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Halogen Derivatives of 1,4-Dioxan

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Methods for obtaining mono-, di-, and poly-chlorinated derivatives of 1,4-dioxan by the direct substitution of hydrogen atoms by chlorine are surveyed, together with synthetic reactions yielding fluoro-, chloro-, and bromo-dioxans. Methods of obtaining halogenoalkylated dioxans containing fluorine, chlorine, or iodine atoms are described. Consideration is given to reactions of halogenodioxans making possible their use in organic synthesis, in particular of solvents for polymers. A list of 110 references is included.

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I. INTRODUCTION

1,4-Dioxan (usually termed simply *dioxan*) continually attracts the attention of chemists because it is a specific and perhaps universal solvent meriting the name "organic water". Furthermore, it forms molecular compounds (dioxanates) with many inorganic and organic substances. Such dioxanates are often used in organic synthesis[1]. Dioxan itself and its derivatives also occupy an important position in organic synthesis. The halogen derivatives, in particular chlorodioxans, are especially valuable.

Halogeno-derivatives of dioxan and their reactions have been only partly dealt with in recent monographs and reviews[2-4]. A considerable number of predominantly experimental studies on halogenodioxans and their use in various types of organic syntheses have been reported during past decades.

Direct chlorination of dioxan is the chief method for obtaining chlorodioxans, with replacement of any hydrogen atom forming an α-chlorinated ether. Direct fluorination and iodination of dioxan have not been reported, the corresponding derivatives being obtained by indirect procedures. Iodinated dioxans are completely unknown. Chloro- and bromo-dioxans are extraordinarily reactive: they are used to obtain alkyl- and aryl-dioxans, alkoxy- and aryloxy-dioxans, dihydrodioxin, dioxin, dioxanone, and other compounds based on the dioxan ring.

II. CHLORODIOXANS

Chlorine does not form stable dioxanates, in contrast to bromine and iodine, which at and below room temperature form with dioxan molecular compounds $C_4H_8O_2.X_2$ (X = Br,I). The direct action of chlorine on dioxan involves a vigorous exothermic reaction accompanied by evolution of hydrogen chloride. If the temperature is not controlled, the reaction may terminate in an explosion. The chlorination of dioxan is strongly accelerated by light and by catalysts such as Lewis acids. Chloro-derivatives of various degrees of substitution right up to octachlorodioxan $C_4Cl_8O_2$ can be obtained by the direct chlorination of dioxan. Chlorodioxans having a specified number of chlorine atoms in the ring can be prepared by maintaining a definite régime of chlorination.

Certain difficulties arise in establishing the structure of chlorodioxans. The chlorination of dioxan may lead to the simultaneous formation of many structural isomers and stereoisomers as well as conformers. Furthermore, the reaction is accompanied by chlorolysis with fission of the dioxan ring. Among 45 possible chlorodioxans (counting optical isomers) only 16 are known. The Table gives data on the numbers and properties of possible isomers.

Chlorodioxans*.

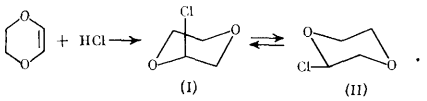
Isomer	N_p	N_k	Properties	Yield, %	Ref.
Mono	1	1	m.p. 62°C/14 mmHg, d_4^{20} 1.276	70	[5]
Di					
2,2	1	1	b.p. 33-35°C/0.5 mmHg, d_4^{20} 1.4797	57	[15]
2,3	2	2	m.p. 53°C (*cis*), 31°C (*trans*)	80—90	[21—23, 25]
2,5	2	1	m.p. 118-120°C	25	[6, 59, 60]
2,6	2	0	—	—	—
Tri					
2,2,3	1	1	m.p. 20, b.p. 60-61°C/1 mmHg	—	[37]
2,2,5	1	0	—	—	—
2,2,6	1	0	—	—	—
2,3,5	4	0	—	—	—
Tetra					
2,2,3,3 (A)	1	1	m.p. 137-140°C	67	[37]
2,2,3,5 (B)	2	1	b.p. 93-95°C/12 mmHg	85	[21, 38, 41]
2,2,3,6 (C)	2	1	m.p. 57-58°C		[21, 38, 41]
2,2,5,5 (D)	1	0	m.p. 59-60°C	33	[21, 38, 41]
2,2,5,6 (E)	2	0	m.p. 70-71°C	—	[62, 67]
2,2,6,6 (F)	1	0	m.p. 100-101°C	25	[37]
2,3,5,6 (G)	5	4	m.p. 143-144°C	10	[21, 38, 60]
Penta					
2,2,3,3,5	1	0	—	—	—
2,2,3,5,5	1	0	—	—	—
2,2,3,6,6	1	0	—	—	—
2,2,3,5,6	4	0	—	—	—
Hexa					
2,2,3,3,5,5	1				
2,2,3,3,5,6	2	2*	m.p. 92 and 94°C	25	[45, 62]
2,2,3,5,5,6	2				
2,2,3,5,6,6	2				
Hepta	2	2	m.p. 56 and 123°C	90	[62, 63]
Octa	1	1	m.p. 108°C	—	[62, 63]

* N_p = number of possible stereoisomers; N_k = number of known isomers; (A)-(G): see Section II, 3b.
** Structure not established.

1. Monochlorodioxan

Monochlorodioxan (2-chloro-1,4-dioxan, dioxanyl chloride) cannot be obtained by the direct action of chlorine on dioxan.

The unstable compound is apparently further chlorinated to dichlorodioxans[5-7]. Monochlorodioxan is usually obtained by the addition of hydrogen chloride to dihydrodioxin in the cold[5]:

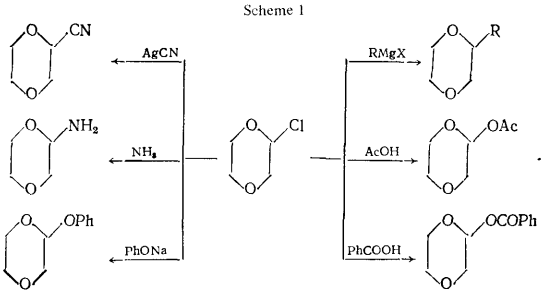


(I) (II)

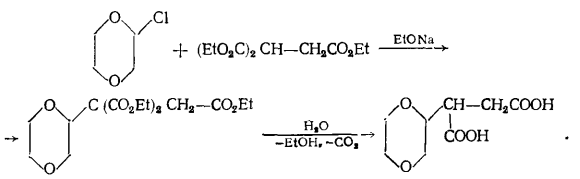
Use of a solvent in this reaction lowers the yield[8]. Nuclear magnetic resonance spectral data have shown[9] that, in virtue of the anomeric effect†, monochlorodioxan exists predominantly in the axial conformation (I), with the position of the conformational equilibrium (I) ⇌ (II) almost unaffected by the polarity of a solvent, (II) being the equatorial isomer.

Monochlorodioxan is unstable and gradually decomposes, especially in the presence of moisture, evolving hydrogen chloride and resinifying. Its instability and great reactivity are explained by the activating influence of ethereal oxygen on the α-chlorine atom. It can be used to obtain other monosubstituted dioxans. Thus heating with silver cyanide yields cyanodioxan, which in turn serves as starting material for the preparation of other monosubstituted derivatives[11]. A series of nucleophilic substitutions of the chlorine atom have been described:

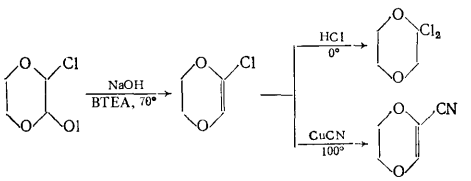
Scheme 1



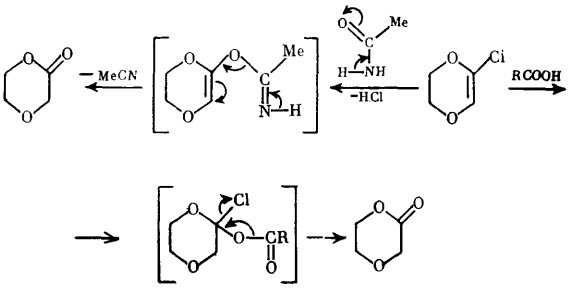
Monochlorodioxan does not form the usual Grignard compounds with magnesium, but it gives 2-alkyldioxans with alkylmagnesium halides RMgX (R = C_2H_5, n-C_4H_9, etc.; X = Cl, Br, I).[8] Amino-, phenoxy-, acetoxy-, and benzoyloxy-dioxans have been obtained in 70–80% yields[12,13]. In the presence of sodium ethoxide monochlorodioxan reacts with triethyl ethane-1,1,2-tricarboxylate to form the 1-dioxanyl triester, which on hydrolysis followed by decarboxylation is converted into dioxanylsuccinic acid[14]:



An important chloro-derivative is 5-chloro-2,3-dihydro-1,4-dioxin, which is usually obtained by the dehydrochlorination of 2,3-dichlorodioxan when heated with dimethylaniline[15] or on pyrolysis[16]. A proposed effective method of dehydrochlorination is the use of 40% caustic soda under the mild conditions of phase-transfer catalysis in the presence of benzyltriethylammonium chloride (BTEA), which gives a 65–68% yield of the chlorodihydro-derivative[17]:

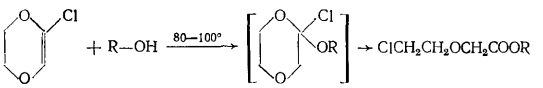


5-Chloro-2,3-dihydrodioxin exhibits the typical properties of a chlorovinyl ether: vigorous addition of hydrogen chloride takes place in the cold in conformity with Markovnikov's rule to give 2,2-dichlorodioxan[15], and it reacts comparatively readily with copper cyanide to form 5-cyanodihydrodioxin[18]. Vigorous reaction takes place also with carboxylic acids to give high yields of dioxan-2-one and the corresponding acid chlorides[16]. This reaction is of practical interest (in the case of acetic acid), since dioxanone has proved a valuable solvent for certain polymers; similar results are obtained with acetamide[19]:



R = Me (84), CH_2Cl (100), Ph (62), *p*-$O_2NC_6H_4$ (38)[2] ‡.

When 5-chloro-2,3-dihydrodioxin is heated with a primary alcohol or a phenol, however, a vigorous reaction leads to fission of the ring and formation of a 2'-chloroethoxyacetic ester, apparently also involving addition at the double bond[16]:



R = Me (54), Et (71), n-Bu (81), Ph (91.5), *p*-MeC_6H_4 (87).

2. Dichlorodioxans

Three of the seven possible structural isomers of dichlorodioxan are known.

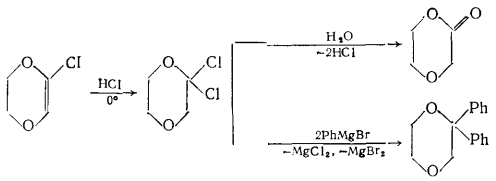
(a) 2,2-Dichlorodioxan

Small quantities of 2,2-dichlorodioxan are detected among the products of the direct chlorination of dioxan, but this reaction is unsuitable for preparative purposes. As already noted, 2,2-dichlorodioxan is obtained in entirely satisfactory yields by the addition of hydrogen chloride to 5-chloro-2,3-dihydrodioxin in the cold[15]. It is not very stable and is

† The anomeric effect is the predominance of the axial conformation of an α-substituent relative to a heteroatom as a consequence of steric or electronic effects, dipole–dipole interaction, the state of hybridisation of the atoms, etc.[10]

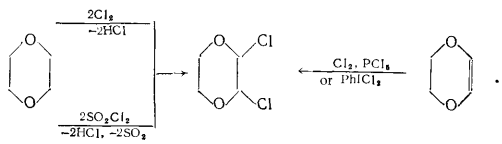
‡ Parentheses enclose percentage yields of dioxanone.

readily hydrolysed to dioxan-2-one, but it reacts normally with phenylmagnesium bromide to give 2,2-diphenyldioxan[15]:



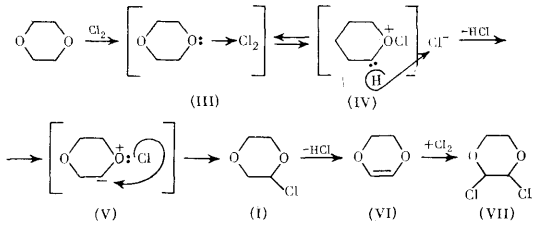
(b) 2,3-Dichlorodioxan

The readily accessible 2,3-dichlorodioxan, which is prepared by the direct chlorination of dioxan, is most important and interesting for the chemistry of the latter, and was first obtained in 1931.[20] It was later shown that chlorination is catalysed by addition of a chloride of copper, iron, manganese, nickel, tin, or iodine[8,21], to give a yield of ~ 90%. The patent literature indicates[22,23] that good yields are obtained by the action of chlorine on dioxan in the vapour phase (120 °C) in the presence of phosphorus(III), phosphorus(V), or antimony(V) chloride as catalyst. Sulphuryl chloride can also be used as chlorinating agent[24], with which an effective procedure has been developed to give an 80% yield[25]; 2,3-dichlorodioxan can be obtained from dihydrodioxin by the addition of chlorine[11,26] and also by the action of phosphorus pentachloride or dichloroiodobenzene[19]:



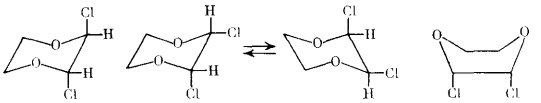
Incidentally, the latter reactions serve as proof of the positions of the chlorine atoms.

The mechanism of the direct chlorination of dioxan to 2,3-dichlorodioxan at 90 °C and at higher temperatures, when polychlorodioxans are obtained, apparently comprises a series of consecutive primary reactions[2,5,6]:



Chlorine acts on dioxan to form an unstable dioxanate (III), which in the presence of Lewis acids is strongly polarised and converted into the ionic dioxanate (IV). The latter eliminates a molecule of hydrogen chloride to form the carbanion (V), which is converted into unstable monochlorodioxan (I). At high temperatures this undergoes dehydrochlorination to dihydrodioxin (VI). Lastly, this product adds a molecule of chlorine to give the final reaction product—stable 2,3-dichlorodioxan (VII).

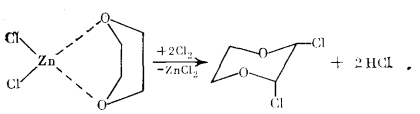
2,3-Dichlorodioxan is known in the form of two isomers (VIII) and (IX), which differ in melting point, infrared spectrum, and dipole moment[15]:



	(VIII) ($Cl_{ax,ax}$)	(IX) ($Cl_{ax,eq}$)	(X) ($Cl_{eq,ax}$)	(XI)
M.p., °C	31	53		
Infrared, cm^{-1}	375	948		
μ, D	0	1.6		

Polarity, polarisability, and n.m.r. spectral data at and below room temperature (down to −42 °C) indicate that both isomers have a chair conformation[27-34]. The more stable *trans*-isomer (VIII) has the diaxial chair conformation ($Cl_{ax,ax}$). The less stable *cis*-isomer (IX) also has a chair conformation, with an axial–equatorial arrangement of the chlorine atoms ($Cl_{ax,eq}$), which undergoes inversion to form an equilibrium mixture with the conformation (X) ($Cl_{eq,ax}$)[31,34]: the statement that it is present as the rigid boat (XI)[29] is incorrect. Chlorination of dioxan in the absence of a solvent gives predominantly the isomer (VIII) with a little (~ 4%) of isomer (IX); in boiling tetrachloromethane a mixture of almost equal quantities of (VIII) and (IX) is obtained, which can be separated by crystallisation. The less stable isomer (IX), when heated with aluminium chloride or sulphuryl chloride, is rapidly and almost quantitatively converted into the *trans*-isomer (VIII)[15].

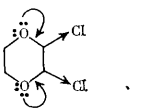
The almost pure isomer (IX) can be prepared by chlorinating dioxan in the presence of zinc chloride[34]. The stereochemistry of the reaction can be attributed to formation of the dioxanate $C_4H_8O_2.ZnCl_2$, in which the dioxan ring is in the boat conformation[35], with the oxygen atoms coordinated with the zinc atom:



Chlorination of such a dioxanate becomes sterically preferred for the formation of *cis*-2,3-dichlorodioxan (IX)[34].

