# SOME ASPECTS OF FURAN AND PYRAN CHEMISTRY

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THE chemistry of furan and pyran compounds has been of academic interest for over a hundred years, but during the last thirty years has become of increasing commercial importance, mainly owing to the establishment of suitable manufacturing processes for furfuraldehyde from pentosan-containing agricultural materials.[1] It is not intended to deal here with all the many aspects of furan and pyran chemistry as comprehensive reviews have recently appeared.[2] This Review deals mainly with those aspects in which there have been noteworthy advances in the last five years, namely, the hydrogenation and oxidation of furan compounds and the chemistry of the tetrahydrofurans and di- and tetra-hydropyrans which has, in the main, followed from the ready accessibility of 2 : 3-dihydro-4-pyran (II) by catalytic dehydration of tetrahydrofurfuryl alcohol (I) : [3]

$$\text{(I.)} \quad \longrightarrow \quad \text{(II.)} \quad + H_2O$$
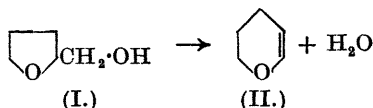
A striking advance has also been made in the conversion of furfuraldehyde into the parent compound, furan (III), which until recently could be made only in small quantities by the decarboxylation of furoic acid, thus : [4]

$$\text{(III.)} \quad + CO_2$$
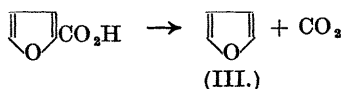
In the vapour phase at 200—280° in the presence of catalysts, especially nickel, furfuraldehyde decomposes to furan, and the yield is improved to 65% by presence of a limited quantity of hydrogen.[5] R. Paul[6] obtained furan among the products of decomposition of furfuryl alcohol over Raney nickel at 150°. The vapour-phase decomposition[7] of furfuraldehyde to furan over lime at 350—450° was the first major advance towards a satisfactory preparation of furan, being a distinct improvement on the passage

[1] H. J. Brownlee and C. S. Miner, *Ind. Eng. Chem.*, 1948, **40**, 201.

[2] (a) F. N. Peters, *ibid.*, 1936, **28**, 755 ; 1939, **31**, 178 ; 1948, **40**, 200 ; A. Wacek, *Angew. Chem.*, 1941, **54**, 453 ; L. N. Owen, *Ann. Reports*, 1945, **42**, 157 ; (b) O. W. Cass, *Ind. Eng. Chem.*, 1948, **40**, 216 ; (c) G. F. Wright and H. Gilman, *ibid.*, p. 1517.

[3] R. Paul, *Bull. Soc. chim.*, 1933, [iv], **53**, 1489 ; B.P. 547,334 ; C. H. Kline and J. Turkevich, *J. Amer. Chem. Soc.*, 1945, **67**, 498.

[4] *Org. Synth.*, Coll. Vol. I, 2nd Edn., 1941, p. 274.

[5] C. L. Wilson, *J.*, 1945, 61 ; B.P. 553,175.

[6] R. Paul, *Bull. Soc. chim.*, 1938, **5**, 1592 ; 1941, **8**, 507.   [7] U.S.P. 2,337,027.

of furfuraldehyde through fused caustic alkali or over soda-lime.[8] More recently, details have been published [9] of the catalytic vapour-phase decomposition of furfuraldehyde in the presence of steam and a dehydrogenation catalyst, such as zinc manganese chromite, at a temperature of 350—450°, with a steam–furfuraldehyde molar ratio of between 2 : 1 and 6 : 1. The overall reaction, in which 85—90% yields of furan are obtained, is :

$$\text{\Large $\bigcup_O$}\!CHO + H_2O \quad \longrightarrow \quad \text{\Large $\bigcup_O$} + CO_2 + H_2$$
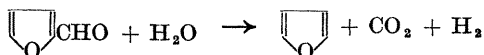
This reaction has now been applied commercially as a continuous process.[2b]

Hydrogenation Reactions of Furan Compounds

By reason of their structure, furan and compounds containing the furan ring can be hydrogenated under various conditions to give a wide variety of products. Only the more important types and technically interesting examples are dealt with here. Information on these subjects has been summarised on several occasions,[10] but such important advances have been made in the last 3—5 years as to make it desirable to review the present position.

The reactions are conveniently classified into those involving :

    1. Hydrogenation of a side chain only ;

    2. Hydrogenation of the nucleus and a side chain ;

    3. Hydrogenolysis of the ring.

1. Side-Chain Hydrogenation.—Hydrogenation of a side chain attached to a furan nucleus without saturation of the nucleus itself has proved possible. Catalysts containing Group VIII metals can be employed under liquid-phase conditions if care is taken to use moderate temperatures, otherwise ring saturation will also occur. For instance, furfuraldehyde may be converted into furfuryl alcohol in 90% yield by use of a cobalt-on-kieselguhr catalyst at 50 atm. hydrogen pressure and 80—100° [11] or by use of a foraminate cobalt catalyst * [12] at 10—30° ; at temperatures above 120°, there is a tendency for tetrahydrofurfuryl alcohol to be formed. Similarly, furfurylideneacetaldehyde (3-furylacraldehyde) (IV) in the presence of

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[8] C. D. Hurd, A. R. Goldsby, and E. N. Osborne, *J. Amer. Chem. Soc.*, 1932, **53**, 2532.   [9] B.P. 575, 362.
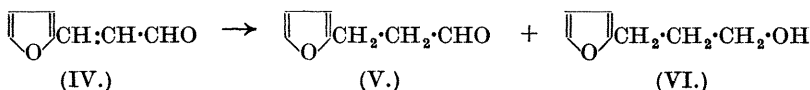
[10] (a) H. Adkins, " The Reactions of Hydrogen with Organic Compounds over Copper Chromium Oxide and Nickel Catalysts ", Univ. of Wisconsin Press, Madison, 1937 ; (b) L. N. Owen, *Ann. Reports*, 1945, **42**, 166 ; (c) B. H. Wojcik, *Ind. Eng. Chem.*, 1948, **40**, 210.
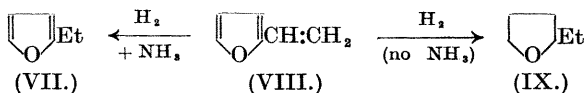
[11] B.P. 605,922.   [12] B.P. 627,293.

* Foraminate catalysts are prepared by extraction of a non-catalytically active metal from the surface layers of granules of alloys of that metal with other, catalytically active metals. Examples of such alloys are nickel–aluminium and –magnesium, cobalt–aluminium, and copper–aluminium, –silicon, and –zinc ; those most commonly used contain aluminium. The extraction is done by either acid or alkaline solutions as required. The foraminate catalysts are different from the Raney catalysts, which are in powder form, and in which the extraction of the non-catalytically active metal is virtually complete. For further information, see B.P. 611,987, 621,749, 623,595, 624,035, and 628,405.

Raney nickel in ethanol at 23° gives 48% of 3-(2-furyl)propaldehyde (V) and 30% of 2-(3-hydroxypropyl)furan (VI):

$$\underset{\text{(IV.)}}{\boxed{}_O\text{CH:CH·CHO}} \rightarrow \underset{\text{(V.)}}{\boxed{}_O\text{CH}_2\text{·CH}_2\text{·CHO}} + \underset{\text{(VI.)}}{\boxed{}_O\text{CH}_2\text{·CH}_2\text{·CH}_2\text{·OH}}$$

whereas at 80° the main product is (VI) and at higher temperatures nuclear hydrogenation begins.[13] The extent of hydrogenation depends to some extent on the nature of the substituents, with aldehyde and amino-groups decreasing the extent of reaction. Thus, furan is more readily saturated than is furfuraldehyde or furfurylamine. A similar suppressing effect is achieved by the addition of ammonia or an amine; thus, using a nickel catalyst at 50° and at 50 atm. pressure, and in presence of aqueous ammonia, a 95% yield of 2-ethylfuran (VII) is obtained from 2-vinylfuran (VIII), which without the ammonia, under otherwise similar conditions, gives an 85% yield of 2-ethyltetrahydrofuran (IX): [14]

$$\underset{\text{(VII.)}}{\boxed{}_O\text{Et}} \xleftarrow[\text{+ NH}_3]{\text{H}_2} \underset{\text{(VIII.)}}{\boxed{}_O\text{CH:CH}_2} \xrightarrow[\text{(no NH}_3)]{\text{H}_2} \underset{\text{(IX.)}}{\boxed{}_O\text{Et}}$$

Similarly, the complete hydrogenation of 2-(2-cyanovinyl)furan is suppressed and with Raney nickel at 50° [10a] mixtures of 3-(2-furyl)propylamine and di-3-(2-furyl)propylamine are obtained. Also 2-furyl cyanide in the presence of ammonia gives furfurylamine over Raney nickel at room temperature.[15]

An alternative method of hydrogenating the side chain and not the ring is to employ copper-containing catalysts, either under high pressure in the liquid phase or at somewhat higher temperatures at atmospheric pressure in the vapour phase. However, here again care is necessary, as too drastic conditions lead to hydrogenolysis of the furan ring, as described below. The use of copper chromite catalysts [10a] for the conversion of furfuraldehyde into furfuryl alcohol at 75—250 atm. and at 150—175° is well known and these conditions have been used in a commercial batch process.[10a] Recent improvements in catalysts have made possible continuous processes, which with a foraminate copper catalyst under 250 atm. at 80° give substantially complete conversion of furfuraldehyde into furfuryl alcohol.[12]

A high yield of furfuryl alcohol is also obtainable when working in the vapour phase below 150°, given careful choice of the form of the copper catalyst; [16] free alkali reduces the activity of the catalyst and an 85% yield of furfuryl alcohol [17] is obtained up to 265° whereas otherwise 2-methylfuran would be the major product. Further work on the conversion of furfuraldehyde into furfuryl alcohol and 2-methylfuran with particular copper catalysts, and of furfuryl alcohol into 2-methylfuran, has recently

