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Progress in the Chemistry of the 1,3-Dioxans

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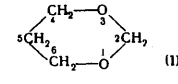
CONTENTS

I. Introduction 264
II. Methods of synthesis of 1,3-dioxans 265
III. Stereochemistry of 1,3-dioxans 267
IV. Chemical changes of the 1,3-dioxans 270
V. Use of the 1,3-dioxans 273

I. INTRODUCTION

In recent years there has been a considerable increase in interest in the 1,3-dioxans. There has been a review of the chemistry of these compounds[1] but it is incomplete and contains references to the literature only up to 1955. The present review fills some of the gaps in this earlier review and surveys the literature for 1955–1965. Furthermore, the present article examines the problem of the stereochemistry of the 1,3-dioxans, which was not considered systematically earlier. In this the authors consider it necessary to express their viewpoint on some of the complicated stereochemical problems relating to works they have carried out.

The first information on 1,3-dioxans appeared in 1865, however, the simplest of them, 1,3-dioxan itself[1], was synthesised only in 1902.[2] Compounds of this type were named 1,3-dioxans (or *meta*-dioxans) only by the external similarity in structure to 1,4-dioxans. However, the latter are simple ethers, whereas 1,3-dioxans are cyclic acetals (ketals).


(I)

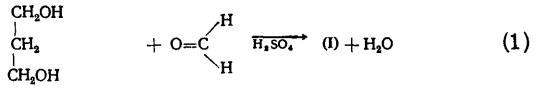
There is no great industrial production of most 1,3-dioxans. However, there are now great possibilities for their rational use. Many substituted derivatives of (I) were found to be good solvents. Some of the compounds of this type are physiologically active and have found application as effective spasmolytic and antihistamine preparations, depressants of the central nervous system, and even antibiotics. A series of 1,3-dioxans seemed an important intermediate product in organic synthesis, particularly in the synthesis of isoprene and other conjugated dienes.

II. METHODS OF SYNTHESIS OF 1,3-DIOXANS

All the preparative methods of synthesis of 1,3-dioxans can be classified in the following main groups.

1. Production of 1,3-Dioxans by the Reaction of Aldehydes and Ketones with Polyhydroxy-Compounds

This method was first proposed by Henry[2] for the synthesis of (I) by the scheme (1):

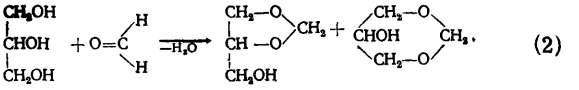


(1)

and was then improved by many authors. Various 1,3-diols and aldehydes were used in the reaction. In addition to sulphuric acid, which several authors have used as catalyst[3-8], other condensing agents have been proposed: hydrochloric acid[9-12], phosphoric acid[13-17], *p*-toluenesulphonic acid[18-26], and ion-exchange resins[27-31]. The use of *p*-toluenesulphonic acid gives good results; when it is employed the resinification and formation of side-products which complicates the condensation catalysed by mineral acids, are not observed. The use of sulphonic cation-exchange resins has still not been extensively studied but there are results which suggest that these are evidently the best catalysts for the reaction considered. In practice, the cation-exchange resins can be used repeatedly, and moreover their use greatly simplifies the purification of the dioxans being synthesised.

An important improvement in the original method of making 1,3-dioxans by the above process was the use of azeotropic distillation of the water formed during the reaction[18,32], which prevented the back reaction of hydrolysis of the dioxans and had special value for obtaining ketals of the type being considered. Besides, in addition to this technique, variations in the method under consideration have been used in which the condensation is effected in an aqueous medium[33].

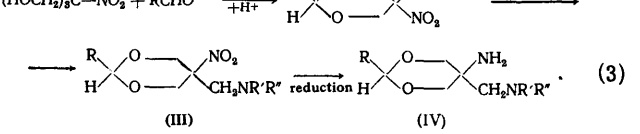
The condensation of polyhydroxy-compounds with aldehydes takes place especially well. The structure of the aldehydes has little influence on the course of the reaction. With ketones the reaction is much more difficult, owing to the greater difficulty in obtaining ketals for stereochemical reasons. It was only in 1938 that Böeseken succeeded in condensing a series of aliphatic, alicyclic, and aromatic ketones with certain glycols in the presence of acid dehydrating catalysts[34]. Before this, only a few examples of the condensation of acetone itself with polyhydroxy-compounds were known[35]. The problem of the production of cyclic ketals of this type was solved by Salmi, by showing that the reason for the lack of success of several authors who had tried to effect the condensation of 1,3-glycols with ketones was because the water is an inhibitor for the reaction. Salmi himself proposed azeotropic distillation of the water formed and by using this method obtained good yields of 1,3-dioxans, effecting the condensation of trimethyleneglycol or 1,3-butyleneglycol with ethyl methyl ketone, pinacolin, cyclopentanone, and acetoacetic ester. The catalyst in Salmi's studies was *p*-toluenesulphonic acid[18]. Many alkyl[36-42], polyalkyl[9,15,21,25,26,43-49], aryl[20,21,50-66], halogenoalkyl[10,21,67-77], hydroxy[78-87], nitro-[88-95], alkoxy-[77,96,97], and alkoxyalkyl[98-100], unsaturated[77,101-104], carbonyl-substituted[105,106], polycyclic[77,107-110], cyano-[77,111], and amino-[48,49,55,56,112] 1,3-dioxans were obtained by this method. Some variants of the method are of interest. Thus, a process has been patented[114] in which a mixture of formaldehyde and 1,3-butyleneglycol is passed continuously over an acid catalyst at high temperature. In this way a mixture of substituted dioxans and dioxolans[115] was obtained from glycerol:



(2)

Still more complex mixtures are obtained from higher alcohols and aldehydes[116,117]. Hill and Carothers[118] obtained tetramethyleneglycol formal and showed that other polyformals are successfully formed in the reaction of glycols of the type $HOCH_2[CH_2]_nCH_2OH$ with formaldehyde in the presence of acid catalysts.

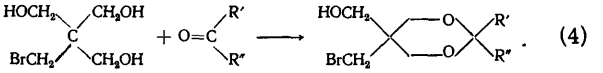
In 1961 Schipper and coworkers[88] proposed an original method for obtaining amino-substituted 1,3-dioxans:



(3)

Another method for obtaining amino-substituted 1,3-dioxans was proposed by Yasnitskii and coworkers in 1963[29-31]. They condensed chloroacetaldehyde with polyhydric alcohols in the presence of cation-exchange resins. The chloromethyl derivatives of 1,3-dioxans thus obtained are comparatively readily converted into alkylaminomethyl derivatives, owing to the rather high lability of the chlorine atom.

Piganiol and coworkers[10,50] obtained interesting, phamacologically active 1,3-dioxans (V) with two functional groups, by condensing pentaerythritol monobromohydrin [2-bromomethyl-2-hydroxymethylpropan-1,3-diol (Ed. of Translation)] with various aldehydes and ketones:



(4)

Of the variants of the method for the production of ketals, note must be made of the work of Kuhn[119], who used unsaturated ketones and esters of laevulinic acid for the production of 1,3-dioxans. By studying a different type of compound containing a ketone group in this reaction, Kuhn succeeded in showing that ketals of the 1,3-dioxan type can be obtained from any α-, β-, or γ-keto-acid except those in which there is a double bond next to the carbonyl group. When that is so ketals are not formed.