2,3-Dichlorodioxan is toxic: contact with the skin or inhalation of its vapour leads to dizziness, headache, nausea, and inflammation of the mucous membrane of the eye, symptons which may continue for several days. Partial alleviation is provided by the inhalation of ammonia[15].

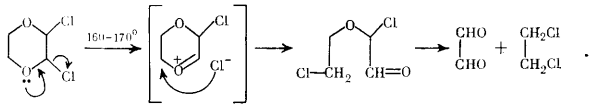
The chemical properties of 2,3-dichlorodioxan are consistent with electronic effects arising from the strong polarisation of the carbon–chlorine bonds and displacement of the *p*-electrons of the ethereal oxygen atoms conjugated with those bonds



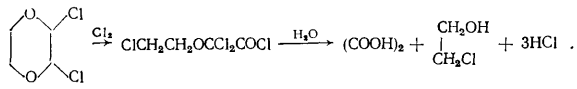
This explains the poor aqueous solubility and the inability to form dioxanates. 2,3-Dichlorodioxan is extremely reactive, mainly in three directions—cleavage of the dioxan ring, nucleophilic replacement of chlorine atoms, and elimination of the elements of hydrogen chloride.

Under the influence of various factors the ring in substituted dioxans is generally opened more readily than is the extremely stable ring of dioxan itself. Thus ring fission

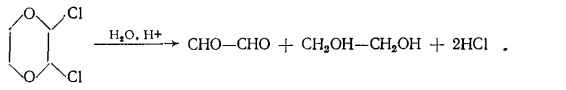
occurs readily when 2,3-dichlorodioxan is heated. Thermal decomposition of this compound is assumed to involve ionisation of one of the chlorine atoms and its migration across the ether link, with intermediate formation of 2,2′-dichloroethoxyacetaldehyde, which then decomposes into glyoxal and 1,2-dichloroethane[36]:



The dioxan ring undergoes cleavage also in the chlorolysis of 2,3-dichlorodioxan to the extremely reactive 2,2,5-trichloro-3-oxavaleryl chloride, which can be hydrolysed to oxalic acid, 2-chloroethanol, and hydrogen chloride[37]:

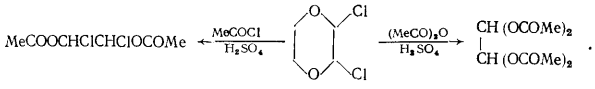


2,3-Dichlorodioxan is comparatively readily hydrolysed when heated with acidified water, being converted into equal quantities of glyoxal and ethylene glycol[20,38]:

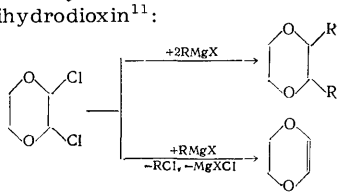


The *cis*-isomer is hydrolysed more rapidly than the *trans*-isomer by a factor of 14.[15] Hydrolysis of this compound has been proposed for the preparation of glyoxal[36,38].

Heating 2,3-dichlorodioxan with excess of acetic anhydride or acetyl chloride mixed with concentrated sulphuric acid also opens the dioxan ring, with the formation respectively of ethanediylidene tetra-acetate (in 70% yield) or 1,2-dichloroethylene diacetate[18]:

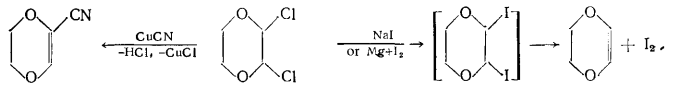


The chlorine atoms in 2,3-dichlorodioxan undergo nucleophilic substitution with rather greater difficulty than do those in the usual α-halogenated ethers. However, several reactions are known in which under certain conditions both chlorine atoms are replaced by various groups to give 2,3-disubstituted dioxans. Thus 37–44% yields of 2,3-dialkyldioxans are obtained by the action of Grignard reagents catalysed by additions of ethereal solutions of anhydrous zinc or cadmium chloride[8,39]. Similarly, arylmagnesium halides yield *trans*-diaryldioxans[26,40–42], substitution in this case being accompanied by elimination of chlorine atoms with the formation of dihydrodioxin[11]:

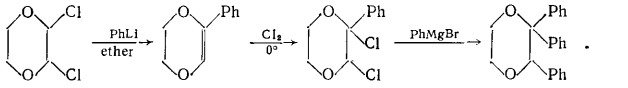


R=Me, Et, n-Pr, n-Bu, CH_2=CH—CH_2, Ph, *p*-ClC_6H_4, *p*-BrC_6H_4; X=Cl, Br .

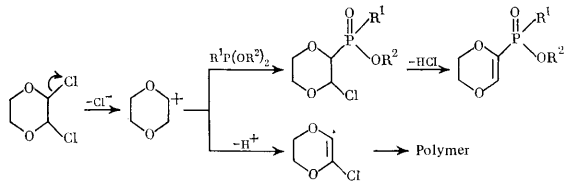
2,3-Dichlorodioxan also undergoes dechlorination when heated with sodium iodide[8] or with a mixture of magnesium and iodine[7], the yield of dihydrodioxin reaching 81% in the latter case. These reactions apparently involve intermediate formation of unstable 2,3-di-iododioxan, which immediately breaks down into dihydrodioxin and molecular iodine. 2,3-Dichlorodioxan reacts quite smoothly with copper cyanide, when 5-cyanodihydrodioxin is formed as a consequence of dehydrochlorination and substitution of the remaining chlorine atom[18]:



Phenyl-lithium reacts similarly to form unstable 2,3-dihydro-5-phenyldioxin (in 31% yield), which on cautious chlorination gives 2,3-dichloro-2-phenyldioxan; the latter can be converted by phenylmagnesium bromide into 2,2,3-triphenyldioxan (yield 54%)[43]:



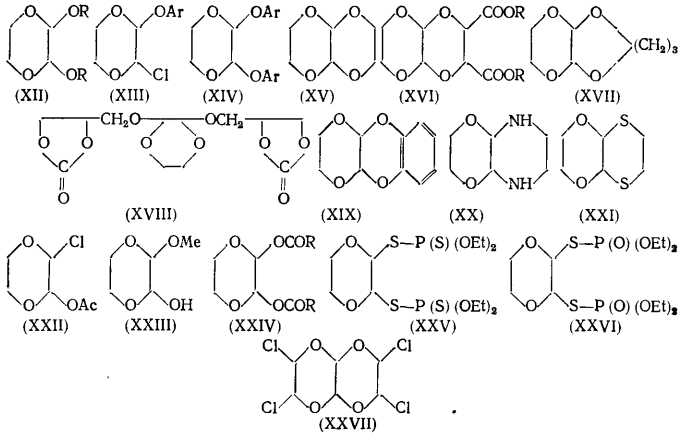
Application of the Michaelis–Becker reaction to 2,3-dichlorodioxan and a sodium dialkyl phosphite yields small quantities (< 20%) of phosphonylated derivatives of dihydrodioxin[44]. The same work showed[44] that the 2,3-dichloro-compound undergoes the Arbuzov reaction with difficulty, and only under comparatively severe conditions does it form with esters of tervalent phosphorus *C*-phosphonylated derivatives of dioxan in relatively low yields (< 40%):



R^1 = Me, Et, *p*-ClC_6H_4, EtO, n-PrO, n-BuO etc.;
R^2 = Et, n-Pr, n-Bu, etc.

The low reactivity of 2,3-dichlorodioxan is most probably due to steric hindrance.