[13] H. E. Burdick and H. Adkins, *J. Amer. Chem. Soc.*, 1934, **56**, 438.
[14] B.P. 596,880.
[15] W. Huber, *J. Amer. Chem. Soc.*, 1944, **66**, 876.
[16] H. D. Brown and R. M. Hixon, *Ind. Eng. Chem.*, 1949, **41**, 1382.
[17] B.P. 621,743.

been published.[18] This control of the direction of hydrogenation of furfuraldehyde to either furfuryl alcohol or 2-methylfuran, depending on the presence or absence of free alkali, has been discussed by J. G. M. Bremner and R. K. F. Keeys.[19] Another recent example of side-chain hydrogenation using copper catalysts in either the liquid or the vapour phase is the conversion of 2-vinylfuran in high yield into 2-ethylfuran.[20]

Two " chemical " methods of effecting side-chain reductions may be mentioned : treatment of furfuraldehyde with formaldehyde and alkali gives a 90% yield of furfuryl alcohol,[21] and reduction of furfuryl alcohol by sodium and ethanol in liquid ammonia gives a 20% yield of 2-methylfuran with 38% of the unchanged alcohol.[22]

2. Nuclear and Side-Chain Hydrogenation.—Saturation of the nucleus in furan compounds proceeds very readily under moderate pressure in presence of platinum, nickel, or similar catalysts and in general no difficulty is experienced in obtaining the tetrahydro-derivative. Examples are too numerous for specific mention. The effect of substituents such as —CHO or —NH$_2$ or of the presence of amines has been mentioned earlier, but satisfactory hydrogenation can be obtained by modifying the catalyst.[10a, 14, 15] In particular, direct hydrogenation of furfuraldehyde to tetrahydrofurfuryl alcohol in high yield has been difficult to achieve in a reasonable time with a nickel catalyst under pressure in the liquid phase. One method which avoids the difficulty is two-stage hydrogenation, over a copper chromite catalyst for the formation of furfuryl alcohol which is then converted with ease over a nickel catalyst into the tetrahydro-derivative. A mixture of the two catalysts is now claimed [10c] to be more economical, operating at 170—180°/75—100 atm. An earlier method avoided a two-stage process by using a nickel chromite catalyst under pressure in the presence of a very large excess of hydrogen—sufficient to maintain vapour-phase conditions. However, the difficulty of direct conversion of furfuraldehyde into tetrahydrofurfuryl alcohol has now [23] been overcome by hydrogenating in the liquid phase in the presence of a foraminate nickel catalyst at a pressure greater than 50 atm. between 130° and 200°. Similar results are obtained with cobalt catalysts.[12] The direct hydrogenation of furfuraldehyde to tetrahydrofurfuryl alcohol has recently been described,[24] a ruthenium catalyst being used, but it is unlikely that this will be preferred to direct continuous hydrogenation over nickel owing to the cost and limited availability of the catalyst.

This section of furan chemistry cannot be left without remarking that so far no satisfactory conditions have been established either for the partial hydrogenation of the nucleus, to give a dihydrofuran, or for the complete hydrogenation of the nucleus without hydrogenation of unsaturated

[18] (a) U.S.P. 2,445,714 ; L. W. Burnette, I. B. Johns, R. F. Holdren, and R. M. Hixon, *Ind. Eng. Chem.*, 1948, **40**, 502 ; U.S.P. 2,456,187 ; (b) C. L. Wilson, *J.*, 1945, 61.   [19] J. G. M. Bremner and R. K. F. Keeys, *J.*, 1947, 1068.
[20] B.P. 621,744 ; 627,492.
[21] A. M. Berkenheim and T. F. Darkova, *J. Gen. Chem. Russia*, 1939, **9**, 924.
[22] A. J. Birch, *J.*, 1945, 809.
[23] B.P. 608,540.   [24] U.S.P. 2,487,054.

substituents. For instance, it has not been possible directly to convert fur-furaldehyde into tetrahydrofurfuraldehyde. Poor yields have been obtained by the saturation of either furfuraldehyde diethyl acetal or diacetate, followed by the removal of the protecting groups.[25, 18b] Recently, the oxidation of tetrahydrofurfuryl alcohol with air over a silver gauze has proved to be a convenient method of producing this hitherto inaccessible material in 60% yield.[26] On storage, tetrahydrofurfuraldehyde forms a dimer, the structure of which has not yet been fully elucidated.[27]

3. Hydrogenolysis of the Furan Ring.—The opening of the furan ring by hydrogen can be effected in both the liquid and the vapour phase by employing either copper-, nickel-, or platinum-containing catalysts under rather more strenuous conditions than those previously mentioned for side-chain hydrogenation. The chief difficulty is to avoid the alternative reaction giving the tetrahydrofuran compound which takes no further part in the hydrogenolysis [28] and, in general, this difficulty is greatest when nickel or platinum catalysts are used. Thus, L. W. Burnette [29] found that, in the vapour-phase hydrogenation of 2-methylfuran over a partly activated Raney nickel catalyst, 2-methyltetrahydrofuran was formed in 50% yield at 200°, together with appreciable quantities of pentan-2-one and pentan-2-ol. Later work [28] with a more active catalyst showed that at 100° 2-methyl-tetrahydrofuran was the main product, but that above that temperature pentan-2-one was formed in increasing yield, the maximum being 75% at 185°; small quantities of pentan-2-ol were also formed.

The earlier work of H. Adkins [10a] indicated that hydrogenolysis of 2-methylfuran was the preferred reaction when a copper chromite catalyst was used in the liquid phase at 200 atm. and 250°; a 30% yield of pentan-1-ol, a 33% yield of pentan-2-ol, and only a 15% yield of 2-methyltetra-hydrofuran were obtained. The reaction has been extended to furan, which gave *n*-butanol in up to 70% yield,[30] and to 2 : 5-dimethylfuran which gave hexan-2-ol. This work showed that the presence of acids, *e.g.*, acetic acid, in the reaction medium was desirable, as alkaline conditions led to a major amount of the saturated ring compound at the expense of the product formed by hydrogenolysis.

Similarly, hydrogenolysis occurs with substituted furan compounds in which the substituents contain oxygen, *e.g.*, furfuraldehyde, furfuryl alcohol, etc. Hydrogenation of furfuraldehyde or furfuryl alcohol to mixtures of 2-methylfuran, pentan-1-ol, and the pentane-1 : 2- and -1 : 5-diols with copper chromite catalyst at 250°, *i.e.*, under more severe conditions than necessary for the formation of furfuryl alcohol from furfuraldehyde, is well known.[10a] A full description of this method of preparation of pentane-1 : 5-diol has been published.[31] High yields of these diols are also claimed [32] for a process using a nickel catalyst at 40 atm. and 200—220°.

[25] A. Hinz, G. Mayer, and G. Schucking, *Ber.*, 1943, **76**, 676.
[26] J. G. M. Bremner, R. R. Coats, A. Robertson, and (Miss) M. L. Allan, *J.*, 1949, S25.   [27] J. G. M. Bremner and A. Robertson, *ibid.*, p. S27.
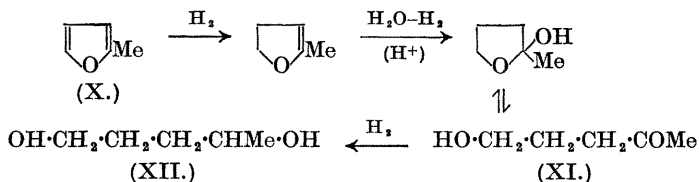[28] C. L. Wilson, *J. Amer. Chem. Soc.*, 1948, **70**, 1313.
[29] L. W. Burnette, *Iowa State Coll. J. Sci.*, 1944, **19**, 9.
[30] B.P. 586,222.   [31] *Org. Synth.*, **26**, 83.   [32] D.R.-P. 555,405.

The effect of the presence of water in the reacting system is marked ; from alkylfurans are obtained diols and keto-alcohols, and from furfuraldehyde or furfuryl alcohol mixtures of diols and triols. Thus, K. S. Topchiev,[33] using a palladium catalyst, hydrogenated 2-methylfuran (X) at room temperature in the presence of water and a limited amount of an acid, such as hydrochloric acid, to give 4-ketopentan-1-ol (XI) ; at higher temperatures pentane-1 : 4-diol (XII) is formed. The mechanism proposed is as follows :

$$\underset{\text{(XII.)}}{\text{OH·CH}_2\text{·CH}_2\text{·CH}_2\text{·CHMe·OH}} \quad \xleftarrow{\text{H}_2} \quad \underset{\text{(XI.)}}{\text{HO·CH}_2\text{·CH}_2\text{·CH}_2\text{·COMe}}$$

A further study of this reaction [34] has shown that, with a nickel catalyst and dioxan as solvent, (X) and water in the presence of small amounts of acetic acid are converted in 61% yield into (XII) in 8 hours at 150°/80 atm. In the absence of dioxan, the yield of (XII) is lower, and more 2-methyltetrahydrofuran is formed. If, however, thereaction is stopped after 1½ hours, 30% of (XI) is found, together with similar amounts of unchanged (X) and 2-methyltetrahydrofuran, and only about 4% of (XII).

