Russian Chemical Reviews **65** (1) 27–39 (1996)
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UDC 547.841.64

Dibenzo-*p*-dioxins. Methods of synthesis, chemical properties, and hazard assessment

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Contents

I.	Introduction	27
II.	Nomenclature and structure	27
III.	Methods for the formation of the tricyclic system of dibenzo-*p*-dioxin	28
IV.	Reactions of dibenzo-*p*-dioxins	31
V.	Toxic properties of compounds of the dibenzo-*p*-dioxin class	35
VI.	Formation and occurrence in nature	36
VII.	Conclusion	36

Abstract. The review surveys and gives a systematic account of the data on the methods of synthesis and chemistry of dibenzo-*p*-dioxins including their halogenated derivatives. The hazard of these compounds to mammals is discussed. The bibliography includes 219 references.

I. Introduction

Never before has the world community been so concerned about the hazard caused by any class of chemicals as in the case of dibenzo-*p*-dioxins. Year after year scientists from all over the world have met at conferences in an attempt to assess the hazard due to these substances generated during the industrialisation of human society.

The first representatives of dibenzo-*p*-dioxins were synthesised late in the 19th century. However, over a long period they remained known only to a narrow circle of researchers, until the terrible consequences of the chemical warfare in Vietnam (1961 – 1971) and an accident in Seveso (Italy, 1976) demonstrated to the whole world the potential danger inherent in these compounds.

The above and some other events associated with the discharge of halodibenzo-*p*-dioxins into the atmosphere have stimulated research dealing with their properties. The development of national ecological programmes in which dibenzo-*p*-dioxins occupy an important place has begun in many countries.

A large number of papers including reviews have been devoted to dibenzo-*p*-dioxins. This comes as no surprise in view of the hazard associated with some representatives of these compounds. The surprising thing is that no surveys of the chemistry of dibenzo-*p*-dioxins have yet been published. The published papers[1–5] do not provide exhaustive information. We have, therefore, ventured to fill this gap to some extent.

Since the danger coming from dibenzo-*p*-dioxins is attributed to their halogenated derivatives, these compounds receive particular attention in the literature. While preparing the present review we also used our practical experience in working with these substances.

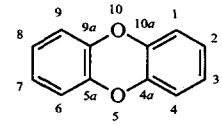
The first mentions of dibenzo-*p*-dioxins date back to 1872, when Merz and Weith[6] obtained octachlorodibenzo-*p*-dioxin while heating potassium perchlorophenoxide at a high temperature and described its properties. In 1894, Zinke[7] found that octachlorodibenzo-*p*-dioxin is produced on heating many other chlorinated compounds. The same was observed by Biltz[8] in 1904 and again by Zinke[9] in 1908.

The parent compound of this class, dibenzo-*p*-dioxin, was synthesised by Ullman and Stein[10] in 1906. Later, various derivatives of dibenzo-*p*-dioxin were prepared by several workers[11–19] and up to the 1970s many of them were regarded as promising compounds for practical purposes. Attempts have been made to develop dyes[20–23] and medicinal preparations[24–28] based on these compounds. It has been suggested that some halogenated dibenzo-*p*-dioxins be used as fireproofing agents.[26,29,30] The possibility of developing promising polymeric materials based on some dibenzo-*p*-dioxin derivatives has been studied.[31,32]

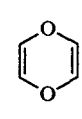
In view of the events mentioned above, since the middle 1970s the primary emphasis has shifted to the investigation of polyhalogenated dibenzo-*p*-dioxins (PHDD) as potential ecotoxicants. In 1972 – 1976, the main approaches to synthesis of these compounds were developed. At present, all the possible polychlorinated dibenzo-*p*-dioxins (PCDD) have been prepared in a pure state; bromine-, fluorine-, and iodine-containing dibenzo-*p*-dioxins as well as compounds incorporating functional groups (NO_2, CN, CH_3, CF_3, etc) have been synthesised.

II. Nomenclature and structure

The molecule of dibenzo-*p*-dioxin **1** is a fused heterocyclic system formed by two benzene rings and an inner six-membered heterocycle incorporating two oxygen atoms. In conformity with the IUPAC rules,[33] the name of dibenzo-*p*-dioxin is based on fusing 1,4-dioxin **2** with two benzene rings. {The names dibenzo-1,4-dioxin and dibenzo[*b*,*e*]dioxin for **1** and *para*-dioxin for **2** can also be found in the literature}.



