicating, probably, that the product was contaminated with unused 2,3,3-trichlorotetrahydropyran, whose boiling point is very close to that of the methoxy derivative. Both of the methoxychloro-compounds were hydrolyzed by heating with dilute hydrochloric acid, a reaction which takes place readily, and the resulting tetrahydropyran-2-ols isolated:



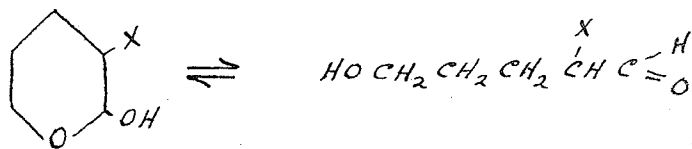
The chlorine atoms in the 3-positions of these 2-methoxytetrahydropyrans were found to be firmly held. A sample of 2-methoxy-3-chlorotetrahydropyran refluxed for eight hours with aqueous sodium hydroxide was recovered unchanged.

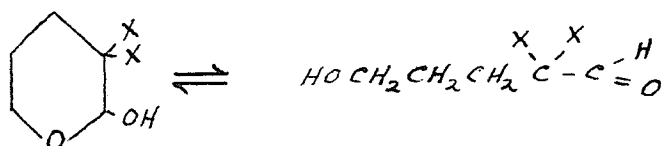
Possible Mechanisms for the Reactions
of the Tetrahydropyran-2-ols

Tetrahydropyran-2-ol and its 3-hydroxy and 3-keto derivatives act almost exclusively as aldehydes in their reactions. They give readily crystalline derivatives characteristic of aldehydes. This is explained by assuming that they exist in equilibrium with δ -hydroxyvaleric aldehyde forms:

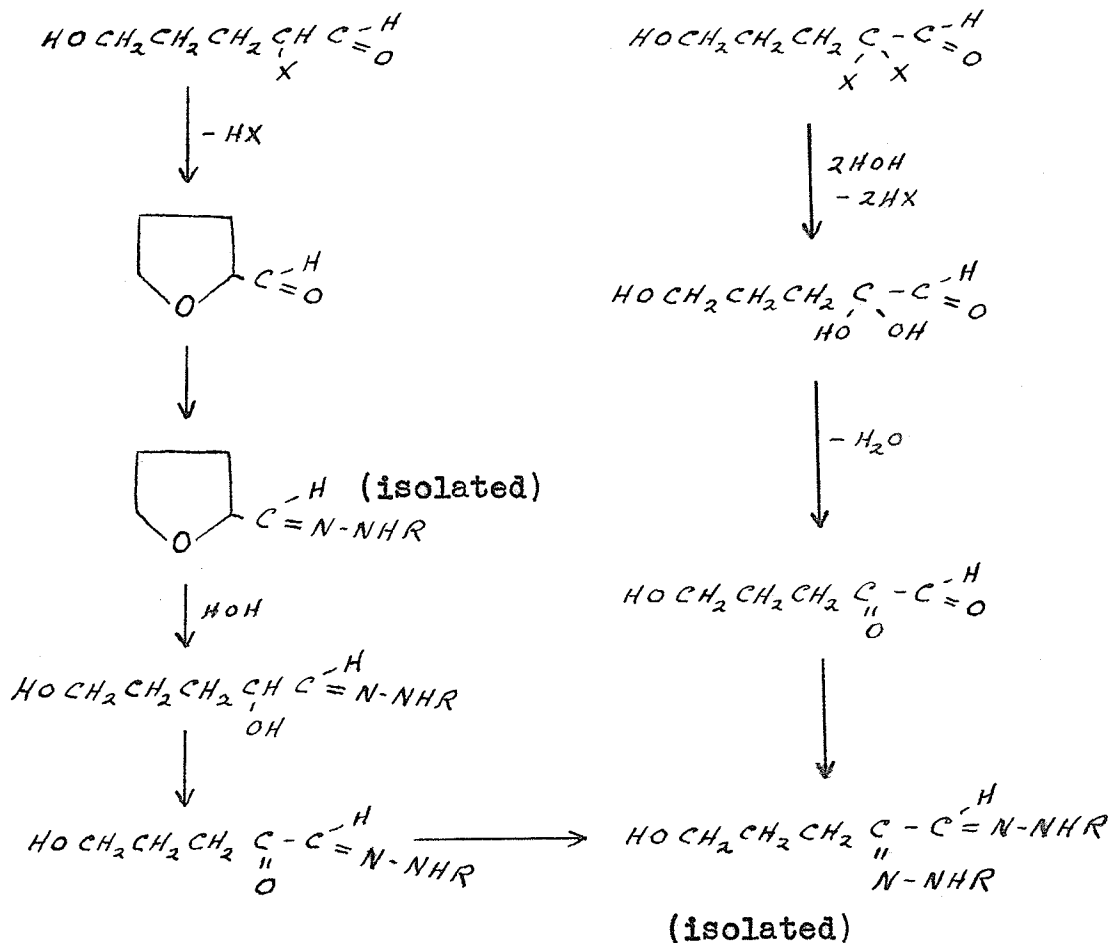


By analogy, the aldehyde properties of the 3-halo- and the 3,3-dihalotetrahydropyran-2-ols are explained by assuming that they also exist in equilibrium with δ -hydroxyvaleric aldehyde forms:





The present work has shown, however, that no aldehyde derivatives containing halogen are obtained from these compounds. Instead one obtains derivatives of tetrahydrofurfural or of 5-hydroxy-2-ketovaleric aldehyde. To explain this kind of result it has been assumed by earlier workers (48, 55) that the α -halogen atoms in the α -haloaldehydes are exceptionally easy to remove. Thus the mechanisms are pictured somewhat as follows:

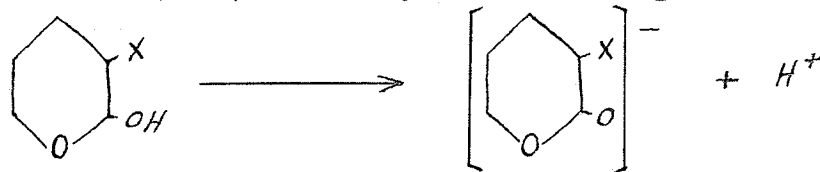


It must be conceded that α -haloaldehydes are possible intermediates in the formation of the derivatives which are obtained from the halo- and dihalotetrahydropyranols. This explanation of these reactions, however, presents a number of difficulties. The α -haloaldehyde forms are said to exist in water solution, but not in non-polar solvents. Yet Paul (45) found that 3-bromotetrahydropyran-2-ol, with phenylhydrazine, lost hydrogen bromide in ether solution. The halo- and dihalotetrahydropyranols are isolated from aqueous reaction mixtures, which indicates that they and their α -haloaldehyde tautomers are fairly stable in water. Yet halogen-free derivatives are formed readily, some even in cold water. If the α -haloaldehydes exist, one would expect to isolate halogen-containing aldehyde derivatives, at least in the cold.

Literature information on the reactions of α -haloaldehydes is scanty. Only comparatively few of these substances are known. Their behavior with such reagents as hydroxylamine, semicarbazide, and phenylhydrazines has not been extensively investigated. Meister (35) claimed the preparation of a liquid oxime of chloroacetaldehyde. Kling (33) prepared crystalline semicarbazones of both dichloro- and chloroacetaldehyde

and found that they lost their halogen content on boiling with water. Franke (16, 17) apparently did not succeed in isolating halogen-containing derivatives from α -bromoisobutyric and α -bromopropionic aldehydes but obtained only derivatives of the hydrolysis products. Information regarding the conditions under which Franke prepared the derivatives is not available. This earlier work on α -haloaldehydes does not throw too much light on our problem but it does suggest that it should not be impossible to obtain halogen-containing semicarbazones and phenylhydrazones from our α -haloaldehydes, if such aldehydes exist.

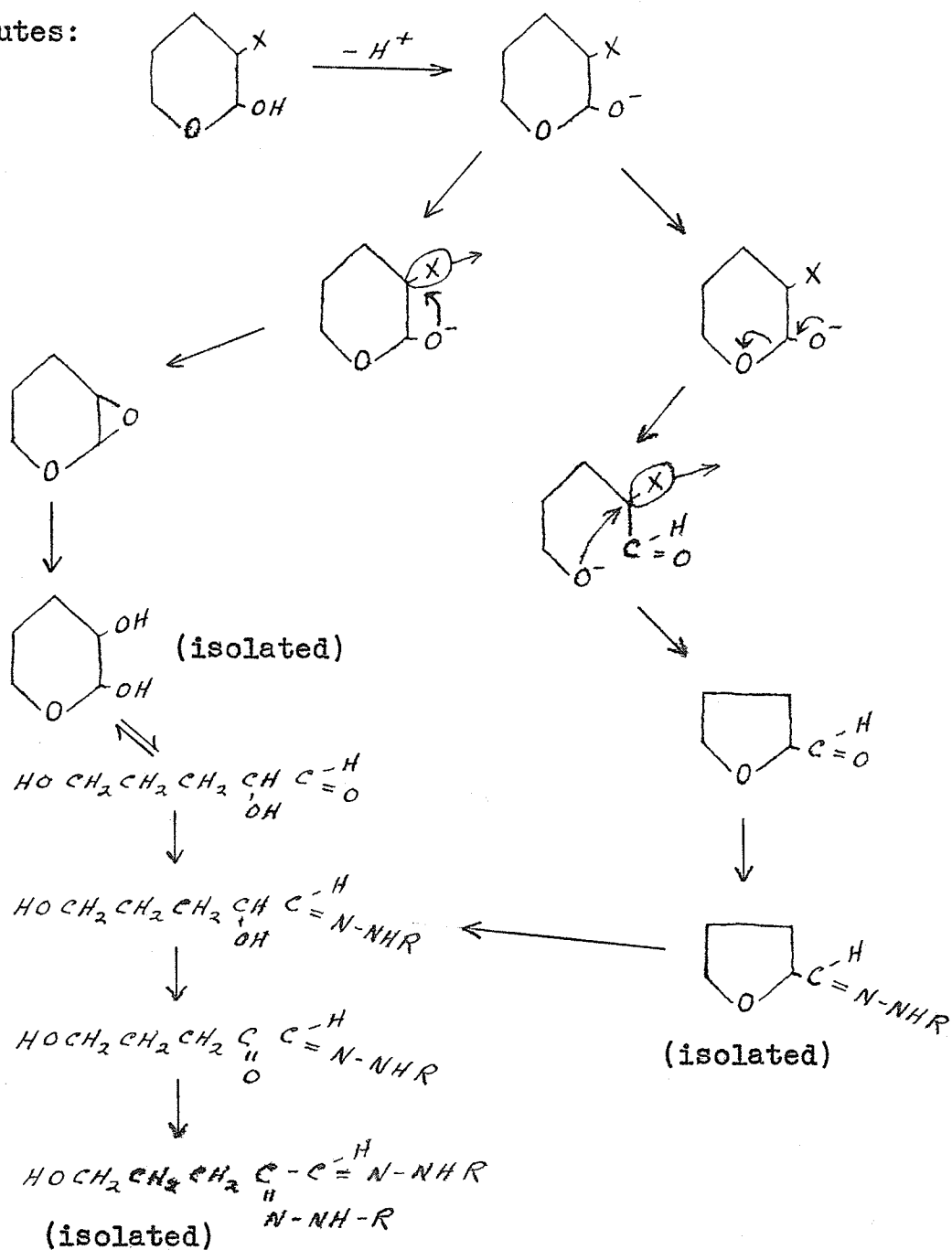
The reactions of the 3-halotetrahydropyran-2-ols can be explained without assuming the existence of α -haloaldehydes. Another explanation is suggested by the fact that these substances can be titrated with aqueous alkali, like an acid. This phenomenon suggests that these halohydrins, in the presence of a proton acceptor, react by dissociating as follows:



Alexander (1), reasoning from work by Bartlett (3) on the chlorohydrins of cyclohexene, believes that the loss of a proton is the first step in the hydrolysis

of halohydrins. If that is the case with the chlorohydrins of cyclohexene, it is certainly probable here, where the halohydrins act like acids.

On this assumption the halohydrins could give the derivatives one actually obtains by the following routes:



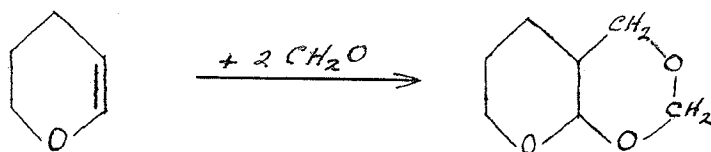
The anion formed by the loss of the proton can stabilize itself in either one of two ways, one leading to tetrahydrofurfural and the other to the epoxide of dihydropyran. The latter path seems to be favored in the presence of strong alkalis. The oxide is not stable and hydrolyzes to the diol.

Examination of a model of the halohydrin molecule suggests that the loss of the proton and the chloride ion might be almost simultaneous, that a hydrogen halide molecule is lost. The residue could then stabilize itself either by forming the oxide or rearranging to tetrahydrofurfural, as pictured.

It is realized that proposing a new mechanism for these reactions is somewhat presumptuous with the rather meagre data that are available. It is suggested, however, that there is as much support for the proposed mechanism as there is for the haloaldehyde intermediates which lose their α -halogen atoms without fail in all their aldehydic reactions.

Reaction of Dihydropyran with Formaldehyde

When dihydropyran was stirred with aqueous formaldehyde, in the presence of a few drops of hydrochloric acid, the mixture warmed up rapidly and became homogeneous in 10 to 15 minutes. The reaction also took place when no acid was added, but it then took two to three hours, with some warming, to bring homogeneity. Two mole proportions of formaldehyde seemed to react. If the reaction was like those carried out by Beets and co-workers (4, 6, 7, 15), there should have been a dioxan formed as follows:



It proved to be difficult to isolate any pure product. Attempts at distillation, even under pressures obtained with a high vacuum pump, always brought considerable decomposition, with liberation of formaldehyde. Some fractionations were attempted at 15-20 mm. but they were complicated by frequent pressure fluctuations and consequent temperature changes. No constant boiling liquid was obtained. All fractions collected were found to contain free formaldehyde, detected by its odor and by the preparation of its

2,4-dinitrophenylhydrazone.

The residue from the fractionations, a viscous liquid boiling above 150° at 20 mm., offered the best hope of being the desired dioxan. A carbon-hydrogen analysis of one sample gave 58.50% carbon and 9.06% hydrogen; the dioxan requires 58.33% carbon and 8.33% hydrogen.

In the presence of acid particularly, there is a competitive reaction, the hydrolysis of dihydropyran to form tetrahydropyran-2-ol, but this is slower than the main reaction. A fraction boiling in the range $80-90^{\circ}$ at 20 mm., making up about 25% of the total product, was found to contain a considerable proportion of the tetrahydropyranol.

If the expected dioxan is produced in the reaction between dihydropyran and formaldehyde, it should be possible to reduce it to an alcohol, as Beets did with his dioxans. In this case the reduction product should be tetrahydropyran-3-methanol:



This substance has been made by another method by Geyer and Mortimer (19).

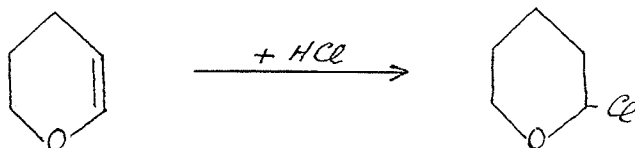
A sample of the presumed dioxan, the high boiling residue from the fractionations, was subjected to reduction with sodium and amyl alcohol. The reduction product, fractionated under reduced pressure, failed to show much constancy in boiling point. One of the fractions collected, b.p. 120-140° at 18 mm., refractive index n_D^{28} 1.460, could contain the expected alcohol. Geyer and Mortimer (19) have reported b.p. 68-69° at 2 mm. and refractive index n_D^{20} 1.4629. The yield of this material was small. No crystalline derivatives characteristic of an alcohol have as yet been obtained from it.

This reaction between dihydropyran and formaldehyde is worth further study. Probably the best approach would be to make no attempt to purify the product from the first reaction but to reduce the crude material, perhaps with lithium aluminum hydride, and then fractionate the reduction product.

EXPERIMENTAL DETAILS

Preparation of 2-Chlorotetrahydropyran

This substance was prepared by the addition of a molecule of hydrogen chloride to dihydropyran:

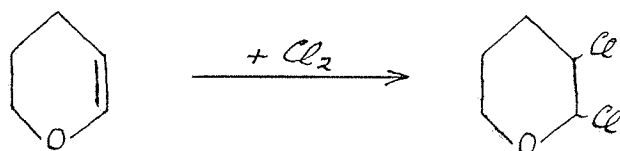


Dry hydrogen chloride, obtained by dropping concentrated sulfuric acid into concentrated hydrochloric acid, was passed into dihydropyran (42 g., 0.5 mole), cooled to 0° , until the weight had increased by 18 g. (0.5 mole of hydrogen chloride). The gas was absorbed smoothly in the course of one to two hours. The product was purified by distillation under reduced pressure. It boiled at $45-46^{\circ}$ at 12-13 mm. The yield was 50 g., 83%.

The product was used to prepare tetrahydropyran-2-ol (page 76) and 2-methoxytetrahydropyran (page 109).

Preparation of 2,3-Dichlorotetrahydropyran

This substance was prepared by the addition of a molecule of chlorine to dihydropyran, using a procedure described by Hawkins and Bennett (23):

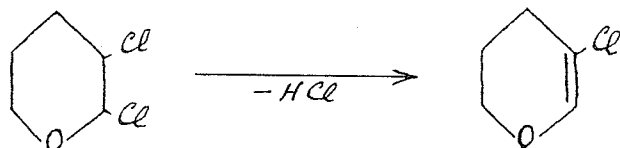


Dry chlorine gas was passed into dihydropyran (84 g., 1 mole), cooled to 0° , until the weight had increased by 71 g. (1 mole of chlorine). The gas was absorbed smoothly in the course of two to three hours. The product was used in the crude form. It can be distilled under reduced pressure but decomposes to some extent. It is reported to boil at 74° at 11 mm.

The crude dichloride was used in the preparation of 3-chlorodihydropyran (immediately following), 3-chlorotetrahydropyran-2-ol (page 79), tetrahydropyran-2,3-diol (page 90), and 2-methoxy-3-chlorotetrahydropyran (page 110).

Preparation of 3-Chlorodihydropyran

This substance was prepared by heating 2,3-dichlorotetrahydropyran, as described by Hawkins and Bennett (23):



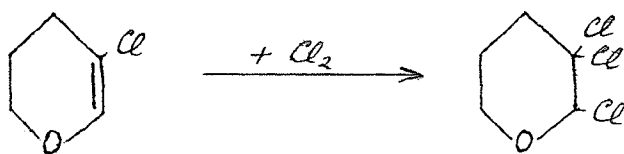
Crude 2,3-dichlorotetrahydropyran (155 g., 1 mole) was heated at atmospheric pressure under a reflux condenser until hydrogen chloride was evolved. The temperature was maintained so that the evolution of hydrogen chloride continued at a moderate rate. After several hours, when the evolution of gas grew less, the residue was distilled

at atmospheric pressure. A colorless liquid (125 g.) distilled at 138-150°. Redistilled at atmospheric pressure, this yielded a purified product (98 g.) boiling at 141-142°. This was a yield of 83%.

The product was used to prepare 2,3,3-trichlorotetrahydropyran, described below.

Preparation of 2,3,3-Trichlorotetrahydropyran

This substance was prepared by a method described by Hawkins and Bennett (23), the addition of chlorine to 3-chlorodihydropyran:

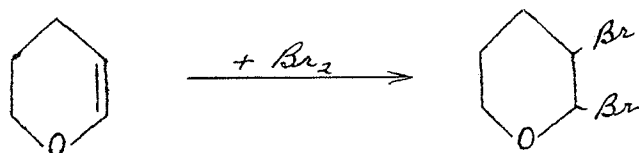


Dry chlorine gas was passed into 3-chlorodihydropyran (59.2 g., 0.5 mole) at room temperature until the weight had increased by 35.5 g. (0.5 mole of chlorine). Distillation of the product at 15-16 mm. gave a liquid (80 g.) boiling at 92-94°, which solidified on cooling to give a solid melting at 31-32°. This was a yield of 84%.