The hydrogenolysis of furfuraldehyde or furfuryl alcohol in the presence of water to give mixtures of diols and triols has also been described.[35] Furfuryl alcohol, water, and glacial acetic acid, with a Raney nickel catalyst at 160°/80 atm., gave a 40% yield of pentane-1 : 2- and -1 : 5-diols and a 45% yield of pentane-1 : 2 : 5-triol.
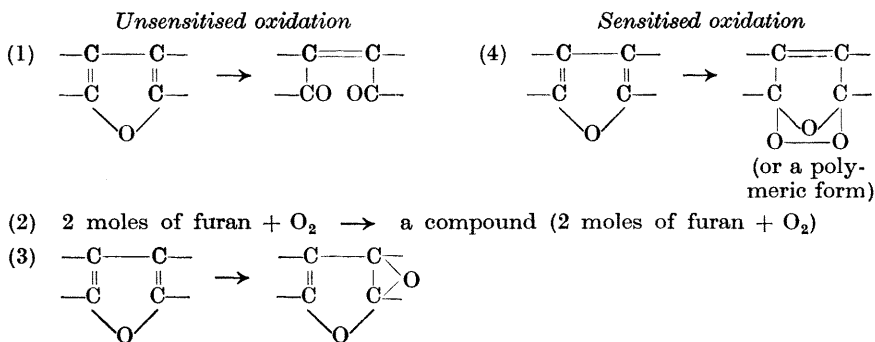
Liquid-phase Oxidation of Furans

1. Autoxidation.—G. O. Schenck was the first to describe systematic work on the course of this reaction and on the products obtained.[36] Complete experimental details have yet to be published, but he found that peroxides were formed from air and furan compounds, and he distinguished between two types of reaction. One, called the " unsensitised " reaction, was best effected by irradiating the compound in presence of oxygen and an inorganic salt, such as calcium chloride, ferrous, nickel, or manganese sulphate ; and the other, the " sensitised " reaction, was carried out by irradiating a solution of eosin in the furan. The products formed are shown in the annexed Scheme.

[33] Russian Patent 48,104 (Chem. Abs., 1937, **31**, 8549) ; K. S. Topchiev, Compt. rend. Acad. Sci. U.R.S.S., 1938, **19**, 497.

[34] L. E. Schniepp, H. H. Geller, and R. W. Van Korff, J. Amer. Chem. Soc., 1947, **69**, 672.

[35] U.S.P. 2,097,493.

[36] (a) F.I.A.T. Review of German Science (1939—1946), Preparative Organic Chemistry, Pt. II, 1948, p. 188 ; (b) G. O. Schenck, Ber., 1944, **77**, 662 ; (c) idem, ibid., 1947, **80**, 289 ; Naturwiss., 1943, **31**, 387.

Unsensitised oxidation   *Sensitised oxidation*

(1)
```
 —C——C—        —C═══C—        (4)   —C——C—        —C═══C—
 —C    C—   →  —CO  OC—              —C    C—   →  —C    C—
    \O/                                  \O/           \O—O/
```
(or a polymeric form)

(2) 2 moles of furan $+ O_2$ → a compound (2 moles of furan $+ O_2$)