Many nucleophilic substitutions of the chlorine atoms in 2,3-dichlorodioxan have been reported, yielding various 2,3-disubstituted dioxans

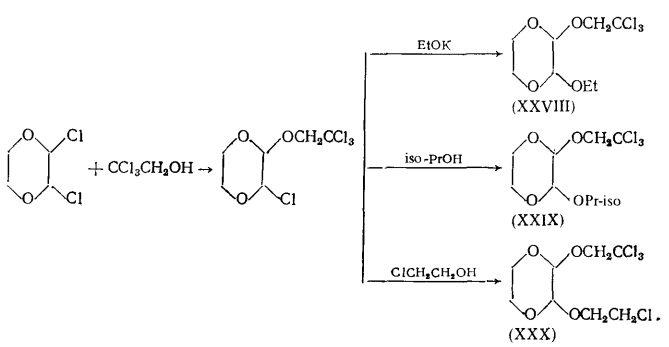


Thus alcoholic sodium ethoxide forms 2,3-diethoxydioxan (XII: R = C_2H_5),[20] but heating with benzyl alcohol gives crystalline 2,3-dibenzyloxydioxan (XII: R = $C_6H_5CH_2$).[45] A monoalkyl ether of ethylene glycol, e.g. 2-ethoxyethanol, forms 2,3-bis-(2-ethoxyethyl)dioxan (XII: R = $C_2H_5OCH_2CH_2$), which has been proposed as a high-boiling solvent for polymers and as a softening agent conferring antistatic properties on films[46]. Under certain conditions the chlorine atoms can

be replaced in stages. Thus heating 2,3-dichlorodioxan with a phenol ArOH (Ar = C_6H_5, o-$CH_3C_6H_4$, p-$CH_3C_6H_4$, 2,4-$Cl_2C_6H_3$) gives 45–52% yields of 2-aryloxy-3-chlorodioxans (XIII)[18,47], in which the second chlorine atom is readily replaced to form 2,3-diaryloxydioxans (XIV) (yields 40–60%)[18]. Heating 2,3-dichlorodioxan with ethylene glycol gives decahydro-1,4,5,8-tetraoxanaphthalene (XV)[18,45,48], the yield of which reaches 77% when the reaction is conducted in pyridine[49]. With the dimethyl or diethyl ester of (+)-tartaric acid 2,3-dichlorodioxan forms the corresponding ester of (−)-decahydro-1,4,5,8-tetraoxanaphthalenedicarboxylic acid (XVI: R = CH_3, C_2H_5), which after saponification and decarboxylation is converted into decahydrotetraoxanaphthalene (XV)[45,50]. Heating 2,3-dichlorodioxan with propane-1,3-diol forms 2,3-trimethylenedioxydioxan (XVII)[51], but 3-hydroxypropylene carbonate gives crystalline dioxan-2,3-bisoxypropylene dicarbonate (XVIII), used for the preparation of water-insoluble resins, which have been suggested as additives for the sizing of yarn and in papermaking[52]. When 2,3-dichlorodioxan is heated with pyrocatechol in xylene, crystalline decahydro-2,3-benzo-1,4,5,8-tetraoxanaphthalene (XIX) is obtained[40,41,45]. Ethylenediamine resembles dihydric alcohols in forming a bicyclic heterocycle, decahydro-1,4-dioxa-5,8-diazanaphthalene (XX)[19], and ethanedithiol forms decahydro-1,4-dioxa-5,8-dithianaphthalene (XXI)[53]. Heating with acetic acid in toluene initially forms 3-chlorodioxanyl acetate (XXII)[54], which with methanolic sodium methoxide gives 3-methoxydioxanol (XXIII)[18]. Diesters (XXIV: R = CH_3, C_2H_5) are obtained when 2,3-dichlorodioxan is heated with potassium acetate in acetic acid or with silver acetate in benzene, and in still higher yields (80–90%) with ammonium carboxylates[18].

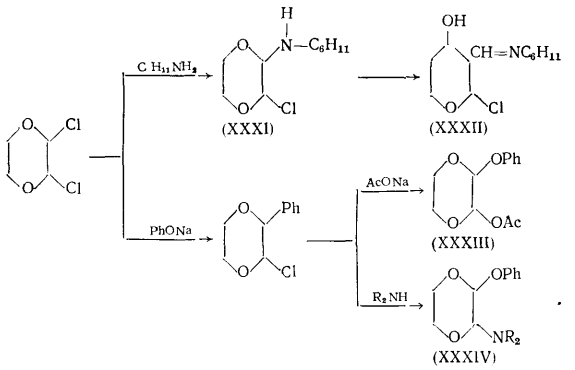
Dioxan rings are present in insecticides having practical value. For example, the diphosphorodithioate (XXV) (Delnav) is obtained by heating 2,3-dichlorodioxan with *OO*-diethyl hydrogen dithiophosphate in the presence of catalytic quantities of zinc chloride or a tertiary amine[55,56]. Delnav exists as *cis*- and *trans*-isomers, the former being considerably more toxic. Another product is Delnav-P-*O* (XXVI), obtained similarly from *OO*-diethyl hydrogen thiophosphate[56]. When *trans*-2,3-dichlorodioxan is dissolved in concentrated sulphuric acid and kept at 40 °C for 24 h, hydrogen chloride is evolved and a compound $C_6H_6Cl_4O_4$ is obtained, to which the structure 2,3,6,7-tetrachlorodecahydro-1,4,5,8-tetraoxanaphthalene (XXVII) was attributed[57].

As already remarked, the chlorine atoms in 2,3-dichlorodioxan can be replaced in stages, with the formation of 3-substituted 2-chlorodioxans, which can be isolated as individual compounds. Such monochlorinated dioxan derivatives undergo further vigorous nucleophilic substitution of the remaining chlorine atom. Thus heating 2,3-dichlorodioxan in benzene with 2,2,2-trichloroethanol gives crystalline 2,2′2′,2′-tetrachloro-3-ethoxydioxan (yield 50%), which on treatment with potassium ethoxide, propan-2-ol, and 2-chloroethanol forms compounds (XXVIII)–(XXX) respectively[58]:



(XXVIII) (XXIX) (XXX)

In the absence of atmospheric moisture 2,3-dichlorodioxan undergoes an exothermic reaction with cyclohexylamine, forming 2-chloro-3-*N*-cyclohexylaminodioxan (XXXI), which when heated undergoes fission of the dioxan ring and conversion into the azomethine (XXXII)[19]:

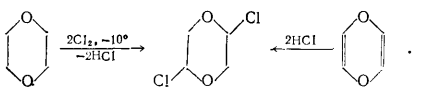


(XXXI) (XXXII) (XXXIII) (XXXIV)

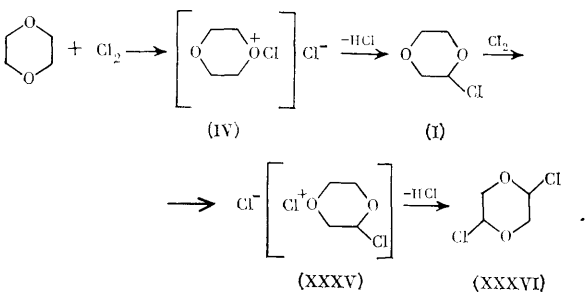
2-Chloro-3-phenoxydioxan, obtained from 2,3-dichlorodioxan and sodium phenoxide, gives 3-phenoxydioxanyl acetate (XXXIII) when heated with sodium acetate, and forms 2-amino-3-phenoxydioxans (XXXIV) with secondary amines[18].

(c) 2,5-Dichlorodioxan

2,5-Dichlorodioxan is obtained by chlorinating dioxan in the cold (between −47 and −5°), when ~ 25% of the crystalline *trans*-isomer is isolated from the complicated mixture that results[6,59]; this product is obtained also by the addition of hydrogen chloride to dioxin[60];



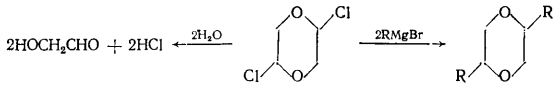
Chlorination of dioxan at low temperatures[2,5,6] also gives initially the chlorodioxanate (IV) and monochlorodioxan (I). In contrast to chlorination at high temperatures, e.g. 90 °C, elimination of hydrogen chloride from chlorodioxan (I) is greatly retarded. As a consequence, a second chlorine molecule is able to form the unstable dioxanate (XXXV) with the second ethereal oxygen atom in chlorodioxan, and 2,5-dichlorodioxan (XXXVI) results from (XXXV) by known reactions:



(IV) (I) (XXXV) (XXXVI)

2,5-Dichlorodioxan is a typical α-chloro-ether, but as a consequence of its molecular symmetry is more stable than the 2,3-dichloro-isomer. Nevertheless, it is gradually hydrolysed by moisture, evolving hydrogen chloride, and when boiled with water the dioxan ring opens to give an almost quantitative yield of glycollaldehyde, which is proof of the structure of 2,5-dichlorodioxan[60]; with alkyl- and

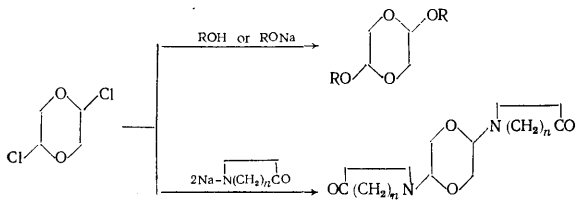
aryl-magnesium bromides mixtures of *cis*- and *trans*-2,5-disubstituted dioxans are formed[6,61]:



R=Me, n-Bu, Ph, *p*-MeC_6H_4 .