2. Production of 1,3-Dioxans by the Reaction of Aldehydes with Unsaturated Compounds

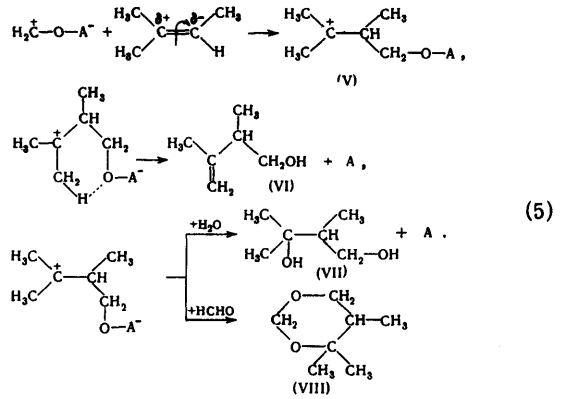
In 1917 Prins first studied the reaction of styrene, pinene, camphene, and anethole with formaldehyde in the presence of sulphuric acid as a catalyst[120]. Since then this reaction, named the "Prins reaction", has obtained wide application. An especially large number of papers devoted to it appeared at the end of the nineteen-thirties[121] after the development of improved procedures for cracking petroleum, which made accessible many unsaturated hydrocarbons. At the same time industrial methods of obtaining aldehydes from hydrocarbons were also developed.

In the condensation of alkenes and some other unsaturated compounds with aldehydes in the presence of aqueous solutions of mineral acids alkyl-1,3-dioxans and butan-1,3-diols are formed. The ratio of the reaction products can be varied by changing the concentration of the catalyst and the temperature of the process.

For a long time the mechanism of the Prins reaction was considered debatable. Several hypotheses were advanced[122-127]. A more or less general standpoint has recently been developed. It is thought that a polarised complex of formaldehyde with the catalyst adds to the alkene according to the Markovnikov rule, Eqn. (5):

$$HCHO + A \rightleftarrows H_2\overset{+}{C}-O-A^-,$$

where A is the catalyst: acid, $SnCl_4$, or other suitable substances.



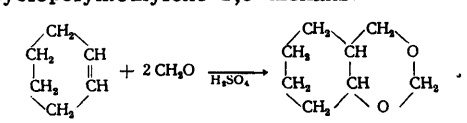
(5)

During this, an intermediate compound (V) is formed, which can then react either as a six-membered ring, or with other components of the reaction mixture. In the first instance an unsaturated alcohol (VI) is formed. In the second, a 1,3-glycol (VII) is formed when the reaction is with water; in the reaction with formaldehyde the 1,3-dioxan (VIII) is formed. Recently there have been many studies of the products of the Prins reaction[128-133]. 1,3-Dioxans can be obtained by this method from both linear and cyclic alkenes. Fitzky[134] and Ritter[135] investigated the preparation of alkyl-1,3-dioxans by the condensation of formaldehyde with propene, 2-methylpropene, trimethylethylene [1,2-dimethylpropene] pent-2-ene, and di-isobutylene [2,2,4-trimethylpentenes (Ed. of Translation)] in the presence of various acid catalysts. The best yields were obtained on using sulphuric acid as catalyst.

Later patents testify to the perfection of the commercial process for the synthesis of 1,3-dioxans[136-143]. A selective method for obtaining 4,4-dimethyl-1,3-dioxan by the reaction of a mixture of hydrocarbons with five or less carbon atoms with formaldehyde in the presence of H_2SO_4 (or H_3PO_4) at 10–85°C and atmospheric or elevated pressure has been patented[144,145]. An interesting variant of this method uses cation-exchange resin[146].

Mottern[147] used the Prins reaction for the selective removal of alkenes having branching at the double bond from fractions obtained as a result of petroleum distillation.

Cyclohexene and other cyclic alkenes also react with formaldehyde at 60–80°C in the presence of sulphuric acid, forming cyclopolymethylene-1,3-dioxans:



(6)

Aldehydes react selectively with ethylenic bonds of arylalkenes (for example, styrene), forming phenyl-1,3-dioxans. Here the catalysts are sulphuric acid[149-151], a solution of sulphuric in acetic acid[152-154], dilute hydrochloric acid[153,155], phosphoric acid[151,156,157], certain salts of hydrochloric acid[158], and other acid catalysts[159-161].

Good methods for obtaining phenyl-1,3-dioxans from arylalkenes and formaldehyde in the presence of sulphuric acid were developed by Shreiner[162], Shortige[163], Emerson[153,164], Beets[149,150,165,166] and their coworkers. Arylalkenes can be replaced by arylalkylcarbinols, but the yields of the dioxans are then reduced to 5–20%.[165-167]

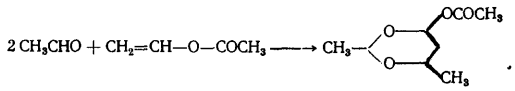
The terpenes (for example, pinene, limonene, camphene, cedrene, allo-ocimene, myrcene) react with formaldehyde in the presence of hydrochloric, sulphuric, and *p*-toluenesulphonic acids to form condensation products and resins, but their nature has not been determined with sufficient precision[152,168,169].

Some substituted alkenes, especially unsaturated halides and ethers, can undergo the Prins reaction, forming various 1,3-dioxans. The condensation of allyl chloride with formaldehyde at 0°C in the presence of concentrated sulphuric acid leads to the production of 4-chloromethyl-1,3-dioxan[170]. Dimethylallyl ethyl ether and formaldehyde readily react in the presence of 25% sulphuric acid at room temperature to form 5-ethoxymethyl-4,4-dimethyl-1,3-dioxan in 73% yield[171].

It must be noted that in the condensation of unsaturated carbonyl compounds (aldehydes, ketones, acids, and their derivatives with formaldehyde) the formation of 1,3-dioxans takes place with some difficulty; unsaturated alcohols and esters react with formaldehyde in the presence of acid catalysts, but the reaction products are difficult to identify, evidently owing to further reaction of the aldehyde with the hydroxyl groups of the molecule.

Recently published patents describe the reaction of branched alkenes, tertiary alcohols, and halogeno-derivatives with aldehydes in the presence of boron trifluoride, which leads to the formation of substituted 1,3-dioxans[172].

In the presence of metallic sodium, acetaldehyde condenses at 0°C with vinyl acetate, as a result of which 6-acetoxy-2,4-dimethyl-1,3-dioxan is obtained[173]:

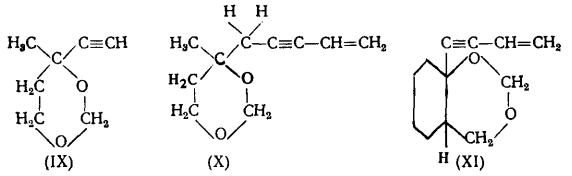


(7)

This reaction is evidently strictly specific both in regard to the reagents and also the conditions used. Cresham and Grigsby[174] studied the condensation of butadiene with formaldehyde in the presence of acid catalysts and hydroquinone (an inhibitor of polymerisation) at 100–120°C. They obtained 4-vinyl-1,3-dioxan in 30% yield. However, according to other results[152] this reaction leads to the formation of a very complex mixture of substances. Evidently the reason for Cresham and Grigsby's success was the use of a polymerisation inhibitor. The Prins reaction with other diene hydrocarbons has not been studied.