The product was used in the preparation of 3,3-dichlorotetrahydropyran-2-ol (page 99), 2-methoxy-3,3-dichlorotetrahydropyran (page 111), and 2-hydroxy-tetrahydropyran-3-one (page 100).

Preparation of 2,3-Dibromotetrahydropyran

The addition of a bromine molecule to dihydropyran is best carried out in a solvent, as described by Paul (42, 45).



Bromine (40 g., 0.25 mole) was added gradually, drop by drop, to dihydropyran (21 g., 0.25 mole) dissolved in dry ether (50 ml.) while cooling to 0° and stirring. The ether was taken off with the water pump. No attempt was made to purify the product by distillation.

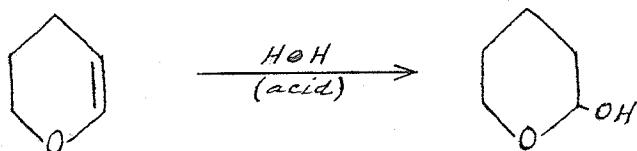
The crude product was used for the preparation of 3-bromotetrahydropyran-2-ol (page 80).

Preparation of Tetrahydropyran-2-ol

This substance was prepared by two methods.

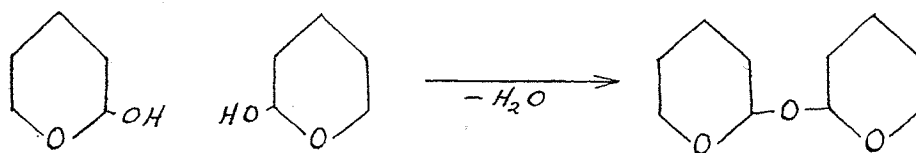
Method 1

This is the method originally used by Paul (41, 44). It consists in treating dihydropyran with water in the presence of a trace of mineral acid:



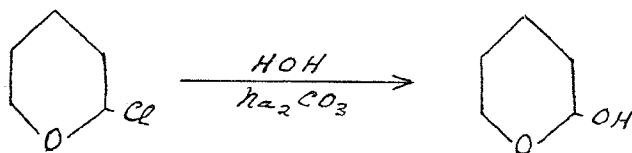
Dihydropyran (42 g., 0.5 mole) was stirred at room temperature with water (50 ml.) and concentrated hydrochloric acid (5 drops). The mixture warmed up gradually as the reaction proceeded. In 45 minutes the dihydropyran layer had disappeared. The solution was stirred for another 15 minutes and then left to cool to room temperature. It was then saturated with potassium carbonate, which caused an organic layer to separate. The organic layer was taken up in ether and the aqueous residue also extracted with ether. The combined extracts were dried over sodium sulfate and the ether distilled off. The residue (45 g.) was distilled at 15 mm. through a short column. It was separated into three fractions: (1) a liquid (25 g.) boiling at 78-80°; (2) a liquid (5 g.) boiling at 108-112°; and (3) a higher boiling residue which showed no constant boiling point.

According to Paul (44), the first fraction is the tetrahydropyran-2-ol; the second is the corresponding ether formed from two molecules of the alcohol:



Method 2

Tetrahydropyran-2-ol was prepared by hydrolysis of 2-chlorotetrahydropyran with sodium carbonate solution:



2-Chlorotetrahydropyran (30 g., 0.25 mole), prepared as described earlier (page 71), was added, drop by drop, to a solution of sodium carbonate (15 g. in 50 ml. of water). There was vigorous effervescence, heat was produced, and an organic layer settled out. The organic layer was taken up in ether and the aqueous residue extracted with ether. The combined extracts were dried over magnesium sulfate and the ether distilled off. The residue (20 g.) was fractionated through a short column at 13-14 mm. Two fractions were collected: (1) a liquid (12 g.) boiling at 75-77°, and (2) a liquid (5 g.) boiling at 105-110°. There was a higher boiling residue.

To confirm that the products by this method were the same as by Method 1, the refractive indices were compared and found to be the same. The lower boiling fraction, tetrahydropyran-2-ol, had refractive index n_D^{24} 1.451; Schniepp and Geller (57) have reported n_D^{25} 1.4514. The higher boiling fraction, the ether, had refractive index n_D^{24} 1.460; Paul (44) has reported n_D^{17} 1.4659.

2,4-Dinitrophenylhydrazone of Tetrahydropyran-2-ol

Tetrahydropyran-2-ol (1 ml.) was added to a saturated alcoholic solution of 2,4-dinitrophenylhydrazine (10 ml.) containing a trace of hydrochloric acid. The mixture was warmed and then allowed to cool. A yellow precipitate settled out. Recrystallized three times from ethanol it melted at 112-113°.

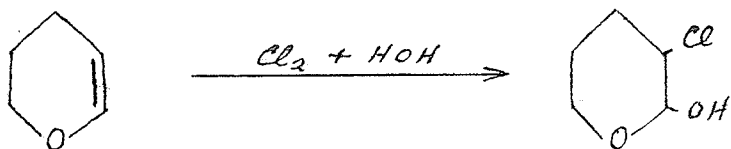
Woods and Sanders (67) have reported the melting point of this substance as 109°. Wilson (63), however, has reported 112-113°.

Preparation of 3-Chlorotetrahydropyran-2-ol

This substance was prepared by three different methods.

Method 1

This consisted in passing chlorine into an aqueous suspension of dihydropyran, a method used by Hawkins and Bennett (21):

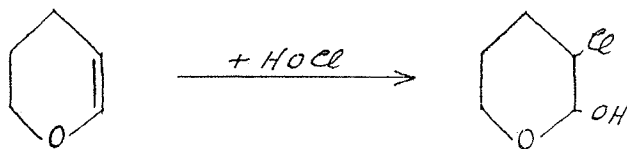


Dihydropyran (84 g., 1 mole) emulsified with water (200 g.) using a mechanical stirrer, was cooled to 0° while chlorine (71 g., 1 mole) was passed in. The mixture was neutralized with sodium carbonate until no more gas was evolved. Extraction with ether, drying, and distilling of the

ether left a yellowish liquid. Cooling in the refrigerator for several days brought down a white precipitate (30 g.) which melted at 58-60°. The product was nearly pure but the yield was low (22%). Recrystallized from dry ether, the product melted at 64°.

Method 2

In this method hypochlorous acid solution was added to dihydropyran. The hypochlorous acid was made by the method of Detoeuf (14), monochlorurea solution acidified with acetic acid. Paul (48) had used this method with somewhat inconclusive results.



Urea (60 g.), precipitated calcium carbonate (40 g.), and water (200 g.) were placed in a 1 liter flask, cooled to 0°, and chlorine passed in until the weight had increased by 36 g. (0.5 mole chlorine). The solution was then diluted to 300 ml. and the excess calcium carbonate filtered off. Washing increased the final volume to 340 ml. Titration with standard sodium thio-sulfate indicated that this solution had a potential hypochlorous acid content of 10%.

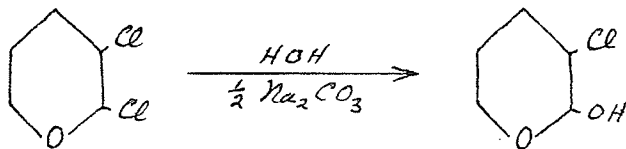
Dihydropyran (42 g., 0.5 mole), glacial acetic acid (25 g.)

and water (200 g.) were added to the monochlorurea solution thus prepared and the mixture cooled to 0° and stirred mechanically. The dihydropyran phase disappeared in two hours. The excess acid was then neutralized with calcium carbonate and the excess carbonate filtered off. The solution was extracted with ether and the extract dried over sodium sulfate. Distillation of the ether left a yellowish liquid, which, after some days in the refrigerator, deposited white crystals (32 g.) of melting point 48-52°.

This method is more laborious than Method 1. It gave a better yield (47%) but the product was less pure.

Method 3

This, the most convenient way of getting good yields of the product, consists in the hydrolysis of 2,3-dichlorotetrahydropyran with an equivalent of sodium carbonate solution, a method used by Hawkins and Bennett (23).



Crude 2,3-dichlorotetrahydropyran (155 g., 1 mole), prepared as described earlier (page 71), was added gradually over a two-hour period to a solution of sodium carbonate (53 g., 0.5 mole) in water (200 g.),

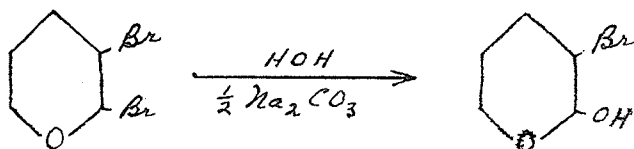
cooled to 0° , and stirred with a mechanical stirrer. Water was added to clear the cloudy solution. Extraction with ether, drying, and evaporation of the ether yielded a yellowish liquid. Left in the refrigerator, this deposited white crystals (86 g.) which melted at $45-50^{\circ}$. This was a yield of 63%.

The product was difficult to purify. Several recrystallizations from anhydrous ether were required to bring it up to melting point 64° , the reported melting point of the pure substance. For most purposes it can be used in the crude form, since the ditetrahydropyranyl ether impurities present are not active chemically.

Preparation of 3-Bromotetrahydropyran-2-ol

This substance was obtained, but in poor yields, by the addition of hypobromous acid to dihydropyran, using monobromurea solution acidified with acetic acid as source of hypobromous acid.

Hydrolysis of the dibromide with sodium carbonate solution proved to be the better method. Paul (45) used an aqueous suspension of lead hydroxide to hydrolyze the dibromide.



Crude 2,3-dibromotetrahydropyran (61 g., 0.25 mole), prepared as described earlier (page 74), was added gradually to sodium carbonate (13.2 g., 0.125 mole) dissolved in water (100 ml.) while cooling to 0° . The solution was extracted continuously with ether, the extract dried over sodium sulfate, and the ether distilled off. The residual liquid when cooled in the refrigerator deposited white crystals (36 g.). This was a yield of 80%. The product recrystallized from anhydrous ether melted at 79° .