In the reaction with phenylmagnesium bromide the yield of 2,5-diphenyldioxan reaches 95%.[6]

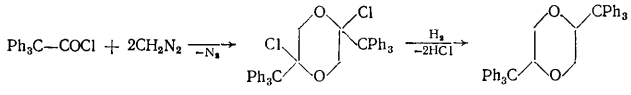
Dioxan derivatives containing substituents at positions 2 and 5 are obtained by the action of nucleophilic reagents on 2,5-dichlorodioxan[62–64]:



n=3–5

R=$CH_2CH{=}CH_2$, CH_2CH_2Cl, $CH_2CH_2CH_2Cl$, CH_2CH_2Br, CH_2CH_2CN, CH(CN)Me, Ph, 2,4-$Cl_2C_6H_3$, $PhOCH_2CH_2$, 4-$ClC_6H_4OCH_2CH_2$, 1-$C_{10}H_7$.

It was reported[65] that reaction between triphenylacetyl chloride and diazomethane gives crystalline 2,5-dichloro-2,5-bistriphenylmethyldioxan (m.p. 133 °C), which on reduction is converted into 2,5-bistriphenylmethyldioxan:



3. Polychlorodioxans

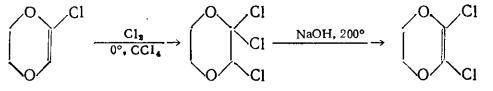
Tri-, tetra-, hexa-, hepta-, and octa-chlorodioxans have been obtained by the direct chlorination of dioxan and also indirectly, and their properties have been described. No report has yet appeared of the existence of pentachlorodioxan.

The results of the direct action of chlorine on dioxan exhibit a peculiar temperature dependence[2]: after the predominant formation of 2,5-dichlorodioxan at subzero temperatures[6,59], another one or two hydrogen atoms are replaced with every additional 10-deg rise in temperature, so that tetrachlorodioxans are formed at +10 °C, but hexachlorodioxans at +20 °C. To obtain heptachlorodioxan the temperature must be raised to 30–40 °C. The yields of polychlorodioxans obtained by low-temperature chlorination are usually small. Further action of chlorine at temperatures above 40 °C leads to gradual chlorolysis with degradation of the ring. When 80 °C is reached, a violent exothermic reaction suddenly begins, with swelling, charring, and even ignition of the reaction mixture. In this case the instability of the various chlorination products makes it very difficult to isolate individual compounds. Under reaction conditions under which this peculiar temperature barrier in the region of 80–90 °C has been surmounted, and especially in the presence of a catalyst such as iodine, tin(II) chloride, etc., the chlorination of dioxan again proceeds comparatively smoothly with, as already noted, the formation predominantly of 2,3-dichlorodioxan. At 110–170 °C highly chlorinated polychlorodioxans are obtained. The high-temperature chlorination of dioxan also yields complicated mixtures, including not only chlorodioxans but also chlorolysis products; its mechanism has remained almost uninvestigated, but is assumed to involve radical reactions.

The stability of polychlorodioxans towards hydrolysis and other chemical actions increases with the number of chlorine atoms in the ring. Thus tetrachlorodioxans (other than the 2,2,3,3-isomer) and more highly chlorinated dioxans can be steam-distilled without appreciable decomposition[62]. Polychlorodioxans exert an insecticidal action similar to that of DDT.[19]

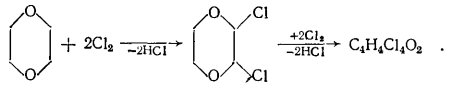
(a) 2,2,3-Trichlorodioxan

2,2,3-Trichlorodioxan has not been obtained by the direct chlorination of dioxan: it can be prepared by the addition of chlorine to 5-chloro-2,3-dihydrodioxin[37]. Thermal alkaline dehydrochlorination converts 2,2,3-trichlorodioxan into 5,6-dichloro-2,3-dihydrodioxin (yield 52%):



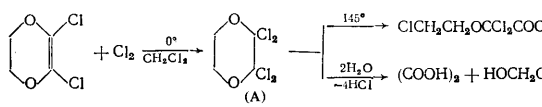
(b) Tetrachlorodioxans

Seven of the possible isomeric chlorodioxans are known (Table, A–G), formed in small quantities in the preparation of 2,3-dichlorodioxan by the chlorination of dioxan at 90 °C.[60] The yields increase with rise in the temperature of the reaction (to 135–140 °C) and increase in its duration[38,41]. It is assumed that the production of tetrachlorodioxans is preceded by the formation of 2,3-dichlorodioxan[21,38,41,45,62]:



The chlorination of 2,3-dichlorodioxan at 135 °C does indeed give an 85% yield of a mixture of isomers, from which individual tetrachlorodioxans have been isolated[37,41,62]. Some have been prepared by other methods.

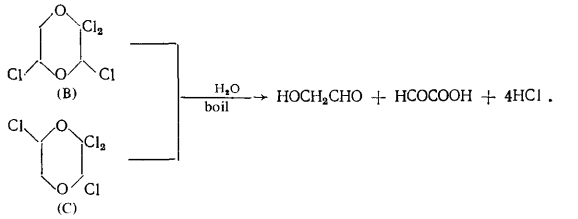
The report[66] that 2,2,3,3-tetrachlorodioxan (A) could be obtained by chlorinating 2,3-dichlorodioxan at 155–160 °C proved incorrect. As shown later, only chlorolysis products of dioxan are obtained, but (A) can be prepared in quite good yield by the addition of chlorine to 5,6-dichloro-2,3-dihydrodioxin[37]. The tetrachloro-isomer (A) is a quite stable compound, decomposing only when heated above the melting point, to form 2,2,2'-trichloroethoxyacetyl chloride, but on prolonged boiling with water it is hydrolysed and converted into oxalic acid, ethylene glycol, and hydrogen chloride:



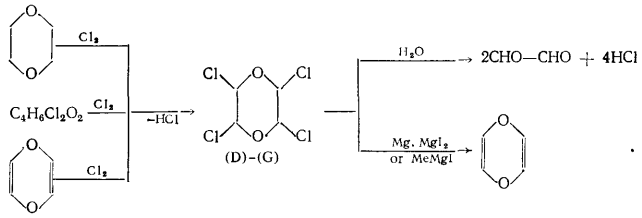
(A)

The structures of tetrachlorodioxans (B) and (C), isolated in small quantities from the products of the chlorination of 2,3-dichlorodioxan, have not been accurately established: the liquid isomer (B) is assumed to be 2,2,3,5-tetrachlorodioxan, and the crystalline isomer (C) 2,2,3,6-tetrachlorodioxan. Both compounds also resist the action of water, being hydrolysed only after prolonged boiling with water (for

5–6 h), which converts them quantitatively into glycollaldehyde, glyoxylic acid, and hydrogen chloride[21,38,41]:



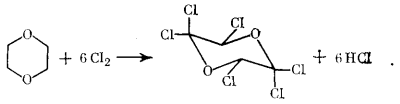
The symmetrical 2,3,5,6-tetrachlorodioxans are especially interesting, with five possible stereoisomers depending on the disposal of the chlorine atoms. The four crystalline stereoisomers that have been prepared and characterised (D)–(G) differ in melting point. Tetrachlorodioxans (D)–(F) are obtained by the chlorination respectively of dioxan[21,38], 2,3-dichlorodioxan[21,41], and 2,5-dichlorodioxan[62,67]; the isomer (G) results from the addition of chlorine to 1,4-dioxin[21,38,60]:



Compounds (D)–(G) are also stable towards water, and can be distilled in steam without appreciable hydrolysis[60], but on being boiled with water for 2–3 h decompose quantitatively into glyoxal and hydrogen chloride[38]. When heated with magnesium, magnesium iodide, or methylmagnesium iodide they are dehydrochlorinated to 1,4-dioxin. Both reactions provide evidence of the positions of the chlorine atoms in these tetrachlorodioxans[60].