Matsoyan and Saakyan's interesting work[175] was published at the end of 1963; it was devoted to the reaction of formaldehyde with enynic and dieneyne hydrocarbons under the conditions for the Prins reaction. It appeared that the latter react selectively at the double bond with the formation of ethynyl- and vinylethynyl-1,3-dioxans. Thus on heating isopropenylacetylene [2-methylbut-1-en-3-yne] with formaldehyde in the presence of 40% sulphuric acid at 60–80°C 4-ethynyl-4-methyl-1,3-dioxan (IX) is formed. Formaldehyde reacts analogously with dienes, the reaction being directed exclusively to the substituted double bond of the divinylacetylene hydrocarbon. The condensation of 5-methylhexa-1,5-diene-3-yne and 5-methylhepta-1,5-diene-3-yne with formaldehyde in the presence of 40% sulphuric acid leads to the formation of 4-methyl-4-vinylethynyl-1,3-dioxan (X; R = H) and 4,5-dimethyl-4-vinylethynyl-1,3-dioxan (X; R = CH_3). Under analogous conditions 1-vi-

nylethynylcyclohexene and formaldehyde gave a bicyclic dioxan (XI):

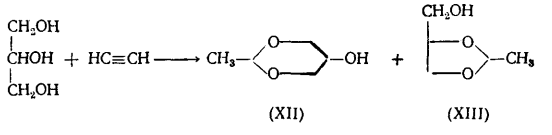


(8)

A quite interesting modification in the Prins reaction was the replacement of mineral acids or their derivatives as catalysts by sulphonic cation-exchange resins[176]. The use of KU-1 cation-exchange resin† for the production of 4-phenyl-1,3-dioxan in the condensation of styrene with formaldehyde greatly facilitates the purification of the reaction product and makes possible the repeated use of the catalyst at the same yield[177] (up to 80%). Similar results have also been obtained for other cation-exchange resins[178,179].

3. Production of 1,3-Dioxans from Acetylene and Polyhydroxy-Compounds

The first information about this method of synthesis was reported in a German patent[180]. As a result of the reaction of a warm solution of glycerol with acetylene in the presence of mercury(II) chloride a mixture of five- and six-membered heterocyclic compounds is obtained, of the *m*-dioxan and dioxolan type. Later, Hill and Hibbert, using the results of Newland on the reaction between acetylene and alcohols in the presence of sulphuric acid and mercury(II) sulphate[181], found that acetylene reacts under these conditions with glycerol to form substituted 1,3-dioxans[182]. The same investigators showed that as a result of this reaction a mixture of five- and six-membered heterocyclic compounds is obtained: 5-hydroxy-2-methyl-1,3-dioxan (XII) and 4-hydroxymethyl-2-methyl-1,3-dioxolan (XIII):

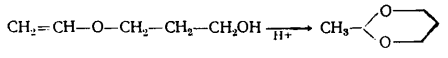


(9)

The details of the cyclisation of this type were found by Hill and Pigeon[183], who showed that in the reaction of acetylene with glycol the vinyl ether

$$CH_2=CH-O-CH_2-CH_2OH,$$

is formed, which in the presence of traces of sulphuric acid is rapidly rearranged into a cyclic ether. Thus under the stated conditions hydroxypropyl vinyl ether is converted into 2-methyl-1,3-dioxan:

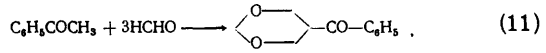


(10)

† KU-1 is a difunctional, strongly acid cation-exchange resin with $-SO_3H$ and –OH active groups, prepared by polycondensation of *p*-phenolsulphonic acid with formaldehyde in acid (Ed. of Translation).

4. Production of 1,3-Dioxans by Various Condensations with Formaldehyde

Fuson and coworkers[184] obtained 5-benzoyl-1,3-dioxan by the action of paraform on acetophenone in methanol solution in the presence of potassium carbonate:

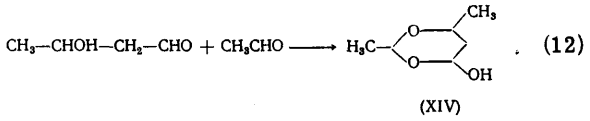


(11)

This type of alkaline condensation is unusual, since it is generally accepted that acetals are obtained in the presence of acid catalysts. However, this example is not unique. Thus, Bergman and Miekely[185] isolated cyclic formals produced by the reaction of the simplest primary amines with an excess of an aqueous solution of formaldehyde at low temperature. Finally, alkaline catalysts are used for obtaining cyclic formals from mixtures of aldehydes.

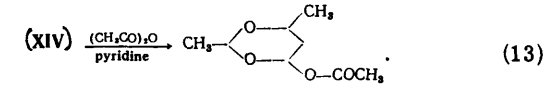
5. Production of 1,3-Dioxans as a Result of the Polymerisation of Aldehydes

In 1935 Shilov[186] reported the formation of 6-hydroxy-2,4-dimethyl-1,3-dioxan in the polymerisation of acetaldehyde in the presence of sodium hydroxide. This problem was developed further in the studies of Späth and Schmid[187], in which the properties of aldol and its derivatives were studied. According to the results of these authors, the monomer of aldol is seldom obtained, except for those instances when the aldol condensation is carried out at high temperature. Evidently, in many instances the aldol reacts as a bimolecular compound. Späth and his coworkers[188] concluded that the presence of the 1,3-dioxan structure in the dimer of aldol is due to intramolecular cyclisation of the hemiacetal formed intermediately. Consequently, simple aldehydes should react with monomeric aldol, forming hemiacetals, which are cyclised into 1,3-dioxans. On heating acetaldehyde with aldol in a sealed tube at 100°C, these authors obtained 6-hydroxy-2,4-dimethyl-1,3-dioxan (XIV):



(12)

Hanschke[189] subsequently produced further proof of the correctness of Späth's hypothesis. The crude product of the polymerisation of acetaldehyde was acetylated with acetic anhydride in pyridine. The acetate isolated seemed identical with the substance obtained by Späth in the acetylation of (XIV):



(13)

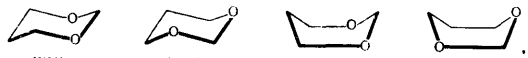
Hence in the polymerisation and condensation of aldehydes, beginning with the simplest, a variety of compounds having the 1,3-dioxan structure are formed, including polymerised 1,3-dioxans[190].

III. STEREOCHEMISTRY OF 1,3-DIOXANS

The stereochemistry of 1,3-dioxans has been little studied, nevertheless its development is extremely important for the further perfection of general stereochemical

ideas, in particular for the development of conformational analysis. Being heterocyclic analogues of cyclohexane (the "pseudocyclohexane ring"), 1,3-dioxans have several important peculiarities. Thus, the presence of oxygen atoms in the 1- and 3- positions of the six-membered ring leads to weakening or, in any case, to a change in the character of the non-bonded interactions of the 1–3 type in this ring. This makes the boat configuration more probable and favourable in this series, in comparison with the boat in the cyclohexane series. Although this in itself is extremely interesting and new, it is far from being the only peculiarity of the stereochemistry of the system being studied. The stereochemistry of 1,3-dioxans has made only the first steps but they already merit attention.