1



2

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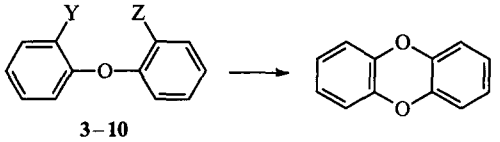
Received 28 August 1995
Uspekhi Khimii **65** (1) 29–42 (1996); translated by Z P Bobkova

The molecule of dibenzo-*p*-dioxin is planar. The crystal and molecular structures of compound **1** and some of its derivatives have been discussed in a number of papers.[34-41] The dipole moment of compound **1** is zero or close to zero, and the dipole moments of some alkyl- and halo-substituted dibenzo-*p*-dioxins have been reported.[42,43] The IR spectra of dibenzo-*p*-dioxins exhibit characteristic absorption bands in the region of 1330–1280 cm^{-1},[1,44,45] which are due to antisymmetric vibrations of the C–O–C group. An exception is provided by octahalo-derivatives, whose absorption in this region is weak.[45] The ^1H NMR spectrum of dibenzo-*p*-dioxin is an AA'BB' system centred at 6.89 ppm.[46] The ^1H NMR spectra of almost all the halogenated dibenzo-*p*-dioxins have also been obtained.[46-53] In concentrated sulfuric acid in the presence of an oxidising agent, dibenzo-*p*-dioxins produce a characteristic green-blue colour (dioxin test), which is attributed to the formation of radical-cations.[54,55] The EPR spectra and the properties of these radical-cations have been discussed in a number of papers.[56-60]

III. Methods for the formation of the tricyclic system of dibenzo-*p*-dioxin

1. Self-condensation of diphenyl ethers

Among diphenyl ethers, *o*-phenoxyphenols, the so-called predioxins, are of practical interest for the preparative synthesis of dibenzo-*p*-dioxins. Various dibenzo-*p*-dioxins can be prepared from these compounds, their yields being frequently quantitative.[61]



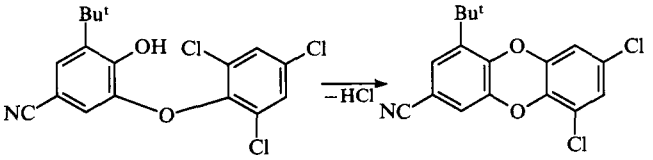
3–10

Z = Y = OH (**3**), OMe (**4**), NH_2 (**5**);

Z = OH, Y = H (**6**), NH_2 (**7**), Br (**8**), Cl (**9**);

Z = OMe, Y = Cl (**10**).

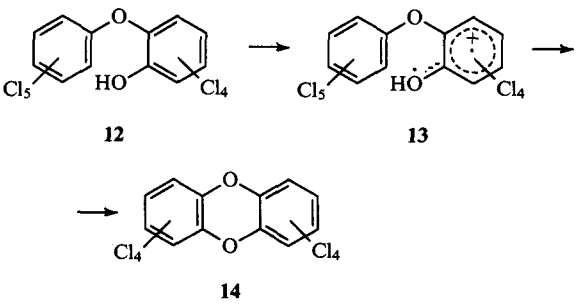
The condensation is often carried out by heating the corresponding ether (**3** and **4**) in hydrobromic acid in the presence of phosphorus.[10] Two functional groups in the ortho-positions are not required for cyclisation to take place. For example, compound **1** can be formed on treatment of 2-hydroxyphenyl phenyl ether **6** with nitrobenzene or selenium.[62] The diphenyl ethers **8–10** containing a hydroxy- (or methoxy-) group and a halogen atom in the ortho-positions undergo condensation in the presence of hydrogen chloride acceptors. The best results have been achieved by using K_2CO_3 in an appropriate solvent.[50,61,63] Electron-donating groups facilitate condensation,[64] as is the case with *tert*-butyl in compound **11**.



11

The tricyclic dibenzo-*p*-dioxin system has also been obtained by the diazotisation of the corresponding amines.[62,65] For example, compound **1** can be obtained from 2-aminophenyl 2-hydroxy-phenyl ether **7** or di(2,2'-aminophenyl) ether **5**.

The closure of the ring in *o*-phenoxyphenols can also occur under the action of UV irradiation in the presence of sensitisers.[66,67] In this case, 3,4,5,6-tetrachloro-2-(pentachlorophenoxy)phenol **12** is converted into octachlorodibenzo-*p*-dioxin[66] (OCDD, **14**). Cyclisation is supposed to occur via the biradical-cation **13**.