(c) Hexachlorodioxans

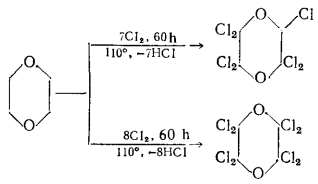
When chlorine is passed into dioxan at 110 °C for a long time (~ 50 h), two isomeric hexachlorodioxans differing in melting point can be isolated from the reaction mixture in a total yield of 25%.[45,62] The one melting at 94 °C and having zero dipole moment was regarded[48] as 2,2,3,5,5,6-hexachlorodioxan (XXXVII):



(XXXVII)

(d) Hepta- and octa-chlorodioxans

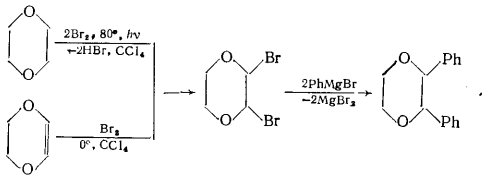
Still more prolonged chlorination of dioxan (at 110 °C for ~ 60 h) gives a good yield of two stereoisomeric heptachlorodioxans, which differ considerably in melting point. Introduction of the eighth chlorine atom into the dioxan ring takes place slowly and with difficulty. The octachlorodioxan isolated from the reaction mixture crystallises well[62,63]:



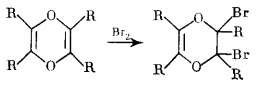
Heptachlorodioxan is so stable that it begins to evolve hydrogen chloride only when heated with concentrated sulphuric acid to 150 °C, without darkening of the reaction mixture. It does not split off hydrogen chloride when heated with aqueous alkalis or with aqueous–alcoholic silver nitrate solution, and a mixture of concentrated sulphuric acid and potassium permanganate has hardly any effect[62]. Heptachlorodioxan possesses well developed insecticidal properties, surpassing the γ-isomer of DDT in its action on individual species of ants[2].

III. BROMO- AND FLUORO-DIOXANS

Bromodioxans have been far less studied than have chlorodioxans. In the cold dioxan forms with bromine a dioxanate $C_4H_8O_2.Br_2$[1,68–70], which when heated decomposes with opening of the dioxan ring and formation of bromoethane, hydrogen bromide, etc.[38,71]. On ultraviolet exposure in tetrachloromethane dioxan is smoothly brominated[72] to crystalline 2,3-dibromodioxan (yield 75%, m.p. 71.5–73.5 °C); this dibromide is obtained also in good yield (92%) by the addition of bromine to dihydrodioxin in tetrachloromethane in the cold[5,26]:



Similarly, 2,3-dihydro-5-phenyldioxin adds bromine to give 2,3-dibromo-5-phenyldioxin[43]. It is interesting that under the same conditions 1,4-dioxin[60] and 2,3,5,6-tetraphenyl-1,4-dioxin[73] add only one bromine molecule to form substituted dihydrodioxins:

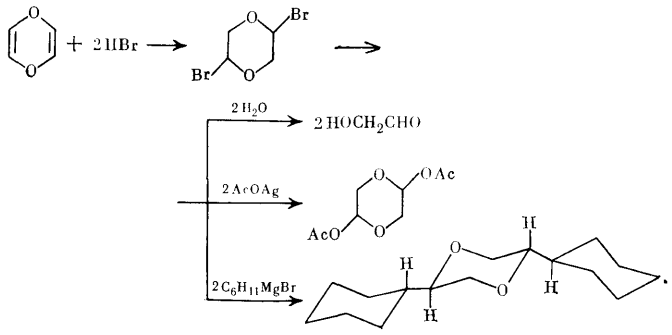


R = H, Ph .

2,3-Dibromodioxan is unstable, and is gradually decomposed by atmospheric moisture, with the evolution of hydrogen bromide. Its structure has been proved by its reaction with phenylmagnesium bromide, when 2,3-diphenyldioxan is obtained[5].

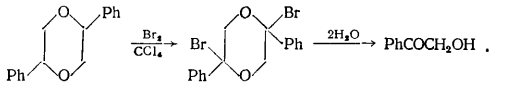
2,5-Dibromodioxan has been obtained in good yield (90%) by passing anhydrous hydrogen bromide into a cold chloroform solution of 1,4-dioxin. It is thermally unstable, darkening at 104 °C, and decomposing at 134 °C. Its structure has been confirmed by hydrolysis: brief boiling with water readily gives a quantitative yield of glycollaldehyde. When 2,5-dibromodioxan is heated with silver acetate in toluene,

both bromine atoms are replaced by acetoxy-groups to form dioxan-2,5-ylene diacetate[74]:

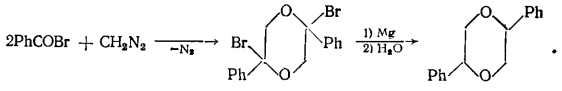


With cyclohexylmagnesium bromide 2,5-dibromodioxan forms (in 20% yield) 2,5-dicyclohexyldioxan as the *trans*-diequatorial conformer (according to n.m.r. spectral data)[75].

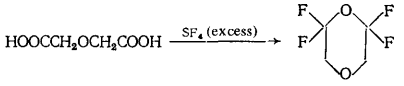
2,5-Diphenyldioxan is readily brominated to 2,5-dibromo-2,5-diphenyldioxan, which on hydrolysis is converted into hydroxymethyl phenyl ketone[6]:



As with the chloro-derivative, the action of diazomethane on benzoyl bromide gives 2,5-dibromo-2,5-diphenyldioxan, which is converted by the successive action of magnesium and water into 2,5-diphenyldioxan (yield 62%)[65]:



The action of sulphur tetrafluoride on a diglycollic ester forms the extremely stable liquid 2,2,6,6-tetrafluorodioxan[76,77]:

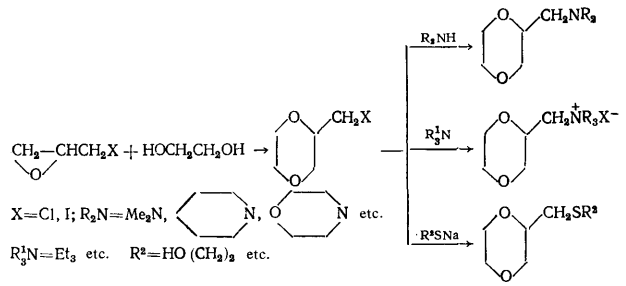


IV. HALOGENOALKYLDIOXANS

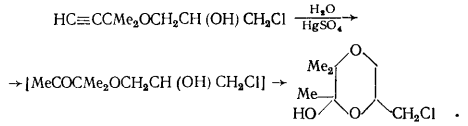
A considerable number of dioxans halogenated in side-chains are known. The halogen atoms usually undergo ready nucleophilic substitution with preservation of the dioxan ring. The best known and most thoroughly studied are the chloro- and iodo-derivatives.