Most authors now ascribe to 1,3-dioxan itself (I) the chair conformation (XV). The following is the basis for this. As long ago as 1937 Otto[191], having measured the dipole moment of (I) and having been satisfied that it is small ($\mu = 1.91$ D) suggested that the most probable conformation of (I) should be the chair form. It is easy to see that forms (XV) and (XVI) are identical, which cannot be said about the boat, of the two possible forms of which (XVII) can be called the symmetrical, and (XVIII) the non-symmetrical boat:



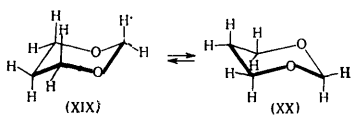
(XV) (XVI) (XVII) (XVIII)

Otto, however, did not make any calculations, but restricted himself to only a qualitative appraisal of these conformations.

Later, Arbuzov[192] pronounced in support of the correctness of Otto's hypothesis. He calculated the dipole moments of the hypothetical planar form (I) ($\mu_{calc} = 1.33$ D), the chair form ($\mu_{calc} = 1.91$ D), and of one of the boat forms ($\mu_{calc} = 2.34$ D).

The information obtained by dipole moment measurements about the conformation of 1,3-dioxan was confirmed by additional results obtained on the basis of an examination of the NMR spectra of this compound[193–195].

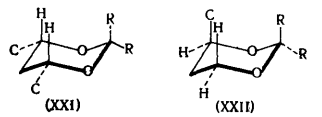
The singlet nature of the peak of the axial and equatorial protons shows the repeated changes of one chair form into the other, (XIX) ⇌ (XX), hence on average in time the axial and equatorial protons of all the CH_2 groups of the ring become equivalent:



(XIX) (XX)

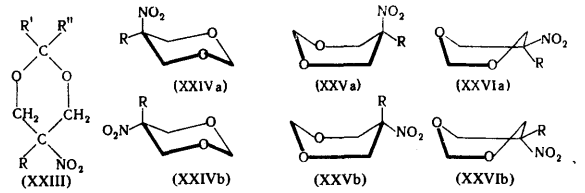
Barbier and coworkers come to the same conclusion in their work, by stating that 1,3-dioxan is present in the chair form and there is a constant chair–chair inversion (XIX) ⇌ (XX). Consequently Barbier's work confirms completely and independently the interpretation of the spectrum which was given above and was proposed by Samitov.

If the problem of the conformation of (I) can evidently be considered as solved, the problem of the predominant conformations of substituted 1,3-dioxans, the configuration and conformations of the stereoisomeric derivatives of 1,3-dioxan is far from clear and should be decided independently for each separate instance. Thus the chair conformation is evidently favourable for some substituted 1,3-dioxans. This is supported by the theoretical works of Barker and coworkers[196,197], Mills[198], and Klyne[199]. These authors theoretically considered the hypothetical formation of definite types of ring in 1,3-dioxans. All the authors mentioned started from the fact that the most stable conformation of the initial polyhydric alcohol exhibits a zigzag-shaped structure of the carbon skeleton. If this is so then, according to Barker, on closure of the ring the latter can and should be formed by two hydroxyl groups present on the same side of the Fischer projection. This means that as a result of such a reaction the dioxan ring must of necessity be closed with two equatorial substituents in the 4- and 6- positions. This is termed the β-*C*-ring (XXI). The other variant of the ring, the β-*T*-ring (XXII) is more difficult to form, in the opinion of the above authors. All this fits in with the general rules of conformational analysis. However, it should be noted that the authors mentioned[196–199] at once reject the boat form for such molecules without discussing its possible variants:



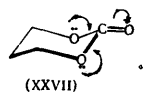
(XXI) (XXII)

Moreover, this is evidently not always true, since a consideration, by the present authors, of this conformation on Stewart–Brigleb models showed that the boat, especially the non-symmetrical boat (XXIII) in the series being considered is incomparably more favourable than in the cyclohexane series. Experimental investigations devoted to this problem are contradictory. There are studies in which the conclusions support the predominance of the chair conformation in substituted 1,3-dioxans. Studies have also been published in which it is stated that substituted 1,3-dioxans exist predominantly in the boat conformation. Of the former, mention must be made above all of the great review paper of Urbanskii[200] at the Butlerov symposium in 1961, in which amongst other data devoted to the study of the stereochemistry of six-membered heterocycles, information was given on the study of the conformation of the 5-nitro-substituted 1,3-dioxans of formula (XXIII). To find the preferable conformations of these substances the dipole moments of all possible conformations of (XXIII) were calculated. These values were then compared with the experimental results.



(XXIII) (XXIVa) (XXVa) (XXVIa) (XXIVb) (XXVb) (XXVIb)

For more complex derivatives of (I) the study of the dipole moments for proof of the conformations becomes difficult[201,202]. Thus dipole moments were calculated for the planar form, and the chair and boat forms of trimethyleneglycol carbonate (XXVII). They were 4.24, 3.56, and 3.28 respectively. The value found is 5.28.[192] Arbuzov[192] explains this anomaly by electronic displacements in the molecule of (XXVII):



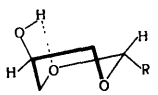
(XXVII)

However, this statement needs additional verification, since it is not confirmed quantitatively.

Most of the information now published shows that the chair conformation is most probable for substituted 1,3-dioxans. Of the studies on which it is maintained that substituted 1,3-dioxans exist in the boat form, mention can be

made of the work of Foster and coworkers [203-206] and that of the authors of the present article [207,208]. These are connected with the use of spectroscopic methods of investigation. Unfortunately, there have been few studies of the 1,3-dioxans by ultraviolet, infrared, Raman, and NMR spectroscopy.

The study of 1,3-dioxans by ultraviolet spectroscopy showed that they absorb in the far vacuum region of the spectrum. However, the number of works devoted to the study of the vacuum ultraviolet spectra of 1,3-dioxans is very small and the conclusions [209-212] do not allow a judgement about the stereochemistry of these substances to be made on their basis. Still fewer papers are devoted to studies of the Raman spectra. There is only one paper [213] on this region and from this it is possible to draw only insignificant information. The study of the infrared spectra of 1,3-dioxans began comparatively recently [214,215]. The first studies confirmed the presence in the infrared spectra of substituted 1,3-dioxans of bands of complex structure but until recently there was no success in finding the number of characteristic bands, without speaking of more far-reaching investigations. However, papers devoted to a more systematic study of this problem have recently appeared [207,208]. Thus, Ledwoch [216] succeeded in finding a set of characteristic bands for the 1,3-dioxan ring (ν = 1025–1035, 1070–1110, 1160–1175, 2745–2795 cm^{-1}), and Foster and coworkers [217-220] found, in a study of the infrared spectra, that some of the *trans*-2-alkyl-5-hydroxy-1,3-dioxans and substituted 5-hydroxy-1,3-dioxans exist in the preferential conformation of the non-symmetrical boat (XXVIII). The reason for the existence of this form was thought by Foster to be that the large group R experiences less non-bonding interactions in this conformation than in the chair. Moreover, the boat (XXVIII) is stabilised due to the formation of a hydrogen bond:



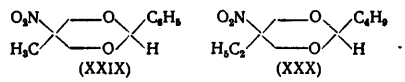
(XXVIII)

Results which show the possibility and permissibility of the boat conformations in a series of 2-substituted 5α-alkoxyethyl-5-alkyl-1,3-dioxans were obtained by the present authors in a study of the NMR spectra of these compounds. These investigations are analysed below.

From all that has been stated it can be concluded that the conformations in the 1,3-dioxan series are somewhat different from the cyclohexane series. Whereas 1,3-dioxan itself evidently exists in the chair form, its derivatives can have not only the most favourable chair conformation, but also the boat conformation, which in the series being considered is more favourable than in the cyclohexane series.