12 **13**

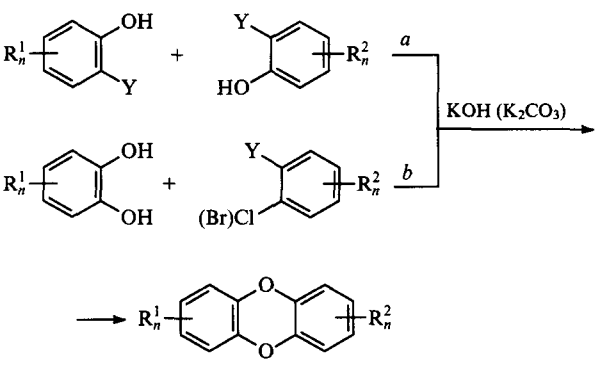
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Fairly pure specimens, suitable as reference materials, can be obtained from diphenyl ethers. However, this method has not found wide application owing to the low availability of the starting compounds.

2. Condensation of halogenated phenols and other hydroxy-compounds

Generally, condensation of halogenated phenols occurs according to Scheme 1.

Scheme 1

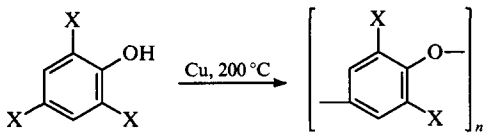


R^1, R^2 = Hal, CN, NO_2, Alk;

Y = Hal, NO_2; n = 1–4.

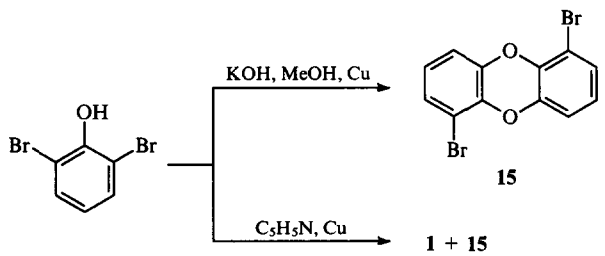
The first representative of halogenated dibenzo-*p*-dioxins, octachlorodibenzo-*p*-dioxin **14**, was synthesised in this way by heating potassium perchlorophenoxide to a high temperature.[6] Octafluorodibenzo-*p*-dioxin[68] and some other PCDD have been obtained in a similar way.[69] Potassium salts are most frequently used for the condensation of halogenated phenols. They are prepared by the following general method. The corresponding phenol is added to a methanol solution of potassium methoxide or potassium hydroxide or to a methanol suspension of potassium carbonate, and the solvent is evaporated. However, potassium phenoxides are normally not isolated in a pure state. Instead, a mixture of phenol and a 5–10-fold excess of the alkaline reagent are refluxed in an appropriate solvent. The use of a calcium salt has also been reported; compound **14** was obtained in 28% yield by heating perchlorophenol in the presence of marble.[70]

Copper and its salts are used as condensation catalysts.[6,45,68-70,71-73] An example of using a palladium-copper catalyst has been reported.[74] However, pure copper is preferred. For example, by heating *o*-bromophenol in the presence of the Cu + $Cu(OAc)_2$ system, compound **1** was obtained in 40% yield.[71] When pure copper was used, the yield increased to 65%.[71] The replacement of *o*-bromophenol by *o*-chloro- or *o*-iodophenol does not result in an increase in the yield. In the latter case, it amounted to 8%.[71] Under similar conditions, *o*-chlorophenol affords compound **1** in 25% yield. When polyhalogenated dibenzo-*p*-dioxins are synthesised using copper without a solvent, the yields usually do not exceed 20%.[45,70,72,73] The main side reaction that decreases the yields of dibenzo-*p*-dioxins is polyoligomerisation.[63,72]



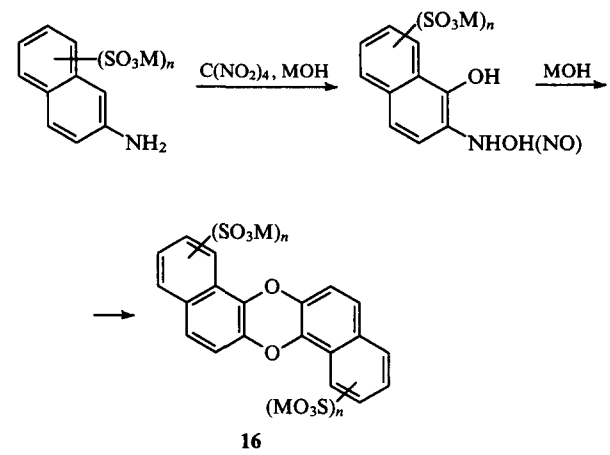
Pyrolytic condensation of potassium chlorophenoxides has been used to prepare 22 isomers of tetrachlorodibenzo-*p*-dioxins.[75] However, purification of the products obtained by this method requires the combination of liquid and gas chromatography, which seriously restricts the applicability of the method.