1. Halogenoalkyldioxans

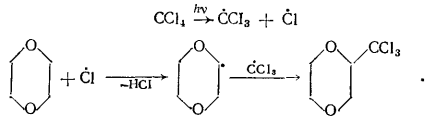
Condensing epoxypropyl chloride and iodide respectively with ethylene glycol in the presence of concentrated sulphuric acid yields 2-chloromethyl- and 2-iodomethyl-dioxans[78], which react readily with secondary and tertiary amines and also with thiols to give alkylated dioxans containing nitrogen or sulphur atoms in the alkyl groups[79,80]:



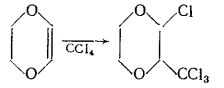
Under the conditions of the Kucherov reaction 1-chloro-5,5-dimethyl-4-oxahept-6-yn-2-ol undergoes hydration and cyclisation to 6-chloromethyl-2,3,3-trimethyldioxan-2-ol[81]:



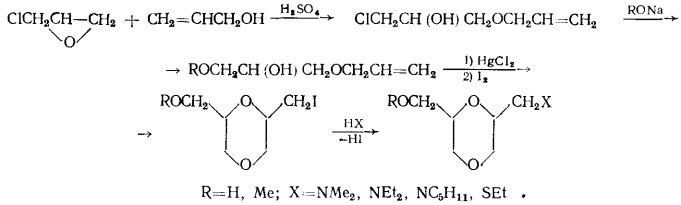
Prolonged (~ 100 h) ultraviolet exposure of a solution of tetrachloromethane in dioxan results in radical reactions, the products of which include crystalline trichloromethyldioxan (m.p. 136–138 °C) together with hydrogen chloride, chloroform, and hexachloroethane[78]:



An analogous mechanism is involved in the addition of tetrachloromethane to dihydrodioxin in the presence of azoisobutyronitrile to form 2-chloro-3-trichloromethyldioxan[82]:

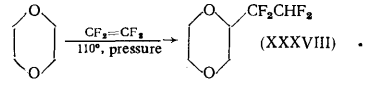


Several 6-substituted iodomethyldioxans have been obtained from epoxypropyl chloride and allyl alcohol, in which the iodine atom is readily exchanged by the action of nucleophiles, as expected, usually forming mixtures of *cis*- and *trans*-2,6-disubstituted dioxans[83–85]:

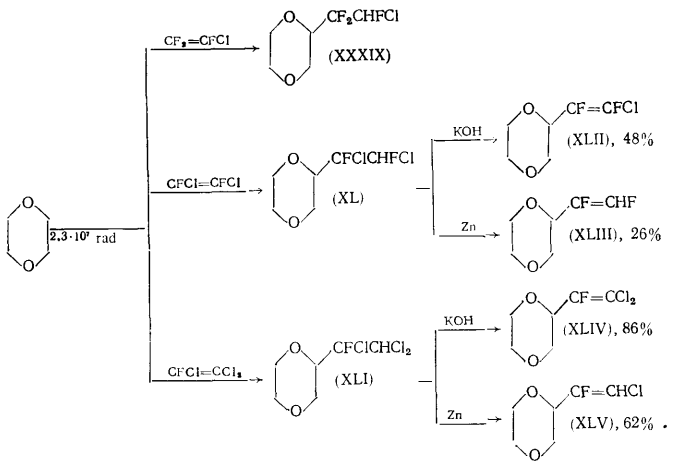


R=H, Me; X=NMe_2, NEt_2, NC_5H_{11}, SEt .

Some interest attaches to fluoroalkyldioxans, obtained from dioxan and organofluorine compounds by free-radical reactions initiated by exposure to ultraviolet radiation or γ-rays, as well as in the presence of peroxy-compounds. According to a patent[86] dioxan reacts with tetrafluoroethylene when heated in the presence of benzoyl peroxide under pressure, with the formation of 1′,1′,2′,2′-tetrafluoroethyldioxan (XXXVIII):

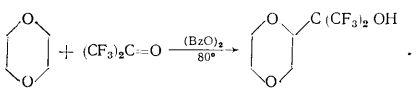


Dioxan reacts with equimolecular proportions of chlorofluoroalkenes on exposure to γ-rays to form liquid chlorofluoroethyldioxans (XXXIX)–(XLI) in yields of ~ 55%[87]:



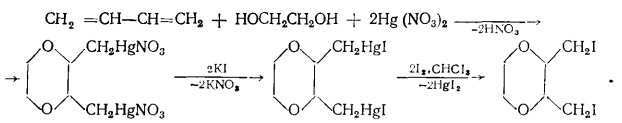
Treatment of the products (XL) and (XLI) with potassium hydroxide or zinc dust converts them into the chlorofluorovinyldioxans (XLII)–(XLV)[88].

Dioxan condenses with hexafluoroacetone on ultraviolet irradiation or on heating with benzoyl peroxide to form crystalline dioxanylbistrifluoromethylmethanol (yield 25%)[89]:



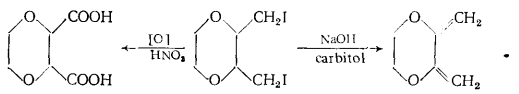
2. Bishalogenoalkyldioxans

Application of Nesmeyanov and Lutsenko's method[92] to buta-1,3-diene and ethylene glycol gave by a series of consecutive reactions 2,3-bisiodomethyldioxan (yield 56%) as a mixture of *cis*- and *trans*-isomers (m.p. 77 and 90 °C) with the latter predominating[90,91]:



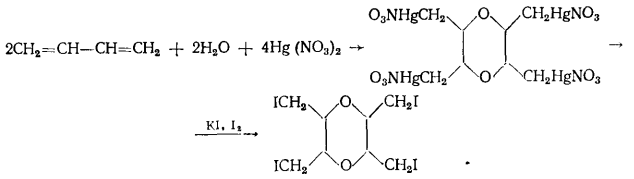
If the reaction is conducted in a strongly acid medium, e.g. in nitric acid, the quantity of the *trans*-isomer is greatly increased.

This *trans*-isomer served as starting material for obtaining a series of 2,3-disubstituted dioxans. Thus oxidation of the di-iodide with nitric acid gives dioxan-*trans*-2,3-dicarboxylic acid (m.p. 175 °C), and heating with alkali in an inert solvent forms a readily polymerisable conjugated diene:

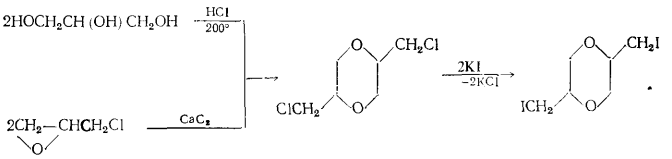


The latter product, 2,3-dimethylenedioxan, forms a crystalline adduct with maleic anhydride (m.p. 82 °C).

If the reaction between butadiene and aqueous mercury(II) nitrate is conducted in the absence of ethylene glycol, and the product is then treated successively with potassium iodide and iodine, 2,3,5,6-tetrakisiodomethyldioxan is obtained, apparently with intermediate formation of 2,3,5,6-tetrakisnitratomercurimethyldioxan[91]:

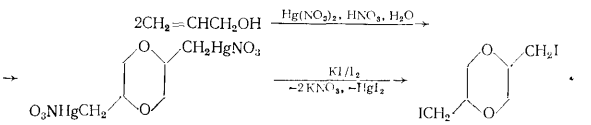


Early papers[93–95] described 2,5-bishalogenomethyldioxans under the names "diepichlorhydrin" and "diepi-iodohydrin". The former was obtained by heating glycerol with hydrochloric acid, and the latter from the former by heating with alcoholic potassium iodide:

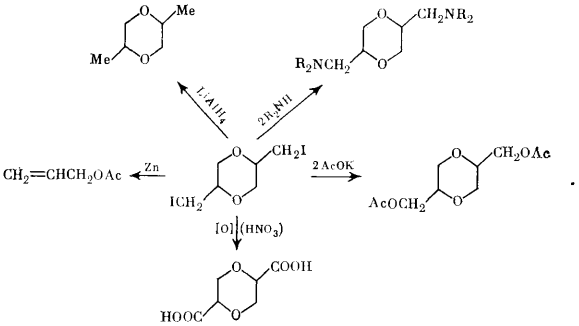


The structure of these compounds was later reliably established as *trans*-2,5-bishalogenomethyldioxans[90,97,98]. According to a patent[99] a 90% yield of *trans*-2,5-bischloromethyldioxan can be obtained by heating epoxypropyl chloride with calcium carbide in the presence of hexacarbonylbistributylphosphinecobalt as catalyst. The resulting dichloride reacts with alcoholic potassium iodide to form crystalline *trans*-2,5-bisiodomethyldioxan (m.p. 158 °C).