Crystalline Derivatives of the 3-Halotetrahydropyran-2-ols

Both 3-chloro- and 3-bromotetrahydropyran-2-ol were found to be aldehydic. They reduced Fehling's solution when warmed. They gave readily 2,4-dinitrophenylhydrazones and 2,4-dinitrophenylosazones, less readily p-nitrophenylhydrazones, p-nitrophenylosazones, and benzylphenylhydrazones. These derivatives contained no halogen. The chlorohydrin and the bromohydrin gave the same product with each of the phenylhydrazines. Comparison of the products with authentic tetrahydrofurfural derivatives showed them to be identical with these.

2,4-Dinitrophenylhydrazones

Dinitrophenylhydrazones were prepared from the 3-halotetrahydropyran-2-ols by three different methods. Each method gave the same halogen-free product.

Method 1

This is a general method recommended by Shriner and Fuson (60).

To 2,4-dinitrophenylhydrazine (0.8 g.) was added concentrated sulfuric acid (4 ml.) and then water (6 ml.) dropwise, with swirling, until solution was complete. To the warm solution 95% ethanol (20 ml.) was added. The chlorohydrin (1 g.) was dissolved in 95% ethanol (40 ml.) and this solution added to the freshly prepared dinitrophenylhydrazine solution. The mixture was allowed to stand at room temperature. Crystallization began after twenty minutes. After allowing to stand overnight, orange yellow crystals (3 g.) were filtered off. Recrystallized several times from absolute ethanol, with decolorizing charcoal, the product was yellow and melted at 133-134°. A qualitative analysis showed that the product contained no chlorine.

The same method was used to make a dinitrophenylhydrazone from the bromohydrin. Here also the product was yellow and melted at 133-134°. It contained no bromine. A mixed melting point test with the product

from the chlorohydrin indicated that the two substances were the same.

Method 2

This is a method used by Hinz, Meyer, and Schucking (25) to prepare the dinitrophenylhydrazone of tetrahydrofurfural.

The chlorohydrin (2.7 g.) was stirred into a solution of 2,4-dinitrophenylhydrazine (3.9 g.) in normal hydrochloric acid (1 liter) at 0° and allowed to stand in the refrigerator overnight. A yellow precipitate was formed. Recrystallized three times from absolute ethanol, it melted at 133-134°.

Carrying out the reaction in the cold, as here, gave a purer product.

This method was used also to prepare a dinitrophenylhydrazone from the bromohydrin and gave the identical product.

Method 3

This is a method recommended by Johnson (30) for the preparation of dinitrophenylhydrazones. It has the advantage that a solution of 2,4-dinitrophenylhydrazine in phosphoric acid is stable and can be kept indefinitely.

2,4-Dinitrophenylhydrazine (1 g.) was heated with 85% phosphoric acid (12 ml.) on the steam bath, diluted with ethanol (8 ml.) and clarified by suction filtration through filter cel. Chlorohydrin (0.7 g.) dissolved in ethanol (3 ml.) was added and the solution left in the refrigerator. A sticky brown solid was eventually filtered off, the filtration being exceedingly slow. Several recrystallizations from ethanol were needed to obtain the yellow crystals, m.p. 133-134°.

2,4-Dinitrophenylosazones

The 2,4-dinitrophenylhydrazone obtainable from the chlorohydrin or the bromohydrin readily goes over into an osazone. Higher temperature and excess reagent favor the formation of the osazone rather than the hydrazone.

The 2,4-dinitrophenylhydrazone (0.7 g.) was added to a solution of 2,4-dinitrophenylhydrazine (0.5 g.) in methanol (200 ml.) containing a few drops of concentrated hydrochloric acid. The mixture was refluxed on the water bath for an hour, when a solid began to separate. It was left to cool to room temperature and the orange solid was filtered off. Recrystallized from acetone or nitromethane, it melted at 242°.

To confirm that the dinitrophenylhydrazones from the chlorohydrin and the bromohydrin were the same, this same product was prepared from dinitrophenylhydrazones from both sources.

p-Nitrophenylhydrazones

The chlorohydrin or bromohydrin (0.5 g.) was added to a solution of p-nitrophenylhydrazine (0.5 g.) dissolved in ethanol (15 ml.) and a drop of glacial acetic acid was added. The mixture was warmed for a few minutes in hot water and then allowed to stand at room temperature. After two days an orange red precipitate had formed. Several recrystallizations from absolute ethanol gave orange yellow crystals melting at 145-146°.

The product, which was halogen-free, was the same whether the chlorohydrin or the bromohydrin was used.

This substance did not precipitate as readily as the 2,4-dinitrophenylhydrazone.

p-Nitrophenylosazones

On prolonged heating with excess p-nitrophenylhydrazine the hydrazone is converted to the osazone.

The p-nitrophenylhydrazone (0.5 g.) was added to a solution of p-nitrophenylhydrazine (0.5 g.) in methanol (100 ml.) containing a few drops of concentrated

hydrochloric acid. The mixture was refluxed on the water bath for four hours and then allowed to cool. A dark red powder settled out. On recrystallization from methanol the product consisted of fine dark red crystals which melted at 246° with slight decomposition.

The product was the same whether the hydrazone used came from the chlorohydrin or the bromohydrin.

Benzylphenylhydrazones

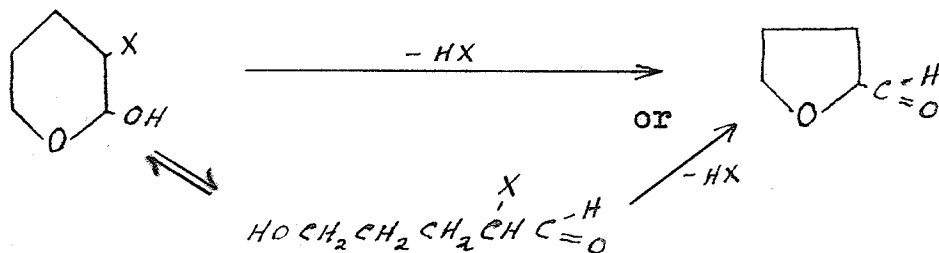
The chlorohydrin or bromohydrin (1 g.) dissolved in water (7 ml.) was added to benzylphenylhydrazine hydrochloride (1 g.) in 95% ethanol (10 ml.). The mixture was warmed in hot water for a few minutes. On cooling a yellow precipitate formed. Recrystallized from methanol the product was obtained as almost colorless needles melting at $74-75^{\circ}$.

The product from the bromohydrin was the same as from the chlorohydrin.

Comparison with Tetrahydrofurfural Derivatives

The melting points of the halogen-free derivatives obtained from the 3-halotetrahydropyran-2-ols were the same as those reported for similar derivatives of tetrahydrofurfural by Hurd and Edwards (26). This suggested that in these reactions the halohydrins had gone over into tetrahydrofurfural, as Paul (48)

had found in the preparation of an oxime:



To confirm that our products were tetrahydrofurfural derivatives they were compared with products obtained from authentic tetrahydrofurfural, prepared in these laboratories by D.G. Hay, using the method of Scheibler, Sotscheck, and Fries (56). They proved to be identical.

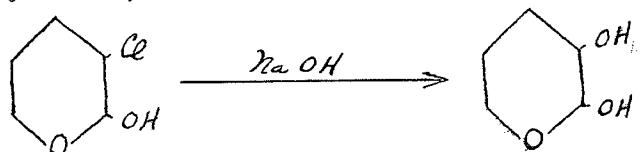
Preparation of Tetrahydropyran-2,3-diol

Titration of 3-chlorotetrahydropyran-2-ol with sodium hydroxide

Chlorohydrin (0.341 g.) was dissolved in water (25 ml.) so as to make a 0.1 M solution. This was titrated with 0.1 N sodium hydroxide solution, using phenolphthalein as indicator. The reaction was slow in the cold but rapid when the chlorohydrin solution was warmed. 26.3 ml. of the sodium hydroxide solution were required, indicating that the chlorohydrin acts like a monobasic acid.

When the reaction was carried out on a larger scale it was found that the yield of sodium chloride was invariably quantitative. Isolation of the organic

product of the reaction proved difficult but was eventually accomplished by two different methods. Carbon-hydrogen analysis and preparation of derivatives indicated that the product was tetrahydropyran-2,3-diol.



Method 1

3-Chlorotetrahydropyran-2-ol (13.6 g., 0.1 mole) was dissolved in water (100 ml.) and a solution of sodium hydroxide (4 g. in 100 ml.) added to it. The mixture was allowed to stand for three to four hours at room temperature. It was then made just acid with a few drops of dilute hydrochloric acid and allowed to evaporate at 35-40°. The residue was extracted with absolute ethanol, leaving behind a quantitative yield of sodium chloride. The alcoholic extract was allowed to evaporate at room temperature. The residue (10 g.) was extracted several times with small portions of ether. Evaporation of the ether left a colorless, high-boiling sirup (8 g.).

This product could not be distilled without decomposition, even under reduced pressure.

Dried in a vacuum dessicator for several days, it gave the carbon-hydrogen analysis expected for

tetrahydropyran-2,3-diol.

Found : 1st run, C, 51.5%, H, 8.18%;

2nd run, C, 51.1%, H, 8.07%.

Calculated for $C_5H_{10}O_3$: C, 50.9%, H, 8.47%.

Method 2

3-Chlorotetrahydropyran-2-ol (68 g., 0.5 mole) dissolved in water (500 ml.) was added to a solution of sodium hydroxide (20 g., 0.5 mole) in water (500 ml.) at room temperature. After standing overnight the solution was made just acid with dilute hydrochloric acid. Anhydrous sodium sulfate (200 g.) was added to the solution and the mixture allowed to stand for a day. The solution was then poured into a fresh quantity of sodium sulfate and the previous drying agent extracted with ether. This procedure was continued until the liquid residue was small and completely soluble in ether. The ether solution was combined with the extracts from the drying agent, was dried and the ether evaporated. The residue (25 g.) was a colorless sirup.