(3)
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 —C——C—        —C——C
 —C    C—   →  —C    C  >O
    \O/           \O/
```

These peroxides are, of course, reactive and can be hydrogenated to give saturated dicarbonyl compounds.

The reactions of 2 : 5-dimethylfuran and its oxidation products are : [36a, b]

CH═CH
Me·CO   CO·Me
(50% yield)

CH₂—CH·OH
Me·CO   CO·Me

$(C_6H_8O_2)_2$

COMe
$[CH_2]_2$
COMe
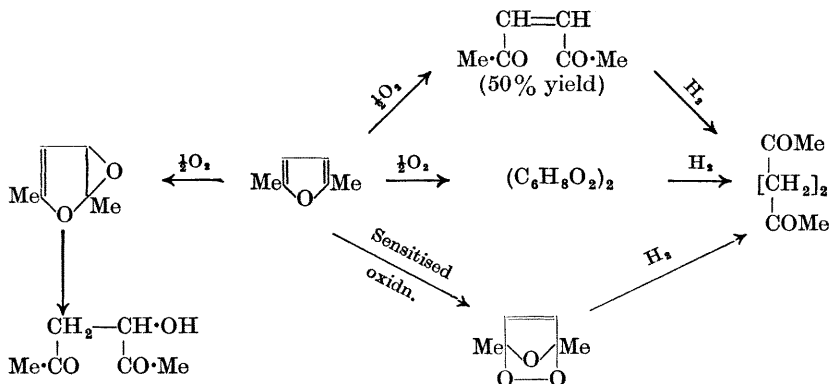
Similarly, of course, 2-methylfuran gives 4-ketopent-2-en-1-al and thence lævulaldehyde.

Another important reaction of the peroxide formed in the sensitised reaction is the rearrangement in alcoholic solution, giving a ψ-ester (XIII) of an unsaturated keto-acid ; the peroxide from 2-methylfuran reacts in this way :

(XIII.)

$HO_2C·CH:CH·COMe$ $HO_2C·[CH_2]_2·COMe$
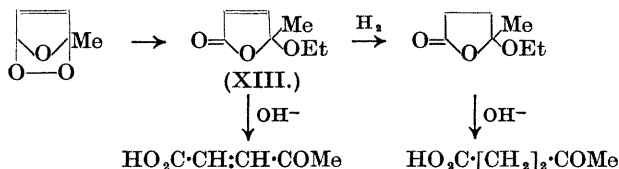
The autoxidation of furfuraldehyde in an alcohol containing eosin is particularly interesting.[36a] The reaction products are formic acid (formed in up to 80% yield) and the ψ-ester of β-formylacrylic acid (XIV), of which the yield depends on the alcohol used. Schenck considers the reaction to take place by an oxidation, followed by rearrangement of the aldehyde
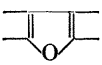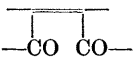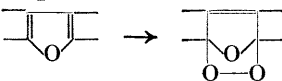
group to a formate group, which is then decomposed by the alcohol present. The overall reaction is :

$$\text{[furan-CHO]} \longrightarrow H \cdot CO_2H + \text{[O=furan-OR]}$$

(XIV.)
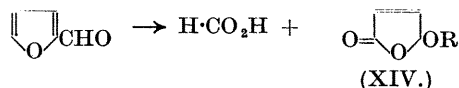
The yield of ester is about 75% when butanol or ethanol is used. When furfuraldehyde is shaken with oxygen at room temperature, β-formylacrylic acid can be detected in the product ; its polymerisation is thought to lead to a mixture of resinous acids, which are responsible for the dark colour developed in furfuraldehyde on storage in air and light.[37]

The formation of β-formylacrylic acid from furfuraldehyde had already been observed when sodium chlorate was used as the oxidising agent in presence of vanadium pentoxide ; the yield was 55%, and formic acid was also formed.[38] If the oxidation was done in presence of osmium tetroxide, tartaric acid was obtained in 48% yield.

Some furan compounds which give reactions similar to (1) and (4) of the Scheme on p. 201 are given in the Table.[36a] The reactions of most of the compounds were not examined in detail, but the Table may be a useful guide to the sort of products that might be expected.

Autoxidation of furan compounds

$$\text{[furan]} \longrightarrow -CO \quad CO- \qquad\qquad \text{[furan]} \longrightarrow \text{[furan-O-O]}$$

2-Methylfuran	Furan
2 : 5-Dimethylfuran	2-Methylfuran
2-Methyl-5-ethylfuran	2 : 5-Dimethylfuran
2 : 5-Diphenylfuran	Furoic acid
2 : 5-Dibromofuran	Furfuryl alcohol
Methyl furoate	Furfuryl acetate
Furfuryl alcohol	3 : 4-Dichlorofuran
Furylpropylcarbinol	Furylacrylic acid

2. Miscellaneous Oxidations.—Oxidation of furans in the liquid phase gives useful results with furfuraldehyde, as in the experiments described above, or with particular furans which may react favourably under these conditions. Thus, 2 : 5-diphenylfuran gives an 80% yield of 1 : 2-dibenzoylethylene on oxidation with concentrated nitric acid,[39] and 3 : 4-dichlorofuran behaves similarly giving dichloromaleic acid.[40]

There have been several studies of the action of hydrogen peroxide or peracids on furans, perhaps the earliest being that of C. F. Cross, E. J. Bevan, and T. Heiberg.[41] Later workers [42] found that, although addition

[37] A. P. Dunlop, P. R. Stout, and S. Swadesh, *Ind. Eng. Chem.*, 1946, **38**, 705 ; A. P. Dunlop, *ibid.*, 1948, **40**, 204.
[38] N. A. Milas, *J. Amer. Chem. Soc.*, 1927, **49**, 2005.
[39] R. E. Lutz and F. N. Wilder, *ibid.*, 1934, **56**, 978.
[40] A. F. Shepard, N. R. Winslow, and J. R. Johnson, *ibid.*, 1930, **52**, 2083.
[41] C. F. Cross, E. J. Bevan, and T. Heiberg, *J.*, 1899, **75**, 747.
[42] J. Böeseken, C. O. Vermij, H. Bunge, and C. Van Meeuwen, *Rec. Trav. chim.*, 1931, **50**, 1023.

did occur with furan, 2-methylfuran, and furfuryl alcohol, by far the greater part of the product was resinified in the acid conditions used ; furfuraldehyde gave an estimated 40% yield of β-formylacrylic acid.

Recent work has now shown that furans can be oxidised to 2 : 5-dialkoxy- or 2 : 5-diacyloxy-2 : 5-dihydrofurans in good yields. The products are, in fact, acetals or ketals of unsaturated 1 : 4-dicarbonyl compounds and can in turn be used for further syntheses. The general method is to oxidise the compound with bromine or chlorine in a hydroxylic solvent such as an aliphatic alcohol or acid ; better results may sometimes be obtained by adding a base to the reactants so that there is no chance of resinification by acid formed in the reaction. The general reaction can be represented :
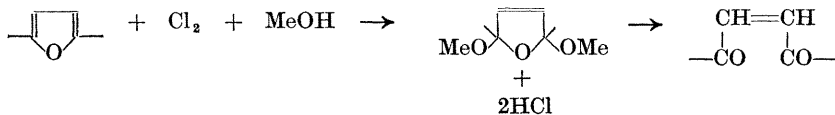
In this way, furan, 2-methylfuran, and furfuryl acetate have given the corresponding dimethoxydihydrofurans in 50—60% yields ; [43] with bromine in acetic acid, furan gives a 70% yield of 2 : 5-diacetoxy-2 : 5-dihydrofuran.[44] Furfurylidene diacetate gives the same type of compound (XV) : [43]
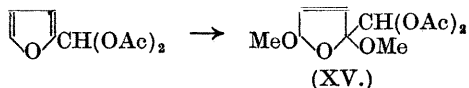
The dimethoxydihydro-compounds can be hydrogenated to give the acetals of the corresponding saturated 1 : 4-diketones [45]—a very convenient route because of the ready availability of many furan derivatives.

A remarkable reaction leading to similar products has been described by L. Vargha, J. Ramonczai, and P. Bite.[46] They found that on shaking the oxime O-toluene-p-sulphonate of 2-acetylfuran in alcohols, the furan ring opened giving an unsaturated diketo-acetal (XVI) in 80% yield. This
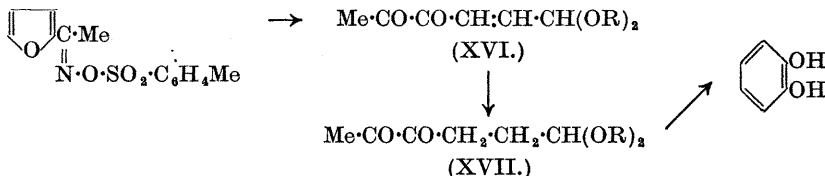
product is what would have been expected from the oxidation of 2-acetyl-furan by chlorine in alcohol. On treatment with dilute acid, even in the

[43] N. Clauson-Kaas, Kgl. Danske Videnskab. Selskab, Mat.-fys. Medd., 1947, **24**, 18 (Chem. Abs., 1948, **42**, 1930) ; N. Clauson-Kaas and F. Limborg, Acta Chim. Scand., 1947, **1**, 619 (Chem. Abs., 1948, **42**, 5902) ; N. Clauson-Kaas and J. Fakstorp, ibid., p. 415 (Chem. Abs., 1948, **42**, 5901) ; B.P. 595,041.

[44] N. Clauson-Kaas, Acta Chim. Scand., 1947, **1**, 379 (Chem. Abs., 1948, **42**, 5447).

[45] B.P. 610,876.

[46] L. Vargha, J. Ramonczai, and P. Bite, J. Amer. Chem. Soc., 1948, **70**, 371.

cold, (XVI) loses acetic acid, but it can be hydrogenated to the dihydro-compound (XVII), which in hot dilute sulphuric acid undergoes intra-molecular dehydration and cyclisation to give catechol.

Di- and Tetra-hydro-furans and -pyrans, Dihydro-furans and -pyrans

1. Dihydrofurans : Synthesis.—(*a*) 2 : 3-*Dihydrofurans*. 2 : 3-Dihydro-furans, like the corresponding dihydropyrans, are anhydrides of keto-alcohols, from which they are formed on heating ; T. R. Marshall and W. H. Perkin first identified 5-methyl-2 : 3-dihydrofuran which they synthe-sised by heating 4-ketopentan-1-ol (prepared from ethyl acetoacetate and ethylene bromide).[47] Unsubstituted 2 : 3-dihydrofuran was first made, in 24% yield, by passing tetrahydrofurfuryl alcohol over a copper–nickel alloy ;[48] a better method is to treat 3-chloro-2-alkoxytetrahydrofurans (made from tetrahydrofuran) with sodium, the yields being 50–75% depending on the alkoxy-group.[49]

(*b*) 2 : 5-*Dihydrofurans*. Early preparations of 2 : 5-dihydrofuran were by heating erythritol with formic acid,[50] and removing the elements of hydrogen bromide from 3-bromotetrahydrofuran.[51] The latter method has been used to make 2 : 2-dialkyldihydrofurans,[52] but according to a later reference [53] mixtures of 2 : 5- and 2 : 3-dihydrofurans are formed by this reaction :

$$\text{Br}\underset{O}{\bigcup}\text{RR}' \xrightarrow{\text{KOH}} \underset{O}{\bigcup}\text{RR}' + \underset{O}{\bigcup}\text{RR}'$$