The condensation of phenols containing functional groups is frequently accompanied by partial elimination of these groups,[76,77] and therefore this method is not used for preparing functionally substituted dibenzo-*p*-dioxins. In some cases, the abstraction of halogen atoms has also been observed.[45,78,79] In fact, whereas the condensation of potassium 2,6-dibromophenoxide in methanol yields 1,6-dibromodibenzo-*p*-dioxin[45,78] **15**, the condensation of the same salt in pyridine[78] gives a mixture of compounds **1** and **15**.



It is not strictly necessary to use salts of phenols. Some workers[1,6–8,45,70,80,81] have shown that pyrolysis of perhalogenated phenols and a number of oxo-compounds gives the corresponding octahalodibenzo-*p*-dioxins. However, it should be noted that this reaction occurs via a different mechanism.

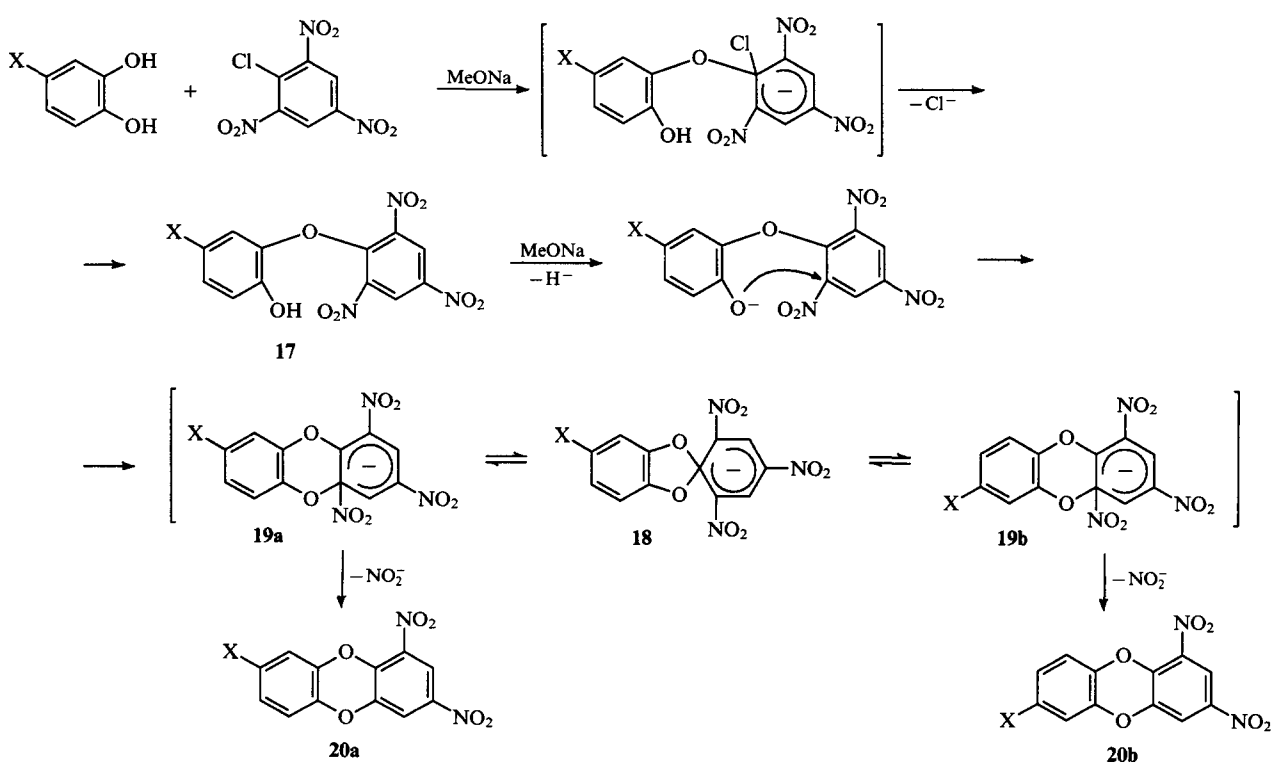
Among other hydroxy-compounds, naphthols[76,82] and hydroxyquinolines[83–85] can be involved in the condensation. The properties of the resulting naphthalene and other analogues of dibenzo-*p*-dioxins have scarcely been studied. At the same time, these compounds may be formed as minor products in the production of dyes. For example, it has been found[86] that in the presence of tetranitromethane in an alkaline medium, aminonaphthalenesulfonic acids are converted into the corresponding salts of sulfodinaphtho[5,6-*b*,*e*]-1,4-dioxin **16**. This reaction was assumed to proceed via the oxidation of the CH and NH_2 groups in the 1- and 2-positions to COH and NHOH (NO) groups followed by the condensation of two molecules.