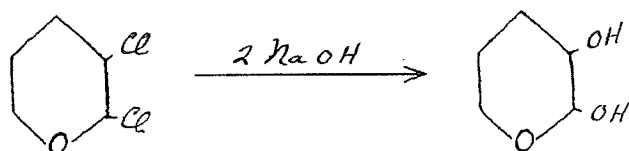
The yield by this procedure was not as good as by Method 1.

Tetrahydropyran-2,3-diol
from 3-Bromotetrahydropyran-2-ol

The diol can be made from the bromohydrin by the same method as from the chlorohydrin. This was indicated by a trial run on a small scale. The reaction was not attempted on a larger scale.

Tetrahydropyran-2,3-diol
from 2,3-Dichlorotetrahydropyran

This is the most expeditious procedure for the preparation of the diol.



A solution of sodium hydroxide (40 g., 1 mole) in water (1 liter) was prepared and left to cool to room temperature. One-half of this solution was added to crude 2,3-dichlorotetrahydropyran (77.5 g., 0.5 mole) and the mixture stirred at room temperature. Heat was produced as the reaction proceeded. In one hour the organic phase had disappeared and the solution was no longer alkaline. More of the sodium hydroxide solution was then added gradually over the next two hours and the stirring continued. The solution turned yellow and eventually brown. The sodium hydroxide was neutralized fairly rapidly. When nearly all of it had been added the solution remained alkaline. It was then made just

acid with dilute hydrochloric acid and allowed to evaporate at 35-40°. After some days, when the water had evaporated, the residue was extracted with absolute ethanol, leaving behind sodium chloride (55 g.). The alcohol was allowed to evaporate at room temperature. The residue was a yellowish sirup (55 g.). It was extracted with many small portions of ether. After drying and evaporation of the ether, there was left a colorless viscous liquid (40 g.). This was the tetrahydropyran-2,3-diol.

The remaining, ether-insoluble product was partially soluble (5 g.) in chloroform but the bulk of it was soluble only in alcohol and water. Its nature has not been determined.

Properties and Derivatives
of Tetrahydropyran-2,3-diol

Tetrahydropyran-2,3-diol is a colorless, viscous liquid, which does not boil without decomposition even under reduced pressure.

It is soluble in water and alcohol and, with some difficulty, in ether.

Its refractive index was found to be n_D^{22} 1.478. Hurd and Edwards (26), who prepared the substance by another method, have reported n_D^{25} 1.480.

It was found to reduce Benedict's solution rapidly when warmed, as did Hurd's compound.

Periodic acid Oxidation

Tetrahydropyran-2,3-diol reduced periodic acid to iodate rapidly at room temperature. According to Shriner and Fuson (60) this reaction is characteristic of α -hydroxyaldehydes and 1,2-diols.

Diol (1 drop) was added to periodic acid solution (2 ml. of a solution containing 0.5 g. of the acid per 100 ml. of water) which contained concentrated nitric acid (1 drop). After shaking the mixture gave an immediate precipitate of silver iodate on the addition of 3% silver nitrate (1 drop).

2,4-Dinitrophenylosazone

Tetrahydropyran-2,3-diol (0.5 g.) was dissolved in absolute ethanol (50 ml.) and 2,4-dinitrophenylhydrazine (0.5 g.) added. The mixture was refluxed for a few minutes. Then concentrated hydrochloric acid (1 ml.) was added and the refluxing continued for a few minutes more. The solution turned brown. On cooling and filtering a solid product was obtained. Several recrystallizations from nitromethane gave orange crystals melting at 242° .

The product was found to be identical with the dinitrophenylosazone obtained earlier from the halo-tetrahydropyrans (page 84). Hurd and Kelso (27), who made tetrahydropyran-2,3-diol by another method, prepared a 2,4-dinitrophenylosazone, m.p. 242° , from their diol by the procedure used here.

Disemicarbazone

Tetrahydropyran-2,3-diol (1 g.), semicarbazide hydrochloride (1 g.) and sodium acetate (1.5 g.) were dissolved in water (10 ml.). The mixture was shaken vigorously and was heated in boiling water for one hour. It was then cooled in the refrigerator overnight. By next day a precipitate had settled out. Recrystallized from aqueous ethanol, with charcoal, it was a white crystalline solid, which melted with decomposition in the range $215-225^{\circ}$, depending on the rate of heating. When immersed in the melting point bath at room temperature, it melted at 215° ; when immersed at 210° , it melted at 225° . Repeated recrystallization failed to give it a sharp and definite melting point.

The same product was obtained from 3,3-dichloro-tetrahydropyran-2-ol (page 100) and from 2-hydroxy-tetrahydropyran-3-one (page 104). It is the disemicarbazone of the aldehyde form of the last of these compounds.

3,5-Dinitrobenzoate

Tetrahydropyran-2,3-diol (1 g.) was dissolved in pyridine (10 ml.) and 3,5-dinitrobenzoyl chloride (3 g.) was added. The reaction mixture was allowed to stand for a week at room temperature. It was then treated with water and 5% sodium carbonate solution. The gummy product, recrystallized three times from an ethanol-ethyl acetate mixture, gave fine white crystals which melted at 174°. Hurd and Kelso (27) reported a 3,5-dinitrobenzoate, m.p. 174.5-175.5°, prepared from their sample of tetrahydropyran-2,3-diol.

Permanganate Oxidation

Tetrahydropyran-2,3-diol (1 g.) was dissolved in water (10 ml.), 5% sodium hydroxide solution (1 ml.) was added, then 2% potassium permanganate solution, with occasional shaking, until the color remained permanent. This took several days and a considerable volume of the permanganate solution (150-200 ml.). The manganese dioxide which had been precipitated was filtered off. The solution was then acidified with dilute sulfuric acid. In a few minutes it had lost the permanganate color. More permanganate was added until the color was again permanent. Sodium bisulfite was then added to decolorize it and the solution evaporated to dryness. The residue was extracted with

acetone and the acetone-extracted product (0.5 g.) was recrystallized from acetone-benzene. After another recrystallization, from water, with charcoal, it melted at 183° . A mixed melting point test with authentic succinic acid indicated that this product was succinic acid.

Nitric Acid Oxidation

Tetrahydropyran-2,3-diol (5.9 g.) was dissolved in water (35 ml.) and concentrated nitric acid (14 ml.) was added. On warming the mixture on the water bath a vigorous reaction took place, with evolution of oxides of nitrogen. When the reaction was over, the mixture was evaporated on the water bath down to about one-third of its original volume. Water (15 ml.) was then added and the evaporation repeated. The addition of water and evaporation was repeated twice more. Then the reaction mixture was evaporated to dryness. The residue solidified. The solid (5 g.) was recrystallized from ethyl acetate, with charcoal; then from a mixture of acetone and benzene. It still melted over a considerable temperature range, $75-85^{\circ}$. Recrystallization from wet ether then gave white crystals melting at 98° .

The product could be α -hydroxyglutaric acid. It has not as yet been analyzed. Ingold (28) has reported the melting point of α -hydroxyglutaric acid as $98-100^{\circ}$.

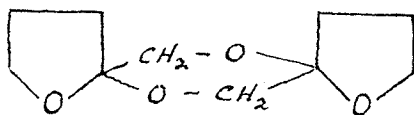
Compounds Related to Tetrahydropyran-2,3-diol

When the reaction between 3-chlorotetrahydropyran-2-ol and sodium hydroxide is carried out under conditions other than those which yield tetrahydropyran-2,3-diol, very little of this substance can be isolated from the products. In two cases, small quantities of other substances were isolated: one a solid melting at 101-102°, the other a solid melting at 190°.

The Compound with m.p. 101-102°

3-Chlorotetrahydropyran-2-ol (13.6 g., 0.1 mole) was dissolved in water (100 ml.) and treated with a solution of sodium hydroxide (4 g.) in water (100 ml.). After standing for two to three hours, the mixture was extracted continuously with ether, first from basic solution for three hours, then from acid solution for three hours. The extracts were dried and the ether evaporated. The residue was negligible. The aqueous solution was then allowed to evaporate in air at room temperature. The residue was extracted with chloroform, then with alcohol, leaving a nearly quantitative yield of sodium chloride. The alcoholic extract yielded a brown liquid from which no pure compound has been isolated. The chloroformic extract gave a white solid, which, recrystallized from ethanol, melted at 101-102°.

This white solid is thought to be the same as the compound of m.p. 103° mentioned by Hurd and Edwards (26). They assigned to it the structure:



Their conclusion was supported by the work of Swadesh and Dunlop (62).

Our product contained no chlorine. Carbon-hydrogen analysis gave C, 59.7%, H, 8.10%. Calculated for Hurd's compound, C₁₀H₁₆O₄ : C, 60.0%, H, 8.10%.

The substance was not aldehydic. It did not reduce Benedict's solution even after prolonged heating.

When warmed with dilute hydrochloric acid, it dissolved rapidly. When the resulting solution was warmed with a methanol solution of 2,4-dinitrophenylhydrazine, a red precipitate gradually formed. This, recrystallized from nitromethane, proved to be the orange-colored dinitrophenylosazone, m.p. 242°, met in other parts of this work.

These reactions are similar to those given by the compound of Hurd and Edwards (26).

The Compound with m.p. 190°

3-Chlorotetrahydropyran-2-ol (13.6 g., 0.1 mole) was dissolved in water (150 ml.) and excess solid sodium hydroxide (5 g.) was added. The solution heated up and turned yellow as the sodium hydroxide dissolved. On standing it became orange yellow and turned cloudy. In most trials the cloudiness did not settle out as a precipitate and could not be filtered off. In one case, however, a white solid precipitated in sufficient quantity to make filtration possible. The solution was made just acid with dilute hydrochloric acid and was filtered. The white solid, after drying for some time, was found to melt at 190°, with some decomposition.

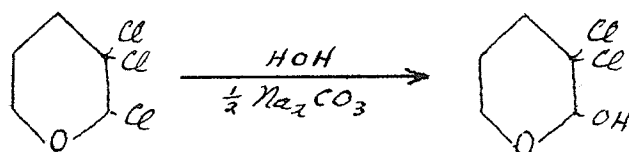
The source of this compound and its melting point suggested that this might be the second $C_{10}H_{16}O_4$ substance obtained by Hurd and Edwards (26) from tetrahydropyran-2,3-diol. Some of the reactions described by these workers were tried and the results indicated that this was the same substance. Its structure is not definitely known.