The bisiodomethyl derivative can be synthesised also by condensing two molecules of allyl alcohol in the presence of mercury(II) nitrate in aqueous nitric acid and then treating the products with iodine and potassium iodide[90,93,95,96]. In these stereospecific reactions *trans*-2,5-bisnitratomercurimethyldioxan is obtained initially in almost quantitative yield, and with potassium iodide and iodine gives a 90% yield of the di-iodide:

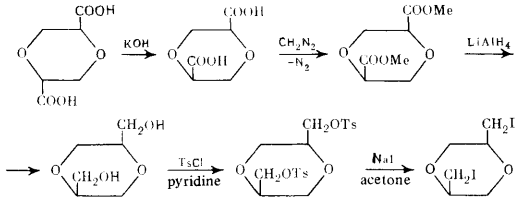


2,5-Bisiodomethyldioxan is of interest in view of the many S_N reactions involving the two reactive iodomethyl groups and yielding *trans*-2,5-dimethyldioxans in which the methyl groups are substituted. Thus heating with concentrated ammonia forms 2,5-bisaminomethyldioxan[93,97], and with morpholine and 2,6-dimethylmorpholine the 2,5-dimorpholino- and 2,5-bis-2′,6′-dimethylmorpholino-dioxans respectively[100]. Brief heating of the di-iodide with potassium acetate in acetic acid involves initial replacement of one iodine atom by an acetate group, but on longer heating two iodine atoms are substituted to give dioxan-2,5-ylenedimethyl diacetate[97]:

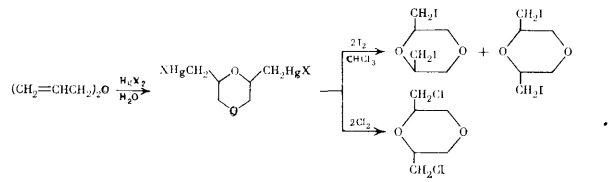


An attempt to reduce the di-iodide with zinc in acetic acid or in alcohol opens the dioxan ring and forms allyl acetate or alcohol respectively, but lithium tetrahydroaluminate in ether reduces it to 2,5-dimethyldioxan[101].

Heating the *trans*-di-iodide with concentrated nitric acid oxidises it to dioxan-*trans*-2,5-dicarboxylic acid[90,98], which when heated with potassium hydroxide isomerises into the *cis*-dicarboxylic acid. This last product can be converted by a series of consecutive reactions into *cis*-2,5-bisiodomethyldioxan (m.p. 97 °C)[97]:

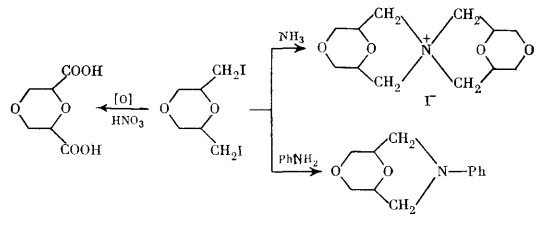


Diallyl ether condenses extremely readily with mercury(II) acetate or chloride in aqueous solution to give an 85% yield of 2,6-bischloromercurimethyldioxan, which on treatment with iodine or chlorine is smoothly converted into respectively 2,6-bisiodomethyl- or 2,6-bischloromethyl-dioxan[92]:



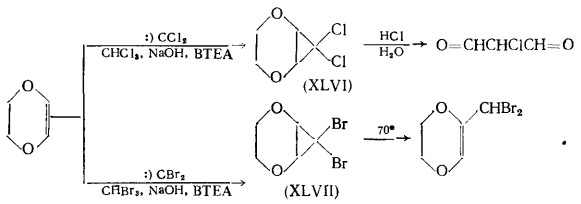
It was established by chemical methods that 2,6-bisiodomethyldioxan is a mixture of *cis*- and *trans*-isomers[98,102]. It is interesting that the former has the higher melting point (90 and 70 °C). The relative stability of the *cis*-isomer is attributed to its greater molecular symmetry, the possibility of its existing as a conformation with a diequatorial arrangement of the iodomethyl groups. In the *trans*-isomer one iodomethyl group occupies an axial position[98].

Here the known facts concerning the greater stability of *cis*- than of *trans*-1,3-disubstituted cyclohexanes can be appropriately compared in terms of the equatorial–polar concept[103]. For steric reasons the former isomer, unlike the latter, forms morpholine derivatives on reaction with ammonia or aniline[98,102]; both isomers are oxidised by hot nitric acid, being converted into the corresponding isomeric dioxan-2,6-dicarboxylic acids without change in the geometric configuration[98]:



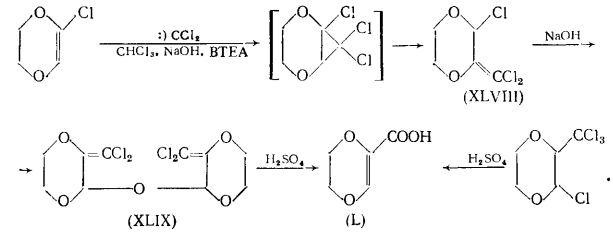
3. Reactions of Halogenocarbenes with Dioxins and Dihydrodioxins

Halogenocarbenes react readily with dioxin and with dihydrodioxin. The adduct of the latter with dichlorocarbene was described first in 1974[104] and then in subsequent papers[105,106]. Detailed investigation showed[107] that, with dichlorocarbene generated from chloroform by the action of 50% caustic soda under conditions of phase-transfer catalysis in the presence of benzyltriethylammonium chloride, dihydrodioxin gives a very good yield (> 90%) of 7,7-dichloro-2,5-dioxabicyclo[4,1,0]heptane (XLVI), which is relatively unstable and is converted into chloromalonaldehyde when boiled with dilute hydrochloric acid[105]:

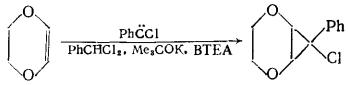


Under analogous conditions dibromocarbene generated from bromoform yields the thermally unstable 7,7-dibromo-2,5-dioxabicyclo[4,1,0]heptane (XLVII), which on moderate heating is converted (with cleavage of the cyclopropane ring) into 5-dibromomethyldihydrodioxin[107].

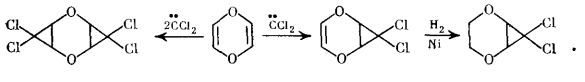
With 5-chlorodihydrodioxin dichlorocarbene does not give a stable adduct at the double bond under conditions of phase-transfer catalysis[108,109]. The bicyclic adduct formed in the course of the reaction is apparently converted into 2-chloro-3-dichloromethylenedioxan (XLVIII), which in an alkaline medium gives the bisdichloromethylenedioxanyl ether (XLIX) (yield 37%), from which dihydrodioxin-5-carboxylic acid (L) is obtained (yield 60%)[108], as also by heating 1-chloro-2-trichloromethyldioxan with sulphuric acid:



The reaction of dihydrodioxin with chlorophenylcarbene generated from benzylidene dichloride and potassium t-butoxide gives 7-chloro-7-phenyl-2,5-dioxabicyclo[4,1,0]heptane[106,110]:



1,4-Dioxin also reacts vigorously with dichlorocarbene generated from methyl trichloroacetate by the action of sodium methoxide[106]. Addition takes place at either one or two double bonds depending on the proportions of the reactants. In the former case 7,7-dichloro-2,5-dioxabicyclo-[4,1,0]heptene is obtained (yield 56%), which on hydrogenation is reduced to the known adduct of dihydrodioxin with dichlorocarbene; in the latter case a double adduct is formed—4,4,8,8-tetrachloro-2,6-dioxatricyclo[5,1,0]octane (yield 34%):



---oOo---

In conclusion it can be stated that halogenodioxans form a group of compounds of interest to organic chemists that has been by no means completely investigated. Individual representatives have a well defined physiological effect and possess insecticidal properties. Among dioxan derivatives the most valuable are those containing chlorine atoms in the ring. Further development of methods of preparation and study of their reactions will undoubtedly give valuable new information for the theory and practice of organic synthesis.

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