A more recent method links the preparation of such compounds with modern developments in acetylene chemistry ; but-2-ene-1 : 4-diol or methyl-substituted butenediols, made by hydrogenation of the product of reaction of acetylene with formaldehyde or a ketone,[54] give 2 : 5-dihydrofurans when passed in the vapour phase over solid dehydrating catalysts [55] or when heated with sulphuric or phosphoric acid.[56] Only the *cis*-form of but-2-ene-1 : 4-diol (which is the isomer predominantly formed on hydrogenating but-2-yne-1 : 4-diol) gives 2 : 5-dihydrofuran, while the *trans*-diol gives only crotonaldehyde.[57]

2. Dihydropyrans : Synthesis.—(*a*) 2 : 3-*Dihydro*-4-*pyrans* (1 : 5-*Epoxy-pent*-1-*enes*). The preparation of dihydropyran by the catalytic dehydration of tetrahydrofurfuryl alcohol has already been mentioned. Tetrahydro-furylmethylcarbinol reacts similarly in the vapour phase, giving 2-methyl-5 : 6-dihydro-4-pyran (XVIII), but diphenyltetrahydrofurylcarbinol is

[47] T. R. Marshall and W. H. Perkin, *J.*, 1891, **59**, 880.
[48] C. L. Wilson, *J.*, 1945, 52. [49] H. Normant, *Compt. rend.*, 1949, **228**, 102.
[50] Henninger, *Ann. Chim.*, 1886, [vi], **7**, 216, 217.
[51] E. D. Amstutz, *J. Org. Chem.*, 1944, **9**, 310.
[52] J. Colonge and P. Garnier, *Bull. Soc. chim.*, 1948, 432.
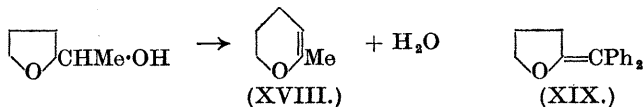[53] H. Normant, *Compt. rend.*, 1948, **227**, 283.
[54] B.I.O.S. Final Report No. 367.
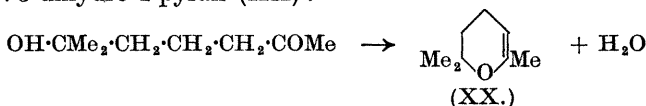[55] B.P. 510,949. [56] B.P. 510,615.
[57] A. Valette, *Compt. rend.*, 1946, **223**, 907 ; cf. J. R. Johnson and O. H. Johnson, *J. Amer. Chem. Soc.*, 1940, **62**, 2615.

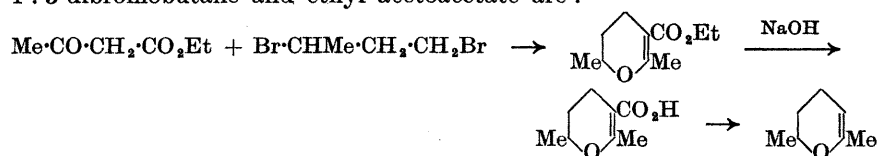dehydrated (although in the liquid phase) without ring enlargement,[58] to give 2-benzhydrylidenetetrahydrofuran (XIX) :

$$\text{(furan)CHMe·OH} \longrightarrow \text{(pyran)Me} + H_2O \qquad \text{(furan)=CPh}_2$$

$$\text{(XVIII.)} \qquad\qquad \text{(XIX.)}$$

This ring enlargement during dehydration is similar to that which occurs when *cyclo*butylcarbinol is dehydrated to give *cyclo*pentene.[59]   The method would not, however, be of much use for the preparation of 2 : 3-dihydro-4-pyrans with substituents in other than the 6-position, since the required tetrahydrofurfuryl alcohols, substituted in the nucleus, are difficult to prepare.

Substituted dihydropyrans can also be obtained by dehydration of the appropriate keto-alcohol ; 5-ketohexan-1-ol gives 2-methyl-5 : 6-dihydro-4-pyran when heated [60] and 6-keto-2-methylheptan-2-ol gives 2 : 2 : 6-trimethyl-2 : 3-dihydro-4-pyran (XX) : [61]

$$\text{OH·CMe}_2\text{·CH}_2\text{·CH}_2\text{·CH}_2\text{·COMe} \longrightarrow \text{Me}_2\text{(pyran)Me} + H_2O$$

$$\text{(XX.)}$$

Trimethylene dibromide and its substitution products react with ethyl acetoacetate to give esters of 5 : 6-dihydro-4-pyran-3-carboxylic acids, and on hydrolysis the parent acids are obtained.   The reactions using 1 : 3-dibromobutane and ethyl acetoacetate are : [62]

$$\text{Me·CO·CH}_2\text{·CO}_2\text{Et} + \text{Br·CHMe·CH}_2\text{·CH}_2\text{Br} \longrightarrow \text{Me(pyran)}^{CO_2Et}_{Me} \xrightarrow{\text{NaOH}}$$

$$\text{Me(pyran)}^{CO_2H}_{Me} \longrightarrow \text{Me(pyran)Me}$$

The free acid is easily decarboxylated, giving the alkyl-substituted dihydropyran.

The dimerisation of unsaturated carbonyl compounds to give dihydropyrans has been extensively studied by K. Alder *et al.*[63]   The compound is heated in presence of about 1% of quinol and the reaction which takes place, usually in good yield, is :
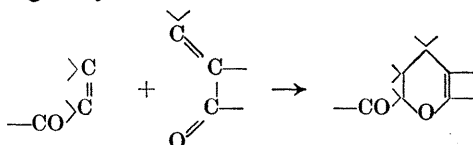
[58] R. Paul, *Bull. Soc. chim.*, 1938, **5**, 919 ; A. L. Dounce, R. H. Wardlow, and R. Connor, *J. Amer. Chem. Soc.*, 1935, **57**, 2556.
[59] M. Dojarenko, *Ber.*, 1927, **60**, 1536.
[60] W. H. Perkin, *ibid.*, 1886, **19**, 2557 ; A. Lipp, *Annalen*, 1896, **289**, 187.
[61] Verley, *Chem. Weekbl.*, 1897, [iii], **17**, 185.
[62] R. G. Fargher and W. H. Perkin, *J.*, 1914, **105**, 1353.
[63] K. Alder, H. Oppermans, and E. Rüder, *Ber.*, 1941, **74** *B*, 905, 920, 926.

Thus, acraldehyde gives (XXI); but-1-en-3-one gives (XXII); 2-methyl-but-1-en-3-one gives (XXIII); and crotonaldehyde gives (XXIV). This dimerisation of crotonaldehyde is interesting, as an isomer (XXVI) is formed if the polymerisation is acid-catalysed.


(XXI.)   (XXII.)   (XXIII.)   (XXIV.)
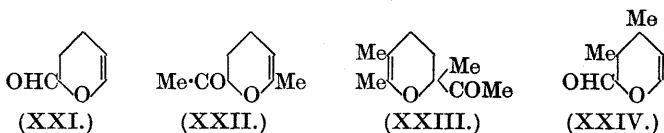
An example of another type of condensation is the preparation of methyl 6 : 6-dimethyl-5 : 6-dihydro-4-pyrone-2-carboxylate (XXV) by condensing methyl oxalate with mesityl oxide in presence of sodium and then cyclising the product by sulphuric acid : [64]

(XXV.)
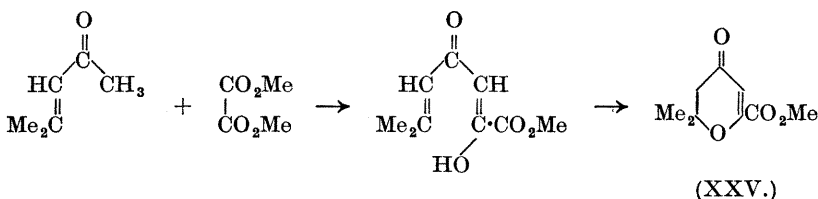
(b) 2 : 3-*Dihydro-6-pyrans* (1 : 5-*Epoxypent-2-enes*). The unsubstituted dihydropyran has been made recently by R. Paul et al.[65] in 75% yield by dehydrobromination of 4-bromotetrahydropyran with potassium hydroxide in ethylene glycol. 4-Bromotetrahydropyran was presumably made from 4-hydroxytetrahydropyran, but the method used is not given. Another method for preparing 2-alkyl-substituted compounds, described in greater detail later, is the removal of the elements of hydrogen chloride from the *trans*-form of 3-chloro-2-alkyltetrahydropyrans.[66] Apart from these there is only one general method described in the literature, namely, condensation of a carbonyl compound with an unsaturated alcohol in the presence of toluene-*p*-sulphonic acid, an entraining agent such as benzene being used to remove the water formed : [67]

$$RR'CO + CH_2{:}CMe{\cdot}CH_2{\cdot}CHMe{\cdot}OH \longrightarrow \quad + H_2O$$
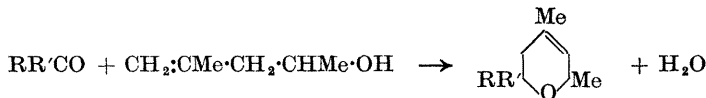
When aldehydes are used, the corresponding 4-hydroxytetrahydropyrans are also formed; from acraldehyde or chloroacetaldehyde 2 : 3-dihydro-6-pyrans substituted by vinyl or chloromethyl respectively can be made.
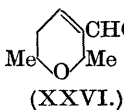
(XXVI.)

The dimerisation of crotonaldehyde, when heated, to give (XXIV) was mentioned earlier; if acid is used as the catalyst, (XXVI) is formed in about 25% yield.[68]

[64] L. Claisen, *Annalen*, 1896, **291**, 132.
[65] R. Paul and S. Tchelitcheff, *Compt. rend.*, 1947, **224**, 1722.
[66] O. Riobé, *Ann. Chim.*, 1949, [xii], **4**, 593.
[67] U.S.P. 2,422,648 ; 2,452,977.   [68] M. Delépine, *Compt. rend.*, 1910, **150**, 394.

3. Dihydro-furans and -pyrans : Reactions.—The dihydro-furans and pyrans fall into two groups, so far as their chemical reactions are concerned. 2 : 3-Dihydrofurans and 2 : 3-dihydro-4-pyrans, which have the double bond in the α-position to the oxygen atom, react very similarly to vinyl ethers, while 2 : 5-dihydrofurans and 2 : 3-dihydro-6-pyrans behave as olefins in which the activity of the double bond is not affected by the oxygen atom.

(a) *2 : 3-Dihydrofuran and 2 : 3-Dihydro-4-pyran* (II). Mild hydrogenation in non-acidic solvents gives the corresponding tetrahydro-compound in excellent yield ; thus, 2 : 3-dihydrofuran gives tetrahydrofuran,[48] 2 : 3-dihydro-4-pyran (II) gives tetrahydropyran,[69] and the substituted compounds react similarly. Under more vigorous conditions, at 200° with cobalt or nickel catalysts, *cyclo*pentanone [formed by rearrangement of (II)] and gaseous products are formed, as well as tetrahydropyran.[70] If (II) is hydrogenated in aqueous emulsion over a copper catalyst at about 200°, pentane-1 : 5-diol is obtained in nearly theoretical yield ;[71] 2 : 3-dihydrofuran would probably react in the same way, giving butane-1 : 4-diol, but has not been tried.

The dihydro-compounds react vigorously with water and other hydroxylic compounds in presence of a trace of acid, giving mainly 2-hydroxy- or 2-alkoxy-tetrahydro-compounds or esters. The reaction has been particularly well studied with (II). In dilute hydrochloric acid, hydration is fairly rapid at low temperature, and the products are 2-hydroxytetrahydropyran (XXVII) and di(tetrahydro-2-pyranyl) ether (XXVIII).[72] The hydroxy-compound is the semi-acetal of 5-hydroxypentan-1-al, and the equilibrium mixture consists mostly of the cyclic form. 2 : 3-Dihydrofuran reacts

(II.)   (XXVII.)   (XXVIII.)
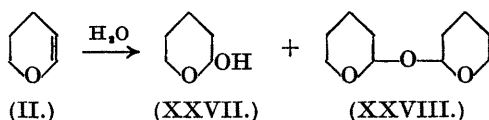