3. Condensation of catechols with halobenzenes

The method of condensation of catechols with halobenzenes[46] suggested in 1972 is, perhaps, the most convenient way of preparing various dibenzo-*p*-dioxins including those incorporating functional groups[47,87–91] (see Scheme 1, pathway *b*). This method is preferred when a high-purity compound is needed. The analytical standards for 22 tetrachlorodibenzo-*p*-dioxins,[92,93] some pentachloro- and heptachlorodibenzo-*p*-dioxins,[49,94] and some other compounds,[79,95–97] including mixed bromine- and chlorine-containing dibenzo-*p*-dioxins,[96] have been prepared by

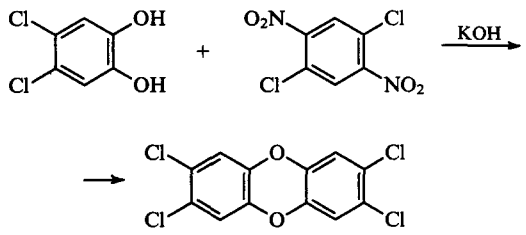
Scheme 2



this procedure. Fluorine-containing dibenzo-*p*-dioxins have also been synthesised and suggested as internal standards for gas-chromatographic and mass-spectrometric analyses of PCDD.[98-100]

The condensation of catechols is carried out under mild conditions by refluxing a mixture of reactants in a solvent. DMSO, DMF, acetone, or, more rarely, alcohols are used as solvents in this reaction. The yield of reaction products is fairly high and obviously does not depend substantially on the nature of the halogen in the halogenated benzene. In fact, the replacement of dichlorobenzene by dibromobenzene in the condensation with catechol[65,101] does not result in a substantial increase in the yield of compound **1**. Good results have been obtained by Kunzevich et al.,[102] who carried out the condensation of the disodium salt of catechol with various chlorine-containing benzenes in hexamethylphosphoramide. The yields of dibenzo-*p*-dioxins varied from 40% to 66% depending on the chlorine-containing reagent used.

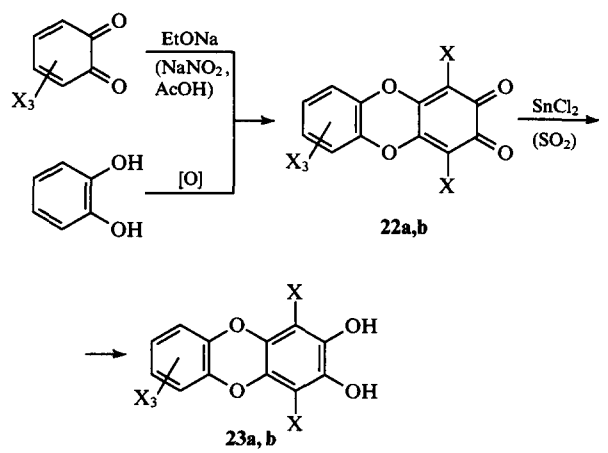
Better results are achieved when the catechol or benzene molecule contains a strong electron-withdrawing group (or several groups). This group generally acts as the leaving group, other functional groups remaining unaffected.[91] For example, the condensation of catechol with picryl chloride (see Scheme 2)[11] affords 1,3-dinitrodibenzo-*p*-dioxin (**20a**, **20b**, X = H) in 85% yield.[11] Catechol reacts with 2,4-dinitrochlorobenzene[103] just as easily. It has been found that a nitro group in the lateral position is replaced by a halogen. Therefore, the condensation of 4,5-dichlorocatechol with 2,5-dichloro-1,4-dinitrobenzene gives 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, **21**) in 90% yield.[104]



21

Halogenated *o*-quinones also undergo condensation. For example, in a study of the properties of tetrabromo(or chloro)-*o*-quinones, it has been found[105-107] that these compounds can condense to give halogenated dibenzo-*p*-dioxin-2,3-quinones **22a**. Reduction of the latter gives the corresponding hydroxy-compounds **23**.

In the presence of strong dehydrating reagents, for example, P_2O_5, the condensation of catechol to compound **1** has been observed,[65] while in the presence of oxygen or sodium nitrite, dibenzo-*p*-dioxin-2,3-quinone **22b** is produced.[105,108,109] The reaction occurs via a radical mechanism involving the oxidation of the dimer **24**, formed from the radical in the first stage of the process, to the quinone **25**, which then undergoes rapid heterolytic ring closure to give compounds **22b** (Scheme 3).