The second important problem of the stereochemistry of the 1,3-dioxans consists in finding the configuration of the geometrical isomers of the 1,3-dioxans. It is easy to see that any (apart from *gem*-substituted) disubstituted 1,3-dioxans, and also tri- and more substituted 1,3-dioxans, should be mixtures of geometric isomers, which often are also diastereomers. This aspect of the stereochemistry of the 1,3-dioxans has been little studied. Very few authors have succeeded in resolving 1,3-dioxans into stereoisomers, and still fewer have firmly established the configuration of these isomers.

In 1928 Hibbert and Carter [221] succeeded in finding experimentally the presence of *cis-trans*-isomers in 2-(-*p*-nitrophenyl)-5-hydroxy-1,3-dioxan and its derivatives (5-methyl, 5-benzoyl, and 5-nitrobenzoyl). In 1942 Verkade and van Roon [84] separated the geometric isomers of 5-hydroxy-2-phenyl-1,3-dioxans. A year later Zenkus [112] synthesised 5-methyl-5-nitro-2-phenyl-1,3-dioxan (XXIX), which was separated into stereoisomers owing to a difference in the solubility of the latter in benzene–cyclohexane mixture. The melting points of these isomers are 118° and 78.4°C respectively. These isomers were then reduced to amino-derivatives, which also seemed stereoisomers and melted at 84° and 48.2°C respectively. A similar operation was also carried out on 2-butyl-5-ethyl-5-nitro-1,3-dioxans (XXX):



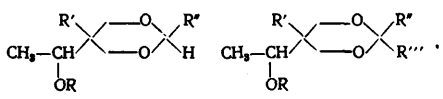
(XXIX) (XXX)

A characteristic for all the older works mentioned was that only the crystalline 1,3-dioxans were separated by fractional crystallisation and the authors refrained from firm statements about the configuration of the substances obtained. In recent years the studies in this field were extended and chromatographic methods were applied to the investigation of stereoisomerism. Thus, Rondestvedt [21] reported on the separation, by use of gas–liquid chromatography, of the geometric isomers of some of the 1,3-dioxans they had synthesised. It is quite interesting that this author applied the method of conformational analysis to the investigation of the systems they synthesised and advanced the hypothesis that the largest substituent should occupy an equatorial position in the molecules of separate isomers. Rondestvedt tried to use infrared spectroscopy for studying these problems. The preparative separation of the isomers, carried out in three instances, was again by fractional crystallisation.

Portoghese and Smissman [222] and later Smissman and coworkers [223], in studying the stereochemistry of the Prins reaction connected the stereoisomerism of 1,3-dioxans with that of the related 1,3-diols. The authors of these works were some of the first to use nuclear magnetic resonance for studying this problem. They succeeded in showing that the Prins reaction is characterised by *cis*-addition in several instances. In studying this process, they found in passing the configuration of some aryl-substituted 1,3-dioxans. Nuclear magnetic resonance was also used by Bagget and coworkers [224] in a work devoted to a proof of the configuration of the stereoisomeric derivatives of 5-hydroxy-1,3-dioxan. In this work hypotheses about the predominant conformations of these stereoisomers were advanced in which it stated that both the *trans*- and the *cis*-isomers have the chair conformation, but whereas the *trans*-isomer does not exhibit the chair–chair type of inversion, the *cis*-isomer does. The latter assumption was made on the grounds that the peak of the protons found in the 4- and 6- positions of the molecule of the *cis*-isomer was a singlet, that is, showed their equivalence. Possibly, however, this statement is not completely correct and the apparent equivalence of the 4- and 6-axial and equatorial protons is due to another reason, as will be discussed below.

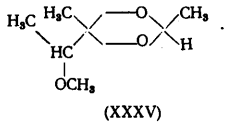
In a series of later studies [216-219] it was suggested that stereoisomers exist in synthesised mixtures of 1,3-dioxans. Quite recently Kaplan [87] succeeded in resolving some 2-alkyl-5-ethyl-5-hydroxymethyl-1,3-dioxans into stereoisomers by gas–liquid chromatography.

In a series of published investigations Bogatskii and coworkers [207,208] examined the problem of the stereochemistry of 2-substituted 5-α-alkoxy-5-alkyl-1,3-dioxans, of the type of (XXXI) and (XXXII):



(XXXI) (XXXII)

During the course of these investigations, initially by gas–liquid chromatography and proton magnetic resonance, the existence of geometrical isomers in substance of type (XXXI) was demonstrated [99,100], after which they were separated into individual isomers by rectification on efficient columns. This was the first example in the literature of the separation of the derivatives of 1,3-dioxans into stereoisomers by rectification. The purity of the isomers obtained was determined chromatographically and was 95 to 99%. To establish the configuration and conformation of the individual isomers, dipole moments and NMR methods were then used. The authors succeeded in showing that the low-boiling isomers of (XXXI) are *trans*-isomers (XXXIII)‡, which exist in the predominant conformation of a chair, and the high-boiling are *cis*-isomers (XXXIV)‡ which exist in the predominant conformation of the non-symmetric boat. The NMR spectra showed that in the specimens examined there was absolutely no sign of inversion of the conformations. A study of the NMR spectra of *cis*- and *trans*-5α-methoxyethyl-2,5-dimethyl-1,3-dioxans raised no doubts on the non-equivalence of the axial and equatorial protons of the methyl groups, which shows the absence of inversion. Comparison of the calculated and measured values of the non-equivalence shows the chair conformation. This conclusion, obtained on the basis of a study of NMR spectra was confirmed by studying the dipole moment. Actually, the dipole moment of the *trans*-isomer (XXXV) was found to be $\mu = 1.15$ D. The value calculated for the chair conformation is $\mu = 1.16$ D.



(XXXV)

A characteristic feature of the spectrum of the *cis*-isomer is the absence of a peak with an anomalously low value of the chemical shift and the singlet nature of the peak of the protons of the $C_{(4)}$ or $C_{(6)}$ CH_2 group. This singlet nature cannot be the result of inversion of conformation, since other regions of the spectrum do not show averaging of the shifts of the axial and equatorial substituents. A comparison of calculated and measured values of non-equivalency shows that such phenomena should take place in the non-symmetrical boat configuration where the calculated non-equivalence of the $C_{(4)}$ protons is $\delta = 0.4$ p.p.m., and that of the $C_{(6)}$ protons $\delta = 0.16$ p.p.m. Conclusions about the configuration *cis*- and the conformation of non-symmetrical boat are in this instance also confirmed by a study of the dipole moments. In *cis*-(XXXV) the dipole moment was found to be $\mu = 2.60$ D and that calculated for the non-symmetrical boat is $\mu = 2.56$ D.

These conclusions about the configuration and conformations of (XXXI) were then confirmed by studying the kinetics of hydrolysis of these isomers, which showed that the low-boiling isomers are hydrolysed much more slowly than the high-boiling ones and the influence of a substituent is greater on the hydrolysis of (XXXIII) than on the hydrolysis of (XXXIV). It is easy to see that this agrees with the results obtained in relation to the configuration and conformation of these stereoisomers.

In the series of stereoisomeric (XXXI) we succeeded in observing a linear relation between the difference in boiling points of the *cis*- and *trans*-isomers (Δt) and the number of carbon atoms in the (XXXI) molecule. Such a relation had been found by Kazanskii and Liberman in the cyclohexane series. This confirms the configurative relationship between the 1,3-dioxan series and the cyclohexane series. However, it is still more interesting that there is also a linear relation between the ratios of the hydrolysis constants of the stereoisomeric (XXXI) and the number of carbon atoms in the same series. Consequently, the dependence of Δt on the number of atoms is not fortuitous but is connected with the extremely intimate configurative features of these compounds.

