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# REACTIONS OF SOME HALOGEN DERIVATIVES OF TETRAHYDROPYRAN-2-OL<sup>1</sup>

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### 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  $\delta$ -hydroxy-valeric 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  $\delta$ -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 halotetrahydropyranols and thus to determine the nature of the aldehydic substances derived from them. Both the chloroand 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°;

<sup>1</sup>Manuscript received November 14, 1955.

Contribution from the Department of Chemistry, the University of Maniloba, Winnipeg, Man. This paper was read before the XIVth Congress of the International Union of Pure and Applied Chemistry in Zurich. CHARLESWORTH AND GIESINGER: HALOGEN DERIVATIVES

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

Can. J. Chem. Downloaded from www.nrcresearchpress.com by 193.61.135.80 on 11/17/14 For personal use only. (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.

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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°. 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

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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  $\alpha$ -keto- $\delta$ -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  $\alpha$ -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

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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).

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# (a) 2,4-Dinitrophenylhydrazones

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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 halotetrahydropyranols were the same.

# (c) p-Nitrophenylhydrazones

The 3-halotetrahydropyranols 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 halotetrahydropyranols 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

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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-di-chlorotetrahydropyran-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  $35-40^{\circ}$ 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

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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.

### ACKNOWLEDGMENTS

The authors are grateful to the National Research Council for a grant which has aided in this research, and to E.I. du Pont de Nemours and Company (Inc.) for a supply of dihydropyran.

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