similarly to give 2-hydroxytetrahydrofuran, the semi-acetal of 4-hydroxybutan-1-al.[48, 49] When alcohols, phenols, or acids are used,[73] the corresponding ethers or esters are formed ; these are unstable in presence of aqueous acids, giving the alcohol and 2-hydroxytetrahydropyran. These reactions are common to all 2 : 3-dihydro-4-pyrans, and a more complex example, where the final product is a diketone, is the reaction of (XXIII) with acidified ethanol. The alcohol adds to the double bond in the usual way, but the ring opens giving, as a final product, 3-ethoxy-3 : 6-dimethyl-

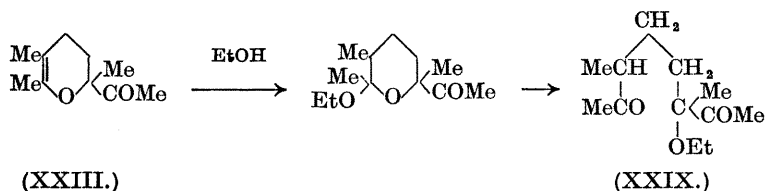[69] B.P. 565,175 ; *Org. Synth.*, **23**, 90.
[70] C. L. Wilson, *J. Amer. Chem. Soc.*, 1948, **70**, 1311.
[71] B.P. 621,735.
[72] L. E. Schniepp and H. H. Geller, *J. Amer. Chem. Soc.*, 1946, **68**, 1646 ; R. Paul, *Bull. Soc. chim.*, 1934, [v], **1**, 971.
[73] G. F. Woods and D. N. Kramer, *J. Amer. Chem. Soc.*, 1947, **69**, 2246.

octane-2 : 7-dione (XXIX) : [74]

(XXIII.)   (XXIX.)

Because of its ease of reaction with hydroxyl groups, (II) has been used for their protection in reactions in alkaline media.[75] The bis-tetrahydro-2-pyranyl ether of catechol, after reaction with butyl-lithium followed by carbonation and hydrolysis, gave a 48% yield of 2 : 3-dihydroxybenzoic acid :

(XXX.)
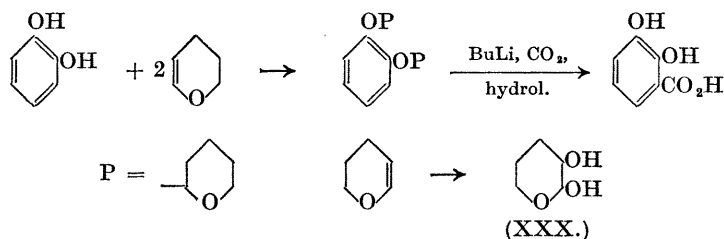
Hydrogenation of 2-hydroxytetrahydropyran over a nickel catalyst gives pentane-1 : 5-diol ; if the hydrogenation is effected in presence of ammonia or an amine, aminopentanols are formed in good yield : [76]
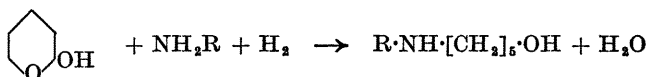
2 : 3-Dihydroxy-tetrahydropyran (XXX) and -tetrahydrofuran can be made from the corresponding dihydropyran or dihydrofuran by reaction with osmic acid and hydrogen peroxide in *tert.*-butanol [77] or with lead tetra-acetate [49] respectively. Both diols behave as α-hydroxy-aldehydes and give 2 : 4-dinitrophenylosazones.

2 : 3-Dihydrofuran decomposes when heated above 375°, to give mainly formyl*cyclo*propane (XXXI) and crotonaldehyde.[78] Although formyl*cyclo*-propane was not isolated as such, the yield at 460° was estimated to be about 40%, calculated on the dihydrofuran consumed, but, at higher temperatures, increasing proportions of propylene and carbon monoxide were formed. Formyl*cyclo*propane gives a small amount of dihydrofuran on pyrolysis at 500°, so that the decomposition is reversible. (II) is decomposed smoothly at about 500°, giving very good yields of acraldehyde

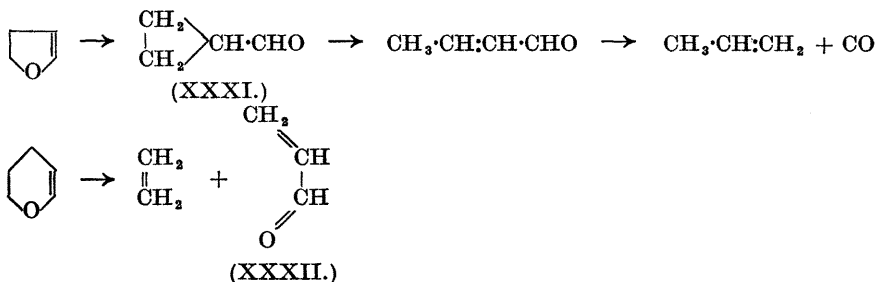[74] J. Colonge and J. Dreux, *Compt. rend.*, 1949, **228**, 582.

[75] W. E. Parham and E. L. Anderson, *J. Amer. Chem. Soc.*, 1948, **70**, 4187.

[76] G. F. Woods and H. Sanders, *ibid.*, 1946, **68**, 2111 ; I. Scriabine, *Bull. Soc. chim.*, 1947, **14**, 454 ; B.P. 576,087.

[77] C. D. Hurd and C. D. Kelso, *J. Amer. Chem. Soc.*, 1948, **70**, 1484.

[78] C. L. Wilson, *ibid.*, 1947, **69**, 3002.

(XXXII) and ethylene ;[79] acraldehyde can also be produced from tetra-hydrofurfuryl alcohol in one stage by use of an aluminium silicate catalyst at 450°.[80] Other work has shown that, with this and similar catalysts, much polymer may be formed at lower temperatures [81] from tetrahydro-furfuryl alcohol. 3-Chloro-5 : 6-dihydro-4-pyran behaves similarly to (I)

$$\text{(XXXI.)} \quad \underset{CH_2}{\overset{CH_2}{|}}\text{CH·CHO} \rightarrow CH_3\text{·CH:CH·CHO} \rightarrow CH_3\text{·CH:CH}_2 + CO$$

$$\text{(XXXII.)} \quad \underset{CH_2}{\overset{CH_2}{\|}} + \underset{CH}{\overset{CH}{|}} \underset{O}{}$$

and gives 2-chloroacraldehyde [82] although the yield is less than that of acraldehyde from (I). These pyrolyses of dihydropyrans are similar to the decomposition of Diels–Alder adducts which (e.g., the decomposition of cyclohexene to buta-1 : 3-diene and ethylene)[83] regenerate the original reactants when heated ; however, no synthesis of 2 : 3-dihydro-4-pyrans by reaction between an ethylene and a substituted acraldehyde has been reported, although cyclohexene has been made by a similar reaction from ethylene and buta-1 : 3-diene.[84]

The reactions of 2 : 3-dihydro-4-pyran (II) with halogens and halogen compounds have been well studied, and the products have proved useful intermediates for further syntheses. Similar reactions of 2 : 3-dihydrofuran have been little investigated because it is not so available, but it would probably react in a very similar way to (II).

Dihydro-4-pyran readily adds chlorine, bromine, hydrogen chloride, or hydrogen bromide,[85, 86] giving 2 : 3-dihalogeno- or 2-halogeno-tetrahydro-pyrans. The halogen atom in the 2-position is removed as hydrogen halide on distillation of the product at atmospheric pressure, giving 3-chloro- or 3-bromo-5 : 6-dihydro-4-pyran (XXXIII). Addition of chlorine to these unsaturated compounds gives 2 : 3 : 3-trihalogenotetrahydro-pyrans.[87] The halogen atom in the 3-position in all these compounds is relatively inert, but that in position 2 resembles that in α-chloro-ethers and reacts readily with Grignard compounds, giving 2-alkyltetrahydro-

[79] J. G. M. Bremner, D. G. Jones, and S. Beaumont, J., 1946, 1018.
[80] C. L. Wilson, J. Amer. Chem. Soc., 1947, 69, 3004.
[81] B.P. 608,538.
[82] B.P. 578,071.
[83] F. O. Rice and M. T. Murphy, J. Amer. Chem. Soc., 1944, 66, 765.
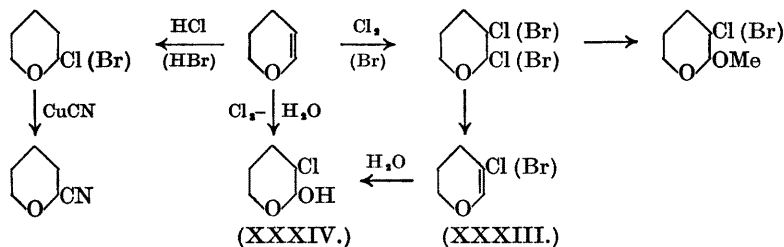[84] L. M. Joshel and L. W. Butz, ibid., 1941, 63, 3350.
[85] B.P. 571,265.
[86] R. Paul, Bull. Soc. chim., 1934, [v], 1, 1403.
[87] U.S.A. Office of the Publ. Board, Dept. of Commerce Report No. P.B.-803.

pyrans [86] or 3-chloro- or 3-bromo-2-alkyltetrahydropyrans ; [88] with cuprous cyanide the corresponding nitriles are obtained.[89]

The alkyl-chloro-compounds have been studied by O. Riobé [66] who found that they could be easily separated into *cis*- and *trans*-forms by distillation. The configurations were assigned on consideration of the physical properties of the geometrical isomers, and of the nature of the products formed on loss of the elements of hydrogen chloride. With alcohols or sodium salts of aliphatic acids, the dihalogeno-compounds give 2-alkoxy- or 2-acyloxy-compounds, and with water give substituted bis-tetrahydropyranyl ethers.[88] Reaction of 2 : 3-dihydro-4-pyran or its derivatives with halogens in a hydroxylic solvent also gives the corresponding halogenated 2-hydroxy- or 2-alkoxy-tetrahydropyran in good yield ; thus 3-chloro-2-hydroxytetrahydropyran (XXXIV) can be made by chlorinating an emulsion of (II) in water,[90] preferably under alkaline conditions so as to avoid formation of (XXVII).

Addition of hydrogen chloride to dihydrofuran gives 2-chlorotetrahydrofuran.[49] 2 : 3-Dichlorotetrahydrofuran, which is formed by chlorinating 2 : 3-dihydrofuran, is most conveniently made by chlorinating tetrahydrofuran (see below) ; the chlorine atom in the 2-position is as reactive as that in 2-chlorotetrahydropyran, and a corresponding series of hydroxy-, alkoxy-, and alkyl-chlorotetrahydrofurans can be made.[49] Like the analogous tetrahydropyrans, the 3-chloro-2-alkyltetrahydrofurans also exist in *cis*- and *trans*-forms, which can be separated by distillation.[91]

The halogen atoms remaining in these 2-alkyl- and 2-alkoxy-tetrahydro-compounds can be removed by various treatments giving interesting products. Treatment of 3-chloro-2-hydroxytetrahydropyran with hydroxylamine gives tetrahydrofurfuraldoxime,[88] formed by the following reactions :
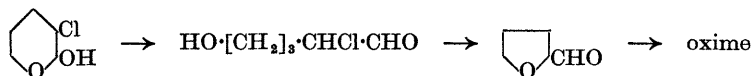
If 3-chloro-2-alkyltetrahydropyrans are distilled from a solution of potassium hydroxide in diethylene glycol, a mixture of two isomeric

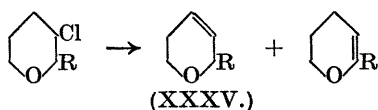[88] R. Paul, *Compt. rend.*, 1944, **218**, 122 ; B.P. 605,107.
[89] F.D. 3781/45, p. 000731. Obtainable from Techn. Information Document Unit, Board of Trade.   [90] B.P. 570,160 ; 598,080.
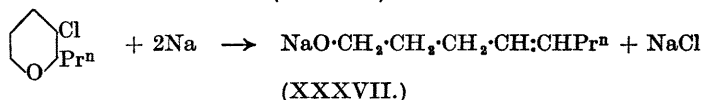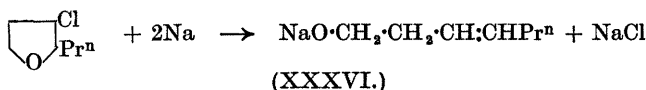[91] L. Crombie and S. H. Harper, *J.*, 1950, 1714.

alkyldihydropyrans is obtained:[66]

(XXXV.)

The *cis*-isomers react very easily and give 80—90% yields of a mixture of the isomeric alkyl-dihydro-2- and -4-pyrans; the proportions vary with the reaction conditions and the alkyl group. The *trans*-isomers react much more slowly, and the products obtained in 90% yield consist almost entirely of the 2-alkyl-5 : 6-dihydro-2-pyrans (XXXV). The results of these experiments, on the assumption that *trans*-elimination of the elements of hydrogen chloride is more rapid than *cis*-, provided the chemical evidence for configuration mentioned earlier. The 3-chloro-2-alkyltetrahydrofurans react similarly.[53]