All the information given above shows that work in this field of study of the stereochemistry of the 1,3-dioxans is developing rapidly and the results obtained up till now show the presence of a trait of similarity and at the same time a series of essential differences between these compounds and cyclohexane. Evidently, 1,3-dioxan systems are a convenient model for studying the problem of the characteristics of the boat conformations.

While this article was being considered by the Editorial Board we were undertaking investigations [338-340] which confirm the conclusions concerning the stability and extensive distribution in this series of the boat conformation and the marked favourability of the $C_{(6)}$ axial position in the 1,3-dioxan ring compared with the cyclohexane rings. It is easily established that the 5-C-axial valency in these systems is unique owing to the considerable weakening of the 1,3-interaction, since there are oxygen atoms in positions 1 and 3 of the pseudocyclohexane ring [339].

The present authors conclude that the ketals of this series are characterised by the presence of a non-symmetric boat conformation, or twist-conformation [338-340]; they have formulated an empirical rule according to which in 1,3-dioxan systems in those instances when inversion of the conformation of the ring is impossible or greatly hindered for steric reasons, the geometric isomers tend to take on the conformation (chair, symmetric or non-symmetric boat, or twist-conformation) with di-equatorial position of the largest substituents or such configuration in which one of the largest substituents occupies a $C_{(6)}$-axial position [339].

It should be noted that interest in the conformational problems in the 1,3-dioxan series is increasing continually, as is shown by the studies [341-345], whose results confirm the above conclusions and the empirical rule given.

IV. CHEMICAL CHANGES OF 1,3-DIOXANS

The chemical changes of 1,3-dioxans are rather varied, but a common feature of them is that, like the reactions of acetals and ketals, they are modified by the presence of a cyclic structure.

1. Hydrolysis and Alcoholysis

The hydrolysis of 1,3-dioxans is effected comparatively readily, although cold water and dilute and cold solutions

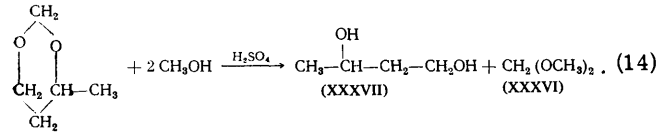
‡ Formulae (XXXIII) and (XXXIV) are not given in the Russian (Ed. of Translation).

of alkalis have little action on 1,3-dioxans[225,226]. However, in an acid medium 1,3-dioxans, like other acetals, are readily hydrolysed in the cold, even extremely dilute solutions of acids being sufficient for this[227-229]. As for all similar reactions of acetals, the hydrolysis of 1,3-dioxans in acid medium is reversible. Therefore it is not profitable to obtain 1,3-diols from 1,3-dioxans since the yield of the latter does not exceed 10–20%.[230,231] True, there are indications that the hydrolysis equilibrium can be shifted to the side of the formation of diols, by bonding the aldehydes formed by chemical means or by carrying out the hydrolysis under pressure[232].

In recent years more and more attention has been paid to the theoretical examination of the hydrolysis of 1,3-dioxans. Dilatometric[233-237], titrimetric[238-240], and spectrophotometric[241-243] methods of studying the kinetics of the hydrolysis of 1,3-dioxans have been developed and employed with success. We stated above the possibility of using a study of the hydrolysis for proving the configuration and conformation of stereoisomeric 1,3-dioxans. Of the studies of the mechanism of this reaction we can single out that of Bender and Silver[244], where the authors succeeded in finding that the rate of hydrolysis of certain substituted 1,3-dioxans in the pH range from 3 to 6 is independent of the hydrogen-ion concentration.

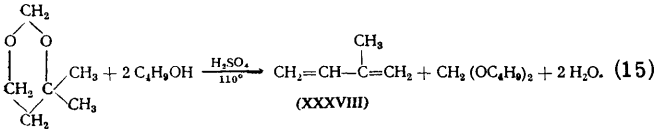
Hydrolysis of the cyclic ketals of the 1,3-dioxan type has been little studied but there are indications that six-membered ketals are less stable than five-membered[245,246], according to conformational considerations. This problem was discussed in the previous section of the present article.

Alcoholysis of 1,3-dioxans leads to the production of diols or alkenes in good yields. Thus on boiling 1,3-dioxans with methanol in the presence of sulphuric acid the splitting of the dioxan takes place very readily, in view of the fact that the methylal formed (XXXVI) is continually removed from the reaction[247,248].



(14)

When the reaction proceeds in methanol as medium its chief products are a glycol (XXXVII), whereas in alcoholysis in the presence of higher alcohols acetals (or formals) of these alcohols are left in the reaction mixture and are, together with diols, the main reaction products. Very often under these conditions the glycols are dehydrated with the formation of conjugated dienes as is shown in Eqn. (15). Consequently, the process considered can serve as a convenient method for obtaining conjugated dienes of type (XXXVIII):[249]

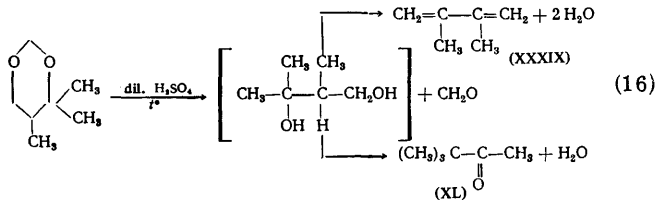


(15)

However, conjugated dienes can be obtained from the 1,3-dioxans without alcohols being present. It has been shown[250] that on boiling substituted 1,3-dioxans with aqueous solutions of mineral acids (1–5%) they are converted directly into dienes. This reaction finds industrial application and many variations of this method have been patented.

It was stated above that dioxans are stable under the action of alkalis in the cold, yet hot alkali solutions can cleave the 1,3-dioxan ring, as also can hot water[252].

An anomaly observed in the course of this reaction merits attention. Thus in the hydrolysis of 4,4,5-trimethyl-1,3-dioxan, in addition to the usual reaction products, a diene (XXXIX) and formaldehyde, ketones of the pinacolin type (XL) are also formed:



(16)

This anomaly can be explained in passing by the occurrence during the course of the reaction of hydrolysis and dehydration with a pinacol rearrangement of the diol formed, Eqn. (16).[253]

2. Thermal and Catalytic Decomposition

This section deals with a wide range of catalytic conversions of 1,3-dioxans connected with cleavage of the ring and in this sense the reactions being considered are close to the previously described hydrolytic cleavage of the 1,3-dioxan systems.

Catalytic pyrolysis of substituted 1,3-dioxans over dehydrating catalysts leads directly to the production in good yields of conjugated diene hydrocarbons. This is the most suitable method industrially for the production of conjugated dienes, in particular isoprene, since the dioxans themselves which are used for these reactions are accessible and cheap, seeing that they are obtained from alkenes by the Prins reaction. There is an extensive literature on this subject, still growing at the present time[254-273], and mainly devoted to the production of isoprene; the different variants of the method mentioned are usually patented.