22a,b

23a, b

X = Cl, Br (**a**), H (**b**).

o-,*p*-Quinones[105-107,110] and cyclic triketones[111] also undergo cyclisation.

4. The mechanism of the formation of the tricyclic dibenzo-*p*-dioxin system

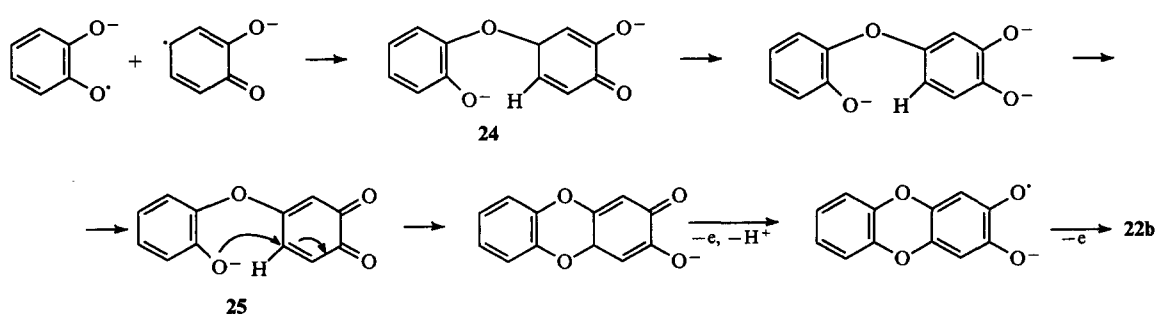
The condensation of halophenols and catechols (or their salts) with halobenzenes is based on aromatic nucleophilic substitution. This substitution must occur by an S_N2Ar mechanism[112] (in other sources,[113] this mechanism has also been called S_NAr). We can follow this mechanism in relation to the condensation of catechol with 2,4,5-trinitrochlorobenzene[103] (see Scheme 2).

The first stage of this process gives *o*-diphenoxyphenol (predioxin, **17**), whose subsequent cyclisation is intramolecular and yields the Meisenheimer spiro-complex **18**. The latter complex is formed as an intermediate in the Smiles rearrangement,[114] and in the example under consideration[103] it was isolated in a pure state (X = H) as the sodium salt. The spiro-complex is then converted to complex **19a,b**, from which the dioxin ring is formed (compounds **20a** and **20b**) after the abstraction of the NO_2^- group. The presence of two isomers in the reaction mixture has been accounted for[63,73,115] by the Smiles rearrangement. The fact that some predioxins[61,63] yield mixtures of isomers of dibenzo-*p*-dioxins is also evidence in support of the rearrangement.[61,63]

The pyrolysis of phenols and other hydroxy-compounds proceeds unlike the reactions of the salts, via a radical mechanism (Scheme 4). In particular, some researchers[1,7,8,18,80] have studied the formation of octachloro- and octabromodibenzo-*p*-dioxins in the pyrolysis of perhalophenols or a number of oxo-compounds, for example, octachlorocyclohexenone **26** and found that these reactions involve the formation of the pentachlorophenoxy radical **27**.

In all probability, the condensation of other phenols occurs by the same mechanism. Octabromo- and 1,2,4,6,7,9-hexabromo-3,8-dichlorodibenzo-*p*-dioxins have been obtained in this way, and it was suggested that the method may find wide application.[18]