The ring fission of tetrahydrofurfuryl halides with sodium, typical of the behaviour of β-chloro-ethers, has been extended to the 3-chloro-2-alkyltetrahydro-pyrans and -furans, to give β- or γ-ethylenic alcohols respectively

$$+ 2Na \longrightarrow NaO \cdot CH_2 \cdot CH_2 \cdot CH:CHPr^n + NaCl$$

(XXXVI.)

$$+ 2Na \longrightarrow NaO \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH:CHPr^n + NaCl$$

(XXXVII.)

in very good yields. Thus, 3-chloro-2-propyltetrahydrofuran gives hept-3-en-1-ol (cf. XXXVI),[92-94] and 3-chloro-2-propyltetrahydropyran gives oct-4-en-1-ol (XXXVII).[66] Some recent work has elucidated the stereochemical relationships in these reactions.[91] The higher-boiling (*cis*-)isomer of 3-chloro-2-methyltetrahydropyran reacted the more vigorously with sodium, but both isomers gave the same alcohol, shown by infra-red analysis to be *trans-n*-hex-4-en-1-ol, this being confirmed by synthesis of the two stereoisomers by unambiguous routes. This ring fission, leading to a *trans*-alk-4-en-1-ol is thought to be general for 3-chloro-2-alkyltetrahydropyrans. The *trans*-form of 3-chloro-2-methyltetrahydrofuran gave solely *trans*-pent-3-en-1-ol, but the *cis*-isomer gave a mixture of *cis*- and *trans*-alcohols, detected by comparison of the infra-red absorption spectra and by chemical evidence. Similarly, the two 3-chloro-2-ethyltetrahydrofurans gave the *trans*-form and the *cis–trans*-mixture of *n*-hex-3-en-1-ol. These unsaturated alcohols can be converted into dienes by pyrolysis of their acetates at 550°.[95]

3-Halogenotetrahydrofurans react very slowly with magnesium, giving compounds which re-arrange to give unsaturated primary alcohols, but they react readily with lithium alkyls to give about 20% yields of the

[92] H. Normant, *Compt. rend.*, 1948, **226**, 733.
[93] Yu. K. Yur'ev, M. G. Voronkov, I. P. Gragerov, and G. Ya. Kondrat'eva, *J. Gen. Chem. Russia*, 1948, **18**, 1804.
[94] S. H. Harper and L. Crombie, *Nature*, 1949, **164**, 1053.
[95] O. Riobé, *Compt. rend.*, 1948, **226**, 1625.

corresponding 3-alkyltetrahydrofurans,[51, 93, 96] this being probably the most convenient method of making them.

The reaction of 3-chloro-2-alkoxytetrahydrofurans with sodium has already been mentioned as a method of preparation of 2 : 3-dihydrofuran ; when these compounds are heated with potassium hydroxide in glycerol, both the chlorine atom and the ethoxy-group are lost and furan is formed in 80% yield.[49] When heated with sodamide, the chloroethoxytetrahydrofuran gives a 50% yield of a 2-ethoxy-2 : 5-dihydrofuran. This is quite stable, except in presence of acid where it yields furan and ethanol quantitatively ; if 2 : 4-dinitrophenylhydrazine is present, the derivative of 4-hydroxybut-2-en-1-al (XXXVIII) is formed.[97]
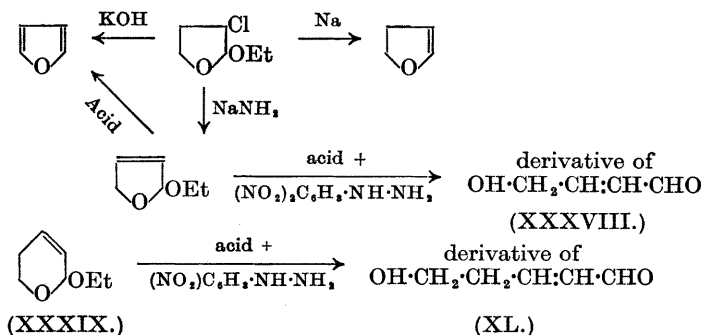

3-Bromo-2-ethoxytetrahydropyran reacts similarly with sodamide [49] or with sodium in alcohol,[98] to give an ethoxydihydropyran, probably (XXXIX). Acid hydrolysis of this compound in presence of 2 : 4-dinitrophenylhydrazine gives a derivative of 5-hydroxypent-2-en-1-al (XL), but the parent compound could not be isolated. If (XXXIX) is steam-distilled from phosphoric acid, a 55% yield of penta-2 : 4-diene-1-al is formed :
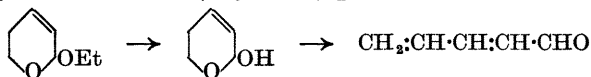
The pentadienal is also formed by treating 2 : 3-dichlorotetrahydropyran with potassium hydroxide.

2 : 3-Dihydro-4-pyran (II) reacts with carbonyl chloride ;[99] addition takes place at room temperature in the absence of added catalyst, giving 5 : 6-dihydro-4-pyran-3-carboxyl chloride (XLI) in about 50% yield :
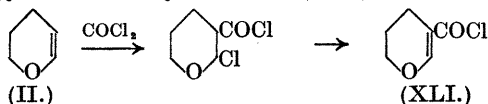
The acid was identified by the formation of much formic acid, but no oxalic acid on ozonolysis, and by its decarboxylation when heated to give (II) and carbon dioxide ; it can easily be hydrogenated to the tetrahydro-compound.[100]

[96] Yu. K. Yur'ev and I. P. Gragerov, *J. Gen. Chem. Russia*, 1948, **18**, 1811.
[97] F. Quennehen and H. Normant, *Compt. rend.*, 1949, **228**, 1301.
[98] G. F. Woods and H. Sanders, *J. Amer. Chem. Soc.*, 1946, **68**, 2483.
[99] B.P. 570,974.   [100] B.P. 612,314.

(*b*) 2 : 5-*Dihydrofuran*. The chemistry of this compound is, at present, undistinguished, and is almost that of the unsaturated ethylenic bond. Oxidation with air in the vapour phase over a molybdenum–vanadium–titanium oxide catalyst gives maleic anhydride.[101] The preparation of 3-chloro- and 3-hydroxy-tetrahydrofuran has been described,[102] and a mixture of 3 : 4-dichloro-, 3-chloro-4-acetoxy-, and 3-chloro-4-hydroxy-tetrahydrofuran [103] is obtained on reaction with chlorine in acetic acid.

(*c*) 2 : 3-*Dihydro-6-pyrans*. The properties of the two isomeric dihydropyrans have been compared by R. Paul.[65] 2 : 3-Dihydro-6-pyran is hydrogenated easily to tetrahydropyran ; it reacts with 0·5N-sulphuric acid at 150°, giving 3-hydroxytetrahydropyran, and with perbenzoic acid to form the epoxide which gives 3 : 4-dihydroxytetrahydropyran on hydrolysis ; with chlorine, 3 : 4-dichlorotetrahydropyran is formed. These products are stable and have the normal properties expected of, say, the corresponding *cyclo*hexane derivatives ; the activity of substituents in the 2-position, which is characteristic of derivatives of the dihydro-4-pyrans, is, of course, absent. The behaviour of the isomeric dihydropyrans on pyrolysis shows another difference. 2 : 3-Dihydro-4-pyran gives acraldehyde and ethylene, but 2 : 3-dihydro-6-pyran at 600° gives butadiene and formaldehyde.[65] This reaction seems to be general for 2 : 3-dihydro-6-pyrans, as the dimer (XXVI) obtained from crotonaldehyde by acid behaves in a similar way at 400—600°.[104] The 2-vinylcrotonaldehyde (XLII), first formed, is unstable and forms penta-1 : 3-diene by loss of carbon monoxide :

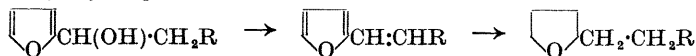(XXVI.)   (XLII.)
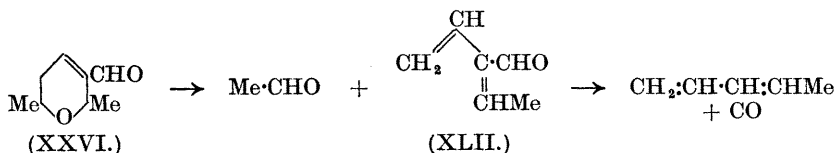
Oxidation of (XXVI) gives the acid (XLIII).[105] When this acid is heated with Raney nickel and hydrogen in alkaline solution, the double bond moves, to give the isomeric acid (XLIV),[106] together with some of the acid formed by hydrogenation. The re-arranged product can also be obtained in 60% yield by heating the sodium salt of the acid with Raney nickel on a water-bath ; the acid is quite stable if heated with alkali in absence of nickel. The product obtained on decarboxylation was identical with one synthesised earlier by Perkin by a different route.
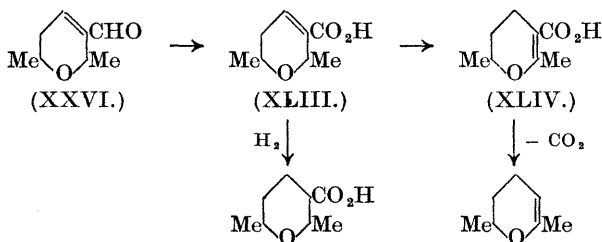
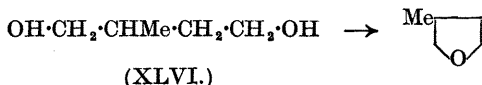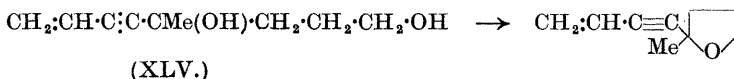[101] U.S.P. 2,215,095.
[102] U.S.A. Office of the Publ. Board, Dept. of Commerce Report No. P.B.-42,455.
[103] B.P. 616,762.   [104] U.S.P. 2,387,366.   [105] U.S.P. 2,378,996.
[106] M. Delépine and A. Horeau, *Compt. rend.*, 1938, 206, 27.

Tetrahydro-furans and -pyrans

1. Synthesis.—(a) *Tetrahydrofurans.* The most convenient synthesis of tetrahydrofuran is by hydrogenation of furan, which is now commercially available ; similarly, 2-methylfuran, which is made by the hydrogenation of furfuraldehyde (p. 197), gives 2-methyltetrahydrofuran. 2-Alkyltetrahydrofurans can be made from the corresponding 2-alkylfurans, themselves made by condensing furfuryl bromide with the appropriate Grignard reagent.[107]   Another route is by dehydration of furylalkylcarbinols,[108] followed by hydrogenation : [109]

$$\text{\Large\textopenbracket}_O\text{\textclosebracket}CH(OH) \cdot CH_2R \quad \rightarrow \quad \text{\Large\textopenbracket}_O\text{\textclosebracket}CH:CHR \quad \rightarrow \quad \text{\Large\textopenbracket}_O\text{\textclosebracket}CH_2 \cdot CH_2R$$