Several catalysts have been proposed for this reaction. Various authors have at different times proposed as catalysts a mixture of H_3PO_4 or $H_4P_2O_7$ with phosphorus furnace slags, kaolin, or bentonite. The catalyst mass was activated by passing steam at 150–300°C under pressure and was regenerated by passage of an air–nitrogen mixture at 400–600°C.[254-256]

Other authors have used oxide catalysts[256,257], a mixture of boric and phosphoric acids[258], zinc chloride and manganese chloride[259,260], various catalysts based on phosphoric acid[261-264], and several other acid catalysts of the most diverse nature[266].

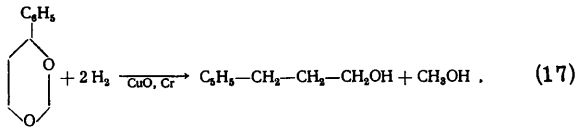
The French authors Coussemant, and Hellin and their coworkers[267-272] have recently made extensive investigations in this field; they studied a series of catalysts based on phosphoric acid and obtained patents on various versions of the industrial production of isoprene from 4,4-dimethyl-1,3-dioxan.

Hamamoto and Mizutani[274] carried out a serious investigation by comparing oxide catalysts, the salts of various metals, and acids, borate catalysts, and catalysts based on phosphoric acid in this reaction[274].

The thermal cleavage of 1,3-dioxans can also take place without catalysts at 200–600°C, but the yields of the cleavage products are lower (not more than 10%). In this reaction the products are usually alkenes, formaldehyde (or other aldehydes), or CO and hydrogen[121].

3. Reduction and Hydrogenolysis of 1,3-Dioxans

The hydrogenolysis of 1,3-dioxans can be used for the synthesis of certain alcohols [275-277]. The hydrogenation of 4-phenyl-1,3-dioxan, leading to the production of 3-phenylpropanol in 85% yield, has been described:



(17)

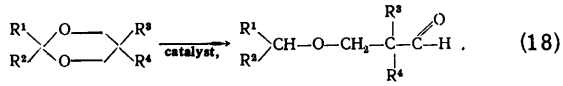
Under analogous conditions 4,4-dimethyl-1,3-dioxan is converted into isopentyl alcohol [278], and the acylated 1,3-dioxans into the corresponding β-monoglycerides [279-282].

1,3-Dioxans arylated in the 4- position are capable of reductive cleavage under the action of sodium in the presence of high-boiling alcohols, for example, di-isobutylmethanol [165-167]. Here also reductive cleavage proceeds selectively leading to the loss of oxygen attached to the $C_{(4)}$ carbon.

Finally, the possibility was recently shown of effecting the hydrogenolysis of 1,3-dioxans under the action of lithium tetrahydroaluminate [283,284] and also their reduction with the aid of organomagnesium compounds [285,286]. These reactions lead to cleavage of the 1,3-dioxan ring and the production of either alkoxy-alcohols [286] or unsaturated alcohols [285], depending on the conditions.

4. Catalytic Isomerisation and Catalytic Changes

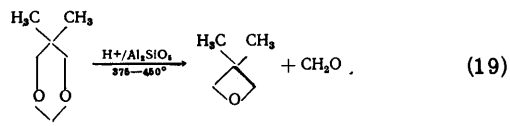
In 1961 Rondestvedt reported the finding of a new type of conversion of 1,3-dioxans—catalytic isomerisation of these substances into β-alkoxyaldehydes according to Eqn. (18) [287-289]:



(18)

This reaction takes place at elevated temperatures in the presence of weakly acid catalysts. For example, on pumice it is effected at 360–450°C and on silica gel at 250–350°C. The ease of rearrangement depends on the nature of the radicals R^1–R^4. For example, the presence of two substituents at position 5 is obligatory, or otherwise further decomposition of the reaction products takes place, into the corresponding alcohol and arylaldehyde. Moreover, it was found that electron-acceptor groups in position 2 hinder the course of the rearrangement, and alkyl and cycloalkyl substituents in the same position facilitate it.

Another interesting reaction was observed by Bartok [290], the conversion of 1,3-dioxans into the oxacyclobutane system:



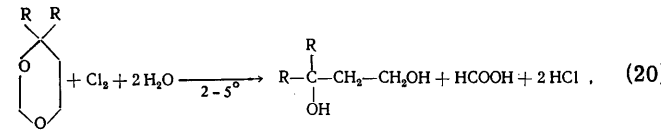
(19)

This conversion is effected on an acid cracking catalyst according to Eqn. (19) at 370–450°C and leads to the production of oxacyclobutane derivatives in 25–30% yield.

5. Halogenations

Of the halogenations of 1,3-dioxans, their chlorination has been studied better than the other reactions.

The chlorination of 4,4-dialkyl-1,3-dioxans in an aqueous medium leads to their hydrolysis with the formation of the corresponding glycols and is not accompanied by the dehydration of the latter. Evidently the unstable 4,4-dialkyl-2-chloro-1,3-dioxan is formed initially, then decomposes in the presence of water to form glycol, and formic and hydrochloric acids [291]:

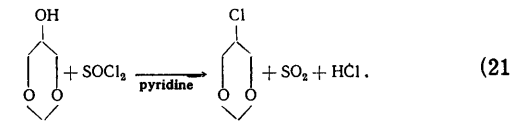


(20)

The chlorination proceeds otherwise in the absence of water. Under these conditions chlorination and bromination lead to the formation of polychloro- and polybromo-derivatives of 1,3-dioxans, which, however, cannot be purified and isolated [292].

There are interesting studies devoted to the action of various halogenating agents—phosphorus(V) chloride, thionyl chloride, etc. [60] Phosphorus(V) chloride breaks the 1,3-dioxan ring, to form trimethylene chloride [293].

Under the action of thionyl chloride on 5-hydroxy-1,3-dioxan, 5-chloro-1,3-dioxan was obtained [68,294]:



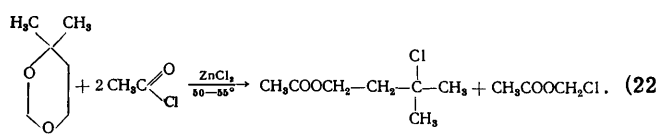
(21)

Halogenation proceeds more easily in the side-chain of substituted 1,3-dioxans. However, here difficulties are encountered since it is constantly necessary to consider the possibility of cleavage of the ring.

6. Action of Anhydrides and Acyl Halides of Organic Acids on 1,3-Dioxans

The action on 1,3-dioxans of anhydrides and acyl halides of organic acids has been little investigated, yet papers have been published which enable the course of the reaction to be predicted. Thus when acetic acid acts on 1,3-dioxan in the presence of concentrated sulphuric acid the ring is broken and the corresponding glycol diacetals are formed. In this way 5-ethyl-5-nitro-1,3-dioxan was converted into 2-ethyl-2-nitropropan-1,3-diol diacetate [295]. It is easy to understand that this reaction is related to the hydrolysis and alcoholysis, with the difference that here attack is by a glycol (not an aldehyde, as in alcoholysis). However, the reaction under consideration does not always proceed so simply. It is known that sometimes it is accompanied by side-reactions and rearrangements. For example, it is known that under the action of acetic anhydride in the presence of sulphuric acid 4-phenyl-1,3-dioxan is converted into 1,5-diacetoxy-2-hydroxy-3-phenylpentanediol [296]. Other authors, for example, Senkus [295], have described similar conversions.