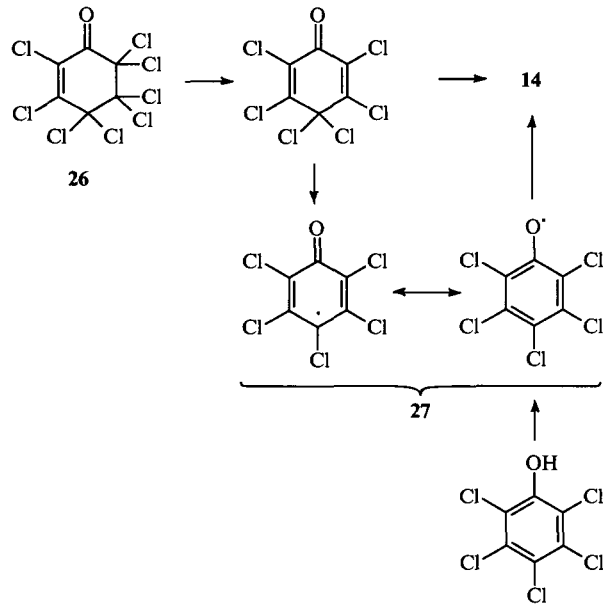
Scheme 3



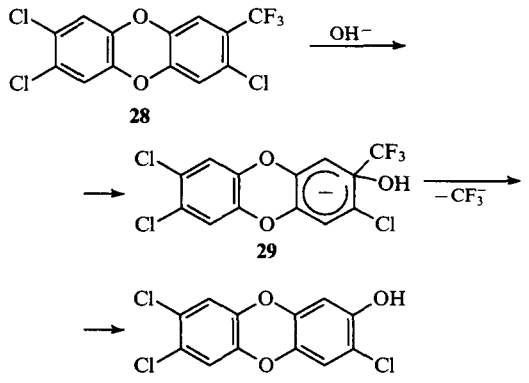
24

25

Scheme 4



with this system occurs via a transition state with a fairly low activation energy. In the case of compound **28**, the stable σ-complex **29** is formed, whose existence is in all probability caused by the presence of the CF_3 group, which has a strong inductive effect. Hydroxylation is the rate-determining step of this process. The radical substitution of chlorine (or CF_3) by the OH group proceeds more slowly than the nucleophilic substitution by a factor of approximately 3.



IV. Reactions of dibenzo-*p*-dioxins

The molecular structure of dibenzo-*p*-dioxin allows one to treat it as a cyclic aromatic diether. Accordingly, dibenzo-*p*-dioxins enter into all the reactions characteristic of aromatic compounds, namely, electrophilic and nucleophilic substitution in the benzene rings, radical reactions, as well as reactions of functional groups. Among the reactions typical of the heterocyclic nucleus, one should note the relatively easy formation of the radical-cation and reactions peculiar to it, and also reactions involving the cleavage of the C–O–C linkage.

There are almost no papers devoted to the general reactivity of dibenzo-*p*-dioxins, including their halo-derivatives. A comparative analysis of the nucleophilic and radical substitution of the functional groups in the aromatic systems of dibenzo-*p*-dioxins by the hydroxy-group has been carried out.[116] In relation to 2-trifluoromethyl-3,7,8-trichlorodibenzo-*p*-dioxin **28** and model compounds (4,5-dichlorocatechol and 5-chloro-4-trifluoromethyl-catechol), it has been shown that the reaction of the OH^- anion

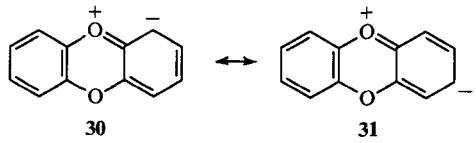
1. Electrophilic substitution reactions

a. Halogenation of dibenzo-*p*-dioxins

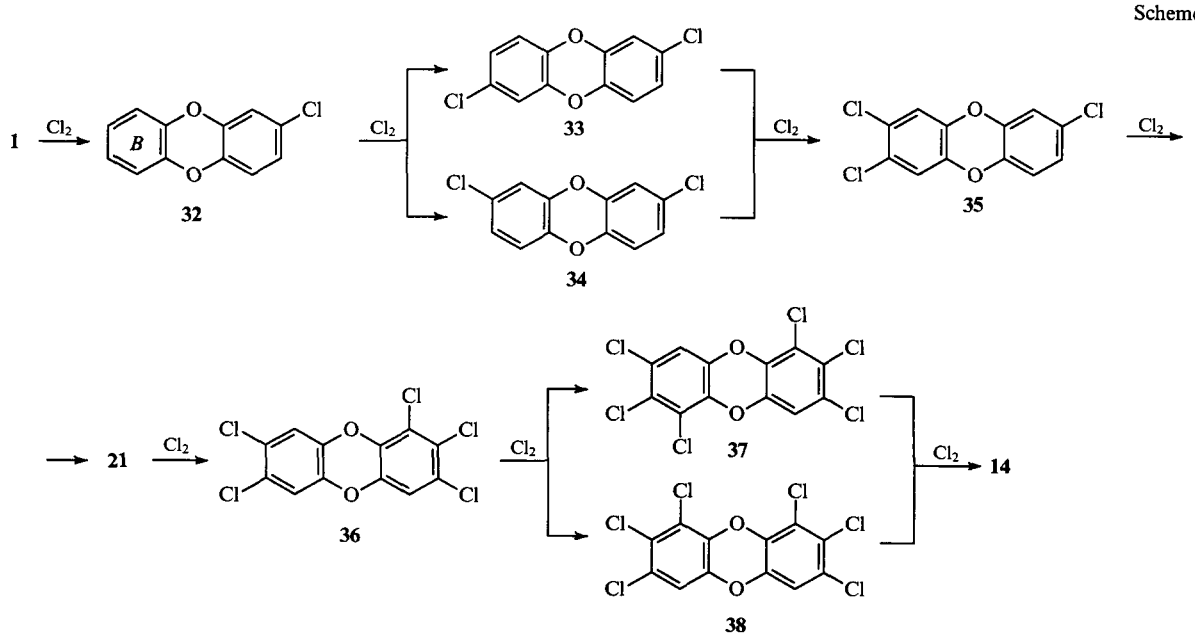
Direct halogenation of dibenzo-*p*-dioxin occurs according to the rules common to aromatic compounds. This process may be used for preparing PCDD.