It had no effect on Benedict's solution. When refluxed with dilute hydrochloric acid it dissolved gradually. The hydrolysis product was extracted continuously with ether and, after evaporation of the ether, taken up in methanol. The methanol solution

warmed with a little 2,4-dinitrophenylhydrazine in the presence of a few drops of hydrochloric acid gave the orange-colored dinitrophenylosazone, m.p. 242° , met previously (page 92).

Preparation of 3,3-Dichlorotetrahydropyran-2-ol

This substance was prepared by hydrolysis of 2,3,3-trichlorotetrahydropyran with one equivalent of sodium carbonate solution:



2,3,3-Trichlorotetrahydropyran (9.5 g., 0.05 mole), prepared as described earlier (page 73), was stirred with a solution of sodium carbonate (2.6 g. in 100 ml. of water) at $35-40^{\circ}$ for 10 hours. The reaction mixture was then extracted continuously with ether. After evaporation of the ether, the residue (7 g.) solidified. Recrystallized from aqueous alcohol, it melted at $88-89^{\circ}$. Analysis : Found : Cl, 41.64%.

Calculated for $C_5H_8O_2Cl_2$: Cl, 41.52%.

The I.G. Farben chemists (36, 69) reported 90° as the melting point of 3,3-dichlorotetrahydropyran-2-ol. Riobe (54, 55) has reported 83.5° and 85.5° .

Properties and Derivatives of
3,3-Dichlorotetrahydropyran-2-ol

This substance was found to be less aldehydic than the 3-halotetrahydropyran-2-ols, but it did reduce Fehling's solution on warming for some time.

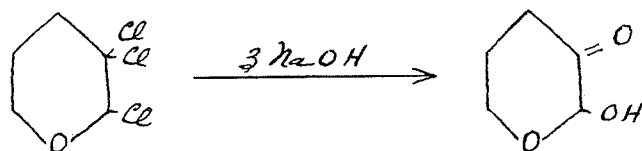
When it was treated with 2,4-dinitrophenylhydrazine reagent at room temperature like the 3-halotetrahydropyran-2-ols (page 82), it did not form a dinitrophenylhydrazone. When the reaction mixture was heated, however, the previously described 2,4-dinitrophenylosazone, m.p. 242° , was precipitated.

When it was treated with semicarbazide hydrochloride, using the same procedure as for tetrahydropyran-2,3-diol (page 93), it yielded the same disemicarbazone as that substance.

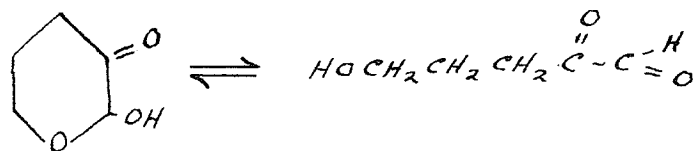
When it was dissolved in warm alcohol, it could be titrated slowly with aqueous sodium hydroxide solution and neutralized two equivalents of the base.

Preparation of 2-Hydroxytetrahydropyran-3-one

This substance was prepared by treating 2,3,3-trichlorotetrahydropyran with three mole proportions of sodium hydroxide:



2,3,3-Trichlorotetrahydropyran (19 g., 0.1 mole) was warmed to 35-40° so that it would remain in the liquid phase, and sodium hydroxide solution (12 g., 0.3 mole, in 150 ml. of water) was added. The mixture was kept at 35-40° and stirred until the organic layer had disappeared, about 10 hours. The reaction mixture, still slightly acid, was then allowed to evaporate at just above room temperature. The residue was extracted with absolute ethanol, leaving behind a nearly quantitative yield (16 g.) of sodium chloride. The alcoholic extract on evaporation gave a very viscous, dark red sirup (10 g.), which could not be distilled without decomposition. No method of purifying it has been found. Its reactions indicated that it was mainly 2-hydroxytetrahydropyran-3-one in equilibrium with an open chain aldehyde form:



Since the product is colored, chromatographic adsorption suggested itself as a method of purification. With a view to using this method, the solubility of

the substance in various solvents was investigated. It was found to be very soluble in water and in ethanol, but appeared to be entirely insoluble in petroleum ether, benzene, chloroform, ether, acetone, carbon tetrachloride, and ethyl acetate. This limited solubility is a serious difficulty in applying the chromatographic adsorption technique.

To test whether the substance was readily adsorbed, a dilute solution in ethanol (1 g. in 500 ml.) was run through a column (15 cm. x 1.5 cm.) of activated alumina. The colored material was found to be completely adsorbed in the top third of the column. Attempts to recover the substance from the adsorbent, using ethanol and water, were unsuccessful.

The red sirup was used in the crude form for the preparation of derivatives. These were found to be products such as one would expect from the aldehyde form of 2-hydroxytetrahydropyran-3-one.

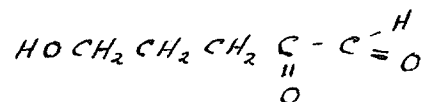
Properties and Derivatives of
2-Hydroxytetrahydropyran-3-one

This substance was found to be strongly aldehydic. It reduced Fehling's solution rapidly when warmed.

2,4-Dinitrophenylosazone

2,4-Dinitrophenylhydrazine (0.4 g.) was dissolved in concentrated sulfuric acid (2 ml.) and water (4 ml.) and 95% ethanol (10 ml.) was added. To this solution was added 2-hydroxytetrahydropyran-3-one (0.5 g.) dissolved in 95% ethanol (10 ml.). There was an almost immediate precipitate. On filtration and recrystallization from nitromethane, the product was found to be the orange-colored dinitrophenylosazone, m.p. 242° , met previously.

The product obtained here had been made earlier from tetrahydrofurfural, the 3-halotetrahydropyran-2-ols, tetrahydropyran-2,3-diol, and 3,3-dichlorotetrahydropyran-2-ol. In all these cases it had precipitated only after the reaction mixture had been refluxed for a time. Here no refluxing was required and the precipitate was almost immediate. This suggests that the following ketoaldehyde was present:

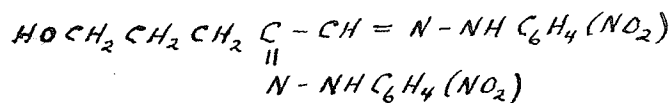


p-Nitrophenylosazone

2-Hydroxytetrahydropyran-3-one (0.5 g.) was added to a solution of p-nitrophenylhydrazine (0.5 g.) in 95% ethanol (15 ml.). Glacial acetic acid (3 drops) was added. The mixture was warmed in boiling water for an hour and allowed to stand. A black precipitate

settled out. Recrystallized from methanol, the product consisted of fine red crystals which melted at 246° , with decomposition.

This product was found to be the same p-nitro-phenylosazone obtained previously from tetrahydro-furfural and from the 3-halotetrahydropyran-2-ols. Its structure can only be:

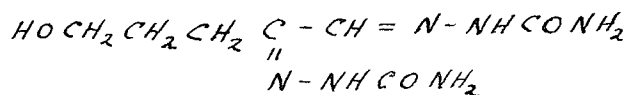


Disemicarbazone

2-Hydroxytetrahydropyran-3-one (1 g.), semi-carbazide hydrochloride (1 g.) and sodium acetate (1.5 g.) were dissolved in water (10 ml.). The mixture was shaken and warmed in boiling water for half an hour. On cooling a precipitate settled out. Recrystallized from aqueous ethanol, with charcoal, the product was a white crystalline solid which melted, with decomposition, in the range $215-225^{\circ}$, depending on the temperature at which it was immersed in the melting point bath. When immersed at room temperature, it melted at 215° ; when immersed at 210° , it melted at 225° . Repeated recrystallization failed to give it a definite melting point.

This product is thought to be the disemicarbazone of the aldehyde form of 2-hydroxytetrahydropyran-3-one.

It has the structure:



Analysis for nitrogen supported this conclusion.

Found : N, 36.55%.

Calculated for $C_{77}H_{140}O_3N_6$: N, 36.52%.

The same product was obtained from tetrahydropyran-2,3-diol (page 93) and from 3,3-dichlorotetrahydropyran-2-ol (page 100) but somewhat less readily.

Permanganate Oxidation

2-Hydroxytetrahydropyran-3-one (1 g.) was dissolved in water (10 ml.), 5% sodium hydroxide solution (1 ml.) was added, then saturated potassium permanganate solution, with occasional shaking, until the color remained permanent. This took several days. The manganese dioxide was filtered off and the filtrate acidified with dilute sulfuric acid. Further decolorization of the permanganate now occurred. When this acid oxidation was complete, the excess permanganate was destroyed with a little sodium bisulfite, the solution evaporated to dryness, and the residue extracted with ether. On evaporation of the ether, a solid was left. This, recrystallized from water, melted at 186° . It was succinic acid.

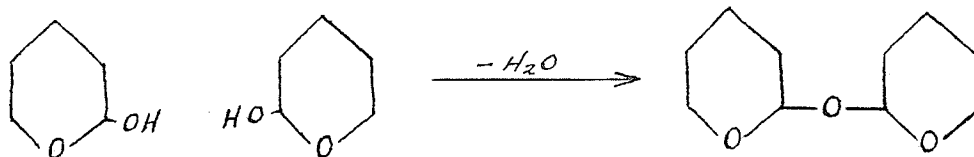
The acid was identified by the preparation of the p-bromophenacyl ester, m.p. 210-211°, and the p-nitrobenzyl ester, m.p. 87-88°, using the procedures of Shriner and Fuson (60). Mixed melting points of these derivatives with samples prepared from an authentic specimen of succinic acid showed no depression.

Nitric Acid Oxidation

2-Hydroxytetrahydropyran-3-one (1 g.) was subjected to nitric acid oxidation, using the same procedure as was used in the case of tetrahydropyran-2,3-diol (page 95). The only product isolated was a high-melting organic solid, whose nature has not been determined.