Acyl halides of organic acids react with 1,3-dioxans in a similar manner. When 4,4-dimethyl-1,3-dioxan reacts with acetyl chloride, breaking of the ring and formation of the corresponding chloro-esters is observed [297]. It is interesting that the yields in this reaction are almost quantitative:



(22)

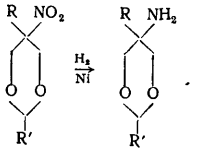
However, here also side-reactions are possible. On boiling alkyl-substituted 1,3-dioxans with small amounts of acyl chlorides in the presence of Friedel–Crafts catalysts, solid resins are obtained[298], probably formed as a result of secondary polycondensation processes.

7. Oxidation

There has been little investigation of the oxidation of 1,3-dioxans. Results have been published which show that in the photo-oxidation of 1,3-dioxan various peroxides can be obtained, depending on the conditions[299]. Oxidation for 100–120 h at 50°C gave a dihydroperoxide, and for 9–10 days at 25°C a hydroperoxide; the latter is then polymerised into a dimer. In 1964 Ikeda and coworkers published an extensive paper[300] devoted to the study of the autoxidation of 1,3-dioxans by atmospheric oxygen and also the oxidation of these substances in the presence of catalysts. The authors of this work obtained five types of oxidation product: peroxides, hydroperoxides, spirocyclic peroxides, $\alpha\beta$-unsaturated ethers, and polymers. The products were obtained in different quantities and proportions, depending on the reaction conditions; without a catalyst, the reaction was directed towards the side of the production of hydroperoxides and spirocyclic peroxides, but in the presence of traces of cobalt(II) derivatives the reaction is directed towards the side of the formation of $\alpha\beta$-unsaturated ethers and polymers, etc. However, the properties of peroxides and hydroperoxides of 1,3-dioxans are still very little investigated.

8. Conversions of Functional Derivatives of 1,3-Dioxans

The patent literature[135] states that in the catalytic reduction of nitro-derivatives of 1,3-dioxans at 110 at pressure and in the presence of Raney nickel in methanol, amino-substituted 1,3-dioxans are obtained exceptionally readily and in good yields:



(23)

Another interesting conversion of substituted 1,3-dioxans is the reaction, studied by Urbanskii and Ekshtein, of 5-nitro- and 5-hydroxymethyl-1,3-dioxans with diazo-compounds, leading to the production of derivatives of 1,3-dioxans[301,302].

In addition to these papers several have been published on the conversions of hydroxy-derivatives of 1,3-dioxans and of halogeno-derivatives[88] and on the production of substances of the 1,3-dioxan type with two keto-groups in positions 4 and 6,[303-305] and several other papers on the synthesis or conversions of functional derivatives[306-315].

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In ending the review of the chemical properties of 1,3-dioxans it must be mentioned that at present only those chemical properties of this class of compound which are related to their industrial use are receiving more serious investigation, namely the hydrolysis and catalytic cleavage of 1,3-dioxans to give conjugated dienes. Information about other properties of this group of substances is extremely scanty.

V. USE OF THE 1,3-DIOXANS

Although it is still impossible to speak of the 1,3-dioxans having such a wide industrial use as, for example, 1,4-dioxan or certain other organic compounds, the available published information shows that many of these substances exhibit extremely valuable properties.

The practical uses of 1,3-dioxans can be classified in several groups. The first is the use of 1,3-dioxans as intermediates for synthesis. In this respect the most promising application is their use for making highly pure alkadienes, 1,3-diols, and β-monoglycerides[228,247,254-273,279-282].

These problems are now receiving attention and the greatest number of works is devoted to this direction. They were characterised above in the section devoted to the chemical properties of 1,3-dioxans. According to patents, some of the 1,3-dioxans can serve as components in the synthesis of polymeric materials[316-318]. Thus 5-methyl-5-($\alpha\beta$-dihydroxyethyl)-1,3-dioxan can be used for obtaining non-saturated polyethers[67].

The second direction predicts the use of 1,3-dioxans as solvents, additives, etc.[319] It was shown that 1,3-dioxans are good solvents for resins and lacquers[121,143,320], and can be used as a solvent in the deparaffinisation of oils. Mixtures with 4,4- or 4,5-dimethyl-1,3-dioxans were especially effective[321]. 1,3-Dioxans are good solvents in Grignard reactions[322].

1,3-Dioxans are good antiknock agents to add to motor fuel and increase its octane number[321]. A derivative of spiro-di-1,3-dioxans, which contain sulphur and halogen can be used as intermediates and accelerators for the vulcanisation of rubbers. The addition of 1,3-dioxans to polymers and elastomers improves their properties, increases the elasticity of the adhesives and sealing compositions based on various resins. 1,3-Dioxans are used in the production of lubricants and cements[223,324]. 2,2-dimethyl-1,3-dioxan can be used in the hydrogenation of butadiene rubbers[325,326]. The possibility of using 1,3-dioxans as denaturing agents in alcohol, for the dry cleaning of clothes, and as addition to paints to prevent their skinning during storage[327] has been noted.

The study of the physiological activity of the 1,3-dioxans is extremely promising. The possibility of using 1,3-dioxans as disinfectants has now been shown[319,327]. Blicke and coworkers investigated some pharmacological properties of a considerable number of 2,2-disubstituted 5-methyl-1,3-dioxans and mentioned their spasmolytic and antihistamine activity[48,49,56]. Subsequently, Mel'tser and coworkers synthesised a series of di-substituted 1,3-dioxans in a search for new depressants of the central nervous system[51]. Information has been published about the sedative-hypnotic action of 1,3-dioxans[328].

According to the patent literature, some 1,3-dioxans exhibit antibiotic action[265,276,329], for example, 6-acetoxy-2,4-dimethyl-1,3-dioxan[329] or the products of condensing carboxyl compounds with 1-(*p*-nitrophenyl)-2-acylaminopropen-1,3-diols[276].

We have obtained results which show the antimicrobial and fungicidal ability of alkoxyalkyl-substituted 1,3-dioxans[330].

Finally, quite interesting information has been obtained about the influence of 1,3-dioxans on plant growth. According to Urbanskii[331] and ourselves[332], 1,3-dioxans stimulate plant growth, especially that of monocotyledons. 1,3-Dioxans have found application in entomology[333-337] and as insect-repellant substances[46,328,337].

Consideration of the progress in the chemistry of the 1,3-dioxans shows that in recent years chemists have paid

increasing attention to these very interesting substances. This is because of the wide possibilities for their use in the synthesis of several important organic substances, the convenience of the system as a model for stereochemical investigations and their high and varied physiological activity. It is evident that in future years we can expect a still more rapid development of the chemistry of the 1,3-dioxans.

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Progress in the Analytical Chemistry of Non-aqueous Solutions

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CONTENTS

I. Introduction 278
II. Theory of the acid-base titration of non aqueous solutions 279
III. Principles of the acid-base titration of non-aqueous solutions 281
IV. Titration in non-aqueous solutions of bases 284
V. Titration in non-aqueous solutions of acids 285
VI. Titration in non-aqueous solutions of salts 287
VII. Titration of monomeric and polymeric compounds in non-aqueous solutions 288
VIII. Analysis of industrial materials 289

I. INTRODUCTION

With the rapid development of chemistry and chemical technology, it is becoming urgently necessary to improve and develop new and more effective methods for the analysis of inorganic and organic compounds. Among the most extensively applied analytical methods, a unique position is occupied by chemical and physicochemical methods based on the titration of various compounds in a medium of non-aqueous liquid solvents and in liquefied gases[1-25]. As a result, the analytical chemistry of non-aqueous solutions has developed into an important independent branch of chemical science. Reactions in non-aqueous solutions have begun to be used not only in the familiar classical