Tetrahydrofuran was made in Germany during the war by a method similar to that already described for 2 : 5-dihydrofuran. But-2-yne-1 : 4-diol was hydrogenated to butane-1 : 4-diol, and when this was heated with 0·3% phosphoric acid at 280°/100 atm. tetrahydrofuran was formed in 93—94% yield ; [54] tetrahydrofuran is also formed under milder conditions, when butane-1 : 4-diol is heated with phosphoric acid [110] at about 165° or by dehydration in the vapour phase over Morden bentonite.[111]   The intra-dehydration of 1 : 4-diols is a general method of making tetrahydrofurans ; other examples are the dehydration of (XLV) [112] by hot potassium hydrogen sulphate, and of (XLVI) [113] by hot sulphuric acid, to the corresponding tetrahydrofuran derivatives.

$$CH_2:CH \cdot C \vdots C \cdot CMe(OH) \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot OH \quad \rightarrow \quad CH_2:CH \cdot C{\equiv}C \underset{Me}{\overset{}{\diagdown}}_O$$

(XLV.)

$$OH \cdot CH_2 \cdot CHMe \cdot CH_2 \cdot CH_2 \cdot OH \quad \rightarrow \quad Me \overline{}\underset{O}{\diagdown}$$

(XLVI.)

Tetrahydrofurans with alkyl substituents in the ring have been made by cyclising unsaturated alcohols. The simplest example is that of pent-4-en-1-ol, which gave a 90% yield of 2-methyltetrahydrofuran when it was warmed with concentrated sulphuric acid.[114]   The necessary γ-unsaturated alcohols were made by reduction of the ketones formed in the reaction between ethyl acetoacetate and the appropriate chlorides, and by this method several alkylated tetrahydrofurans have been made.[115, 116]   Addition of chlorine or bromine to the unsaturated alcohol, and then cyclisation in presence of quinoline, gives alkylated 3-bromotetrahydrofurans [115, 117] from which, as mentioned earlier, 3-alkyltetrahydrofurans can be made.

(b) *Tetrahydropyrans.* Tetrahydropyran itself is easily made in good

[107] R. Paul, *Bull. Soc. chim.*, 1935, [v], **2,** 2227.   [108] *Idem, ibid.*, p. 2220.

[109] *Idem, ibid.*, 1938, **5,** 1053.   [110] U.S.P. 2,251,292.

[111] A. N. Bourns and R. V. V. Nichols, *Canadian J. Res.*, 1948, **26,** B, 81.

[112] I. N. Nazarov and I. V. Torgov, *J. Gen. Chem. Russia*, 1948, **18,** 1480.

[113] Yu. K. Yur'ev and I. P. Gragerov, *ibid.*, p. 1811.

[114] R. Paul and H. Normant, *Compt. rend.*, 1943, **216,** 689.

[115] J. Colonge and A. Lazier, *Bull. Soc. chim.*, 1949, **15,** 17.

[116] H. Normant, *Compt. rend.*, 1948, **226,** 1734.   [117] D.R.-P. 696,725.

yield by hydrogenating the available 2 : 3-dihydro-4-pyran, in either the liquid or the vapour phase,[69] and 2-alkyltetrahydropyrans are made by reaction of 2-chlorotetrahydropyran with Grignard reagents ; [66] others are available by hydrogenation of dihydropyrans described earlier.

Dichlorodiethyl ether is a convenient starting material for preparing 4-substituted tetrahydropyrans by reaction with such compounds as ethyl malonate.[118]   However, the interest in these compounds has been more in the introduction of the tetrahydropyran ring into, say, drugs than in the chemistry of the compounds prepared.

2. Reactions.—Ring fission of tetrahydro-pyrans and -furans with various reagents has led to numerous useful aliphatic compounds difficult to obtain by other routes.   Since the last Annual Report,[2] tetrahydropyran has been shown to give an 85% yield of 5-chloropentan-1-ol acetate when warmed with acetyl chloride in the presence of zinc chloride as catalyst, the benzoate being similarly obtained by use of benzoyl chloride.[119]

The fission of tetrahydrofuran with thionyl chloride under the influence of numerous catalysts has been investigated.   The use of zinc chloride favours the formation of 1 : 4-dichlorobutane, whereas sulphuric acid leads mainly to 4 : 4'-dichlorodibutyl ether.[120]   The superiority of sulphuric acid as a catalyst in the fission of tetrahydrofuran with phosphorus oxychloride (to give a 70% yield of 4 : 4'-dichlorodibutyl ether) has been established,[121] but the method gives poor yields when applied to tetrahydropyran and 2-methyltetrahydrofuran.

Tetrahydrofuran when caused to react with oxonium salt-forming substances (R^+X^-) gives compounds of the type [122]

$$\left\{ RO \cdot [CH_2]_4 \cdot (O \cdot [CH_2]_4)_n \cdot O \cdot [CH_2]_4 \cdot O\underset{\qquad}{\diagdown} \right\}^+ \quad X^-$$
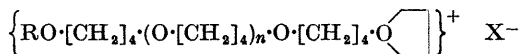
These with water, alcohols, or aqueous acids give

$$RO \cdot [CH_2]_4 \cdot (O \cdot [CH_2]_4)_n \cdot O \cdot [CH_2]_4 \cdot Y$$

where Y = OH, OMe, OAc, or Cl.   Many combinations of compounds giving suitable catalytic cations are quoted.

The products formed by inter-polymerising tetrahydrofuran with propylene or ethylene oxide in presence of a mixture of zinc chloride and thionyl chloride, and replacing the chlorine in the polymer by methoxyl, have found some application as synthetic lubricants.

Tetrahydro-furan and -pyran are readily attacked by oxidising agents. Tetrahydrofuran hydroperoxide (XLVII) has been isolated from tetrahydrofuran which has been exposed to air ; [123] it gives γ-butyrolactone as a major product on decomposition, together with 2-hydroxytetrahydrofuran. The oxidation of tetrahydrofuran with air is best done under pressure using a cobalt catalyst, the main product being γ-butyrolactone ; [124] tetrahydro-

[118] U.S.P. 2,242,575 ; G. H. Harnest and A. Burger, *J. Amer. Chem. Soc.*, 1943, **65**, 370.

[119] M. E. Synerholm, *ibid.*, 1947, **69**, 2581.   [120] Ref. 102, Report No. P.B.-631.

[121] K. Alexander and L. E. Schniepp, *J. Amer. Chem. Soc.*, 1948, **70**, 1839.

[122] F.D. 3781/45, p. 001047 ; F.I.A.T. Final Report No. 293.

[123] A. Robertson, *Nature*, 1948, **162**, 153.   [124] B.P. 608,539.

pyran, treated similarly, gives δ-valerolactone. γ-Butyrolactone is also produced when tetrahydrofuran or simple 2-alkyltetrahydrofurans are

(XLVII.)
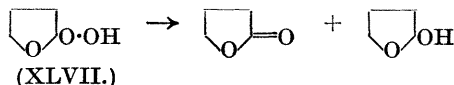
treated with nitrogen tetroxide and oxygen ; [125] as the conditions become more severe, increasing amounts of succinic acid are formed.[126]   Very good yields of succinic acid can be obtained from tetrahydrofuran by oxidation with nitric acid,[127] and tetrahydropyran gives glutaric acid,[128] but there is no mention of alkyl-succinic or -glutaric acids being made from appropriate alkyl tetrahydro-furans or -pyrans by this method.   Tetrahydrofuran has also been oxidised electrolytically to succinic acid.[129]

Tetrahydrofuran is substituted by chlorine even at 0°, and the products consist mostly of 2 : 3-dichlorotetrahydrofuran (XLVIII), with some 3-chloro-2-(4-chlorobutoxy)tetrahydrofuran (XLIX) which is formed by fission of the tetrahydrofuran ring to chlorobutanol and reaction of this with the active 2-chlorine substituent in dichlorotetrahydrofuran.[130]   This

(XLVIII.)   (XLIX.)
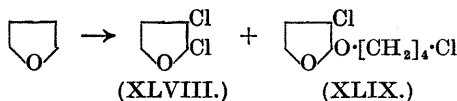
is certainly the most convenient method of making dichlorotetrahydrofuran. There is no published work on the chlorination of tetrahydropyran, but of course 2 : 3-dichlorotetrahydropyran is readily available from the chlorination of dihydropyran.

The inter-dehydration of tetrahydrofurans in the vapour phase with amines, hydrogen sulphide, or hydrogen selenide to give pyrrolidines, thiophans, and selenophans has been recently reviewed by L. N. Owen ; [2] tetrahydropyran reacts in a very similar way, but the yields are not usually as good as when tetrahydrofurans are used.

Tetrahydrofuran reacts with nickel carbonyl under pressure in presence of nickel chloride or iodide, giving carboxylic acids.   A small continuous unit was operated in Germany during the war years in which adipic acid was made by the reaction of tetrahydrofuran, nickel carbonyl, and carbon monoxide in presence of nickel iodide at 270°/200 atm.   Under certain conditions an 80% yield of adipic acid was claimed ; some δ-valerolactone and valeric acid were also formed.[131]   Under more drastic conditions, at 300°/800 atm., over nickel chloride as catalyst, a mixture of acids is formed, among them being butyric and butane-2-carboxylic acid.[132]

[125] B.P. 610,166.   [126] H. Schmid and A. Maschka, *Monatsh.*, 1949, **80**, 235.
[127] Belg. P. 444,240.   [128] D. G. Jones, unpublished.   [129] Canadian P. 450,353.
[130] H. Normant, *Compt. rend.*, 1948, **226**, 185 ; D.R.-P. 703,956.   Ref. 120, Report No. P.B.-675.   [131] B.I.O.S. Final Report No. 351.   [132] U.S.P. 2,432,474.