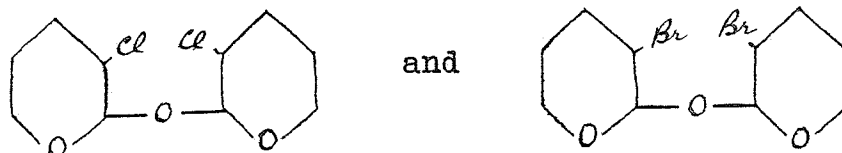
Preparation of the Ditetrahydropyranyl Ethers

The ditetrahydropyranyl ether derivable from two molecules of tetrahydropyran-2-ol,



was obtained as a by-product in the preparation of tetrahydropyran-2-ol, described earlier (page 74).

The halogenated ethers



were isolated in small amounts in some runs of the

preparations of the 3-halotetrahydropyran-2-ols. When the dihalides were treated with sodium carbonate solution, as described earlier (pages 79-81), the bulk of the organic phase dissolved gradually in the aqueous reaction mixture. There was usually left, however, a small quantity of an oil which did not dissolve. When this was separated from the aqueous solution, before the extraction with ether, and was cooled in the refrigerator, it solidified. The solid proved to be the ether.

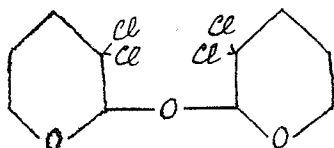
These ethers were obtained also when attempts were made to purify the 3-halotetrahydropyran-2-ols by distillation under a pressure of 15-20 mm. Invariably there were signs of decomposition in the distilling flask and the distillate, when it crystallized, proved to be the ether rather than the halohydrin.

Refluxing a 3-halotetrahydropyran-2-ol for an hour by heating it on an oil bath at 180-200° and then allowing it to stand for a few days in the refrigerator, gave a solid product which was the corresponding ether.

The halogenated ethers are white crystalline solids. They were identified and distinguished from the corresponding halotetrahydropyrans by their melting points. Paul (42, 48) has reported the melting

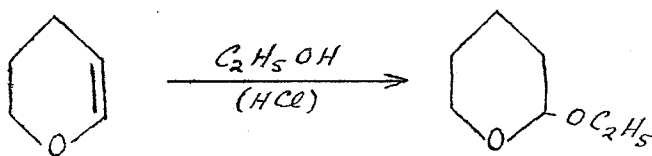
point of the brominated ether to be 110° and that of the chlorinated ether 108° .

When 2,3,3-trichlorotetrahydropyran was left in contact with water for several months, the whole mixture solidified. Recrystallization of the solid from aqueous ethanol gave white crystals melting at $136-137^{\circ}$, the reported (37) melting point of the ether



Preparation of 2-Ethoxytetrahydropyran

This substance was prepared by the method Paul (41, 44) had used for 2-methoxytetrahydropyran, the addition of the alcohol to dihydropyran in the presence of dry hydrogen chloride:



Dihydropyran (21 g., 0.25 mole) was dissolved in absolute ethanol (50 ml.). Absolute ethanol (3 ml.) saturated with dry hydrogen chloride was added. The mixture warmed up. When the initial reaction was over, it was heated to reflux for two hours and allowed to stand overnight. The acid was then neutralized with

a little powdered calcium carbonate and the alcohol taken off under reduced pressure. The residue, distilled under reduced pressure, yielded a liquid (16 g.) boiling at 40-41° at 13 mm. The product boiled at 141-142° at 742 mm. and had refractive index n_D^{25} 1.426.

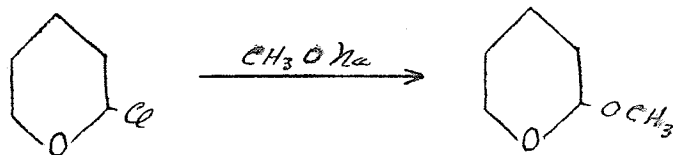
Woods and Kramer (66), who prepared 2-ethoxytetrahydropyran by the same method, have reported b.p. 146° at 760 mm. and n_D 1.4248.

Analysis: Found : C, 63.67%, H, 10.91%.

Calculated for $C_7H_{14}O_2$: C, 64.62%, H, 10.77%.

Preparation of 2-Methoxytetrahydropyran

This substance was prepared by treating 2-chlorotetrahydropyran with sodium methylate:



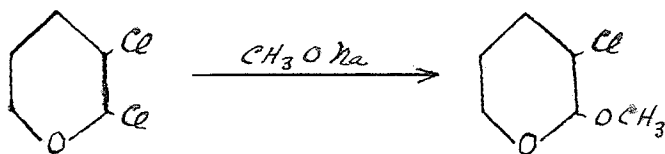
2-Chlorotetrahydropyran (30 g., 0.25 mole), prepared as described earlier (page 71), was added slowly to sodium methylate (13.5 g., 0.25 mole) suspended in methanol (50 ml.) and cooled to 0° in ice water. The mixture was allowed to stand overnight. It was then heated to reflux for two hours, cooled, and the liquid filtered from the precipitated salt. The latter was dissolved in water, freeing a further quantity of

organic liquid, which was extracted with ether. The water solution, on evaporation, gave a quantitative yield of sodium chloride. The ether extract was added to the original product in methanol and the mixture dried over magnesium sulfate. The ether and methanol were distilled off at atmospheric pressure. The residue, distilled under reduced pressure, gave a liquid (12 g.) boiling at 35-36° at 20 mm. and at 126-127° at 745 mm. It had refractive index n_D^{21} 1.428.

Paul (41, 44), who prepared 2-methoxytetrahydropyran by another method, reported b.p. 128° at atmospheric pressure and refractive index n_D^{15} 1.4262.

Preparation of 2-Methoxy-3-chlorotetrahydropyran

This substance was formed when 2,3-dichlorotetrahydropyran was treated with sodium methylate:



Crude 2,3-dichlorotetrahydropyran (39 g., 0.25 mole), freshly prepared as described earlier (page 71), was added gradually to a slight excess of sodium methylate (14 g.) suspended in methanol (50 ml.) and cooled to 0°. There was vigorous reaction. When all the reagent had been added and the initial reaction was over, the mixture was heated to reflux for two hours. After

cooling, water was added to dissolve the precipitated salt. The organic product was then extracted with ether and the extract dried. The water solution gave a quantitative yield of sodium chloride (14 g.). The ether extract, after evaporation of the ether and methanol, gave a liquid product (22 g.) boiling at 69-70° at 18 mm. and having a refractive index n_D^{27} 1.458.

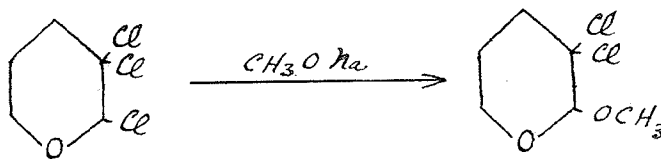
Analysis : Found : Cl, 23.65%.

Calculated for $C_6H_{11}O_2Cl$: Cl, 23.58%.

Jones and Bremner (31), who prepared 2-methoxy-3-chlorotetrahydropyran by another method, reported b.p. 38-40° at 2 mm. and refractive index n_D^{20} 1.4576.

Preparation of 2-Methoxy-3,3-dichlorotetrahydropyran

This substance was obtained by treating 2,3,3-trichlorotetrahydropyran with sodium methylate:



2,3,3-Trichlorotetrahydropyran (19 g., 0.1 mole), prepared as described earlier (page 73), was added to a slight excess of sodium methylate (6 g.) suspended in methanol (25 ml.) and cooled to 0°. The mixture had to be warmed to start the reaction but had to be cooled again after starting to keep it from becoming

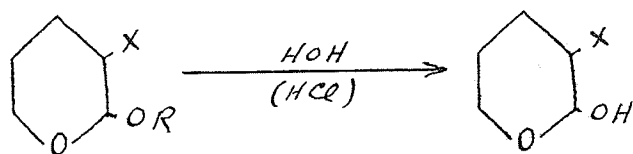
violent. When the initial reaction was over, the mixture was warmed to reflux for two hours. Water was then added to dissolve the precipitated salt and the solution was extracted with ether. The ether extract, after drying and evaporation of the ether and methanol, was distilled under reduced pressure and yielded a liquid product (10 g.) boiling at 84-86° at 13 mm. and having refractive index n_D^{26} 1.498.

A chlorine analysis, which gave 44.99% chlorine as compared with the calculated 38.38%, indicated that the product was not pure. The probable impurity was unreacted 2,3,3-trichlorotetrahydropyran whose boiling point, 92-94° at 15-16 mm., is close to that of the product. There was not enough sample left to purify by fractionation.

Jones and Bremner (31), who prepared 2-methoxy-3,3-dichlorotetrahydropyran by another method, reported the boiling point as 40-42° at 2 mm.

Hydrolysis of the Ethers

The tetrahydropyran-2-ethers are hydrolyzed by refluxing with dilute hydrochloric acid to produce the corresponding tetrahydropyran-2-ols:



2-Methoxy-3-chlorotetrahydropyran

2-Methoxy-3-chlorotetrahydropyran (2 g.) was refluxed with dilute hydrochloric acid (15 ml.) for an hour and a half. The acidity was then neutralized with powdered calcium carbonate, the excess carbonate filtered off, and the solution extracted with ether. The ether extract, on drying and evaporation, yielded 3-chlorotetrahydropyran-2-ol (1.5 g.).

Bis-(3-chlorotetrahydropyran)-2-ether

The ditetrahydropyranyl ether (2.5 g.) was refluxed with dilute hydrochloric acid (35 ml.) until the solid had gone into solution, about 10 hours. The acid was then neutralized with powdered calcium carbonate, the mixture filtered and the filtrate extracted with ether. Drying and distillation of the ether left a residue (2 g.) which solidified on cooling in the refrigerator. The product was 3-chlorotetrahydropyran-2-ol.

Chlorotetrahydropyranyl Ethers
with Sodium Hydroxide Solution

2-Methoxy-3-chlorotetrahydropyran (2 g.) was refluxed with 5% sodium hydroxide solution (10 ml.) for eight hours. Isolation of the organic material led to the recovery of the bulk of the original ether.

Bis-(3-chlorotetrahydropyran)-2-ether was similarly refluxed with sodium hydroxide solution for several days and no apparent reaction resulted.

Reaction of Dihydropyran with Formaldehyde

Acid-catalyzed

Dihydropyran (84 g., 1 mole) was stirred at room temperature with aqueous formaldehyde (160 ml. of 40% solution) containing a trace of concentrated hydrochloric acid (3 to 4 drops). The mixture warmed up and became homogeneous in 10 to 15 minutes. At this stage it had become quite hot. The solution was stirred until it had cooled to room temperature. It was then extracted with ether and the extract dried over anhydrous calcium sulfate. After evaporation of the ether, the residue was fractionated under reduced pressure, 15 to 20 mm. There was considerable decomposition during the fractionation, indicated by liberation of formaldehyde and consequent pressure fluctuations. The temperature rose gradually for the most part and no constant boiling liquid product was found.

Fractions such as the following were collected, the quantities varying from run to run as indicated:

- (1) under 30°/20 mm. (10 to 15 g.);
- (2) 30° - 90°/20 mm., mostly 80-90° (25 to 30 g.);
- (3) 90° - 125°/20 mm. (5 to 10 g.);
- (4) 125° - 150°/20 mm. (10 to 15 g.);
- (5) Residue (25 to 30 g.).

Fraction (1) had a strong odor of formaldehyde and

on standing deposited a white solid, probably para-formaldehyde.

All fractions contained some free formaldehyde. This was indicated by the fact that they all gave its 2,4-dinitrophenylhydrazone, identified by comparison with a sample prepared from authentic formaldehyde.

Fraction (2) should contain the hydrolysis product of dihydropyran, tetrahydropyran-2-ol, which is formed when dihydropyran is treated with water in the presence of acid. This fraction was re-fractionated several times and finally a portion, b.p. 77-78°/14 mm., was obtained which was the tetrahydropyranol. This made up about half the total. It was identified by the preparation of its 2,4-dinitrophenylhydrazone, m.p. 112-113°, and by an analysis: found: C, 58.73%, H, 9.52%; calculated for $C_5H_{10}O_2$: C, 58.82%, H, 9.80%.

Fraction (5) is the most likely to contain the expected dioxan, which is probably high-boiling. This conclusion was supported by an analysis: found: C, 58.50%, H, 9.06%; calculated for the dioxan, $C_7H_{12}O_3$: C, 58.33%, H, 8.33%. A sample of this material was reduced with sodium and amyl alcohol.

High vacuum distillation was attempted but the large quantities of formaldehyde pulled off made it impractical.

In some runs the reaction mixture was refluxed for a time after it became homogeneous, since there was a possibility that the reaction had not gone to completion. In these cases the mixture turned yellow and became quite viscous. Fractionation then gave less of the low-boiling fractions, but the residue tended to resinify.

Uncatalyzed Reaction

When the reactants were mixed in the same proportions, but omitting the trace of acid, and the mixture was warmed, the dihydropyran layer disappeared in two to three hours. Extraction with ether and fractionation, as described for the catalyzed reaction, led to a series of liquid fractions, all containing formaldehyde, such as were obtained in the catalyzed reaction.

Reduction of the Presumed Dioxan

Into a three-neck flask fitted with a condenser with calcium chloride tube, a mercury-seal stirrer, and a dropping funnel and gas inlet, were placed sodium (15.6 g.) and dry toluene (35 ml.). The mixture was heated to reflux temperature in an atmosphere of propane, while stirring vigorously. The presumed dioxan (24 g.) dissolved in sec. amyl alcohol (50 ml.) was added gradually. The refluxing and stirring were continued until all the sodium had disappeared. When the reaction

seemed to be over, the solution was poured into ice water. The aqueous mixture was extracted with ether and the extract dried over anhydrous calcium sulfate. The ether, toluene, and amyl alcohol were taken off under reduced pressure. The residue (15 g.) was distilled at 18 mm. and separated into three fractions: (1) up to 120°; (2) 120° - 140°; (3) residue. No constant boiling product was isolated.

The fraction boiling at 120-140°/18 mm. had refractive index n_D^{28} 1.460. This could contain the expected tetrahydropyran-3-methanol. Geyer and Mortimer (19) have reported its boiling point as 68-69°/2 mm. and refractive index n_D^{20} 1.4629.

An attempt to prepare a 3,5-dinitrobenzoate from the product was not successful.

CONCLUSIONS

1. 2-Chlorotetrahydropyrans can be converted to tetrahydropyran-2-ols by hydrolysis with sodium carbonate solution.
2. All the tetrahydropyran-2-ols have aldehyde properties but these are somewhat less pronounced in the 3-halo- and the 3,3-dihalotetrahydropyran-2-ols.
3. For tetrahydropyran-2-ol, tetrahydropyran-2,3-diol, and 2-hydroxytetrahydropyran-3-one, the aldehyde properties are due to δ -hydroxyvaleric aldehyde forms in equilibrium with the ring structures.
4. The 3-halotetrahydropyran-2-ols have a tendency to lose hydrogen halide and as a result are converted into tetrahydrofurfural, or tetrahydropyran-2,3-diol, and finally 2-hydroxytetrahydropyran-3-one, the extent of the change depending upon the reagent and the conditions. This tendency to form aldehydic substances accounts for the aldehyde properties of the halotetrahydropyrans. There is no evidence of α -halo- δ -hydroxyvaleric aldehyde forms.
5. 3,3-Dichlorotetrahydropyran-2-ol also has a tendency to lose its halogen content. This converts it to 2-hydroxytetrahydropyran-3-one, which is in equilibrium with an aldehyde form.

6. In the presence of phenylhydrazines, the 3-halo-tetrahydropyran-2-ols tend to go over into tetrahydrofurfural and thence with excess reagent to 2-hydroxytetrahydropyran-3-one. Thus they give phenylhydrazones of these two substances. Under similar conditions, 3,3-dichlorotetrahydropyran-2-ol gives derivatives of 2-hydroxytetrahydropyran-3-one.
7. With strong alkali the 3-halotetrahydropyran-2-ols are converted to tetrahydropyran-2,3-diol and 3,3-dichlorotetrahydropyran-2-ol is converted to 2-hydroxytetrahydropyran-3-one. The same two substances can be prepared more expeditiously by the action of the alkali on 2,3-dichlorotetrahydropyran and 2,3,3-trichlorotetrahydropyran, respectively.
8. Tetrahydrofurfural, the 3-halotetrahydropyran-2-ols, tetrahydropyran-2,3-diol, and 3,3-dichlorotetrahydropyran-2-ol, all yield derivatives of the aldehyde form of 2-hydroxytetrahydropyran-3-one. These derivatives are obtained more rapidly, however, from 2-hydroxytetrahydropyran-3-one itself.
9. Tetrahydropyran-2,3-diol and 2-hydroxytetrahydropyran-3-one both give succinic acid when oxidized by permanganate. With nitric acid, tetrahydropyran-2,3-diol gives what appears to be α -hydroxyglutaric acid.

Probably other intermediate oxidation products can be obtained from both substances with milder reagents.

10. Ditetrahydropyranyl ethers tend to be formed from the tetrahydropyran-2-ols when these are subjected to heat or are left standing for some time in the presence of a trace of acid. These ethers are therefore common impurities in the tetrahydropyran-2-ols.
11. Refluxing the ditetrahydropyranyl ethers with dilute acids re-converts them to the tetrahydropyran-2-ols. This hydrolysis reaction takes place more readily for the alkyl tetrahydropyranyl ethers.
12. 2-Chlorotetrahydropyrans react readily with sodium alkoxides to form 2-alkoxytetrahydropyrans.
13. Dihydropyran reacts with formaldehyde, the reaction being catalyzed by acid. The product, however, is difficult to isolate because it decomposes when attempts are made to distil it.

SUGGESTIONS FOR FURTHER WORK

Malonic Ester Condensations with the 2-Chlorotetrahydropyrans

In this work trial runs were made of malonic ester condensations with 2-chloro- and 2,3-dichloro-tetrahydropyran, using sodium and absolute ethanol as condensing agent. The results were disappointing. A competitive reaction of sodium ethylate with the 2-chlorotetrahydropyrans is thought to be one reason for the failure (pages 57-59).

Schudel and Rice (58) carried out the reaction with 2-chlorotetrahydropyran using sodium hydride as condensing agent and toluene as solvent and isolated a number of tetrahydropyran-2-malonic esters. There is little doubt that the same reaction would go with 2,3-dichloro- and 2,3,3-trichlorotetrahydropyran to give the corresponding malonic esters.

Purification of 2-Hydroxytetrahydropyran-3-one

2-Hydroxytetrahydropyran-3-one decomposes when attempts are made to purify it by distillation. Extracting the impurities from it, or vice versa, by the use of organic solvents also fails, because the crude material is very soluble in water and alcohols and apparently insoluble in other common organic solvents. The fact that it is a colored material

suggests the chromatographic adsorption technique.

A trial run using aluminum oxide as adsorbent indicated that the substance is readily adsorbed from its solution in ethanol. Difficulty was encountered, however, in recovering it from the adsorbent.

The solubility of the material in such a limited number of solvents is a serious handicap (pages 101-102). Probably other, less commonly used solvents, should be investigated. Other adsorbents should also be tried. There may be a combination of solvents and adsorbent that will make possible the use of the chromatographic adsorption method to purify this substance.

Oxidation Products from Tetrahydropyran-2,3-diol
and 2-Hydroxytetrahydropyran-3-one

Tetrahydropyran-2,3-diol and 2-hydroxytetrahydropyran-3-one should give an interesting series of oxidation products (page 54). Permanganate oxidation of either one leads to succinic acid. Nitric acid oxidation of tetrahydropyran-2,3-diol gives what appears to be α -hydroxyglutaric acid. Milder oxidizing agents should give others of the possible products.

Reaction of Dihydropyran with Formaldehyde

The m-dioxan expected as a product of this reaction seems to be too unstable to isolate by

distillation (pages 68-69). No other method of purification suggests itself. Probably the best procedure would be to take the crude product on to the next stage and hope that a pure product can be isolated by fractionation there. Beets and co-workers (4, 6, 7, 15) isolated m-dioxans and reduced them to alcohols. One of their procedures for the reduction of m-dioxans, or perhaps reduction with lithium aluminum hydride, applied to the crude product here, might make possible the isolation of the expected alcohol from the reduction product.

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