The presence of the heterocycle influences the order in which the hydrogen atoms in the dibenzo-*p*-dioxin molecule are replaced. This is determined by the overall mesomeric and inductive effects of the oxygen atom on the benzene ring.[112,117]

The mesomeric effect is illustrated by the resonance structures **30** and **31**, which determine the occurrence of ortho- or para-substitution with respect to the oxygen atoms in the dioxin ring.



Scheme 5

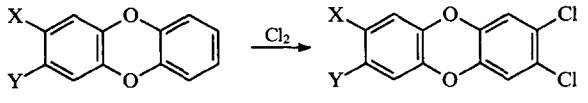


However, the ortho-position is deactivated by the inductive effect of oxygen to a larger extent than the para-position. Therefore, the first stage of the halogenation of dibenzo-*p*-dioxin **1** yields the isomer **32** (Scheme 5). The order in which subsequent substitution occurs is an interesting theoretical problem. Due to the deactivating influence of the first halogen atom, the second substitution should occur in ring *B*. The most theoretically probable substitution positions are 7 and 8 (compounds **33** and **34**). When further halogenation is carried out, the hydrogen atoms in the 3- and 7-(or 8-)positions, which are equivalent in terms of the substitution order, are successively replaced by the halogen. As a result, the highly toxic 2,3,7,8-tetrahalodibenzo-*p*-dioxin **21** is formed. Further substitution involves the 1-position (compound **36**) and then the 6- or 9-position (compounds **37** and **38**). The remaining free positions are equivalent in terms of the substitution order, and exhaustive halogenation yields the weakly toxic octahalodibenzo-*p*-dioxin **14**. According to published data, the toxicities of the remaining halogenated dibenzo-*p*-dioxins are intermediate between those of 2,3,7,8-tetra- and octahalo-substituted compounds.[2,118]

The chlorination of dibenzo-*p*-dioxin **1** proceeds to a greater extent than the bromination. It has been shown[46,119] that chlorination yields a mixture of products with various degrees of substitution that are difficult to separate. Therefore, this method was[46] considered to be unsuitable for the synthesis of individual chlorinated dibenzo-*p*-dioxins. Bromination of dibenzo-*p*-dioxin **1** normally comes to a halt at the stage where 2,3,7,8-tetrabromodibenzo-*p*-dioxin is formed.[102,120] Under certain conditions, this compound can be obtained in a quantitative yield.[102]

It has been reported that chlorination in the second stage gives mostly the 2,7-isomer, while in the case of bromination, the 2,8-isomer predominates;[19,102] however, this conclusion is questionable. In fact, the yield of the 2,7-dichloro-isomer obtained by the chlorination of dibenzo-*p*-dioxin **1** was only 3%. This fact made it possible to suggest[46] that the 2,8-dichloro-isomer is more soluble and this is why it had not been isolated by the authors of the previous paper.[19] In any case, there are no serious reasons for believing that chlorination in this stage differs from bromination.

The foregoing considerations are also valid for the halogenation of dibenzo-*p*-dioxins in which the hydrogen atoms of one ring have been completely replaced by chlorine:[46] substitution occurs in the 7- and 8-positions of the free ring. The presence of other halogens in the molecule also does not change the order in which substitution occurs. In the chlorination of 2,3-dibromo- (**39**) and 2,3-difluoro- (**40**) derivatives, 2,3-dibromo-7,8-dichloro- (**42**) and 2,3-difluoro-7,8-dichlorodibenzo-*p*-dioxins (**43**) have been isolated.[119] The nitro-group deactivates ring *A* to such an extent that 2-nitrodibenzo-*p*-dioxin (**41**) is halogenated in the unsubstituted ring *B*,[121,122] yielding 7,8-dichloro-2-nitrodibenzo-*p*-dioxin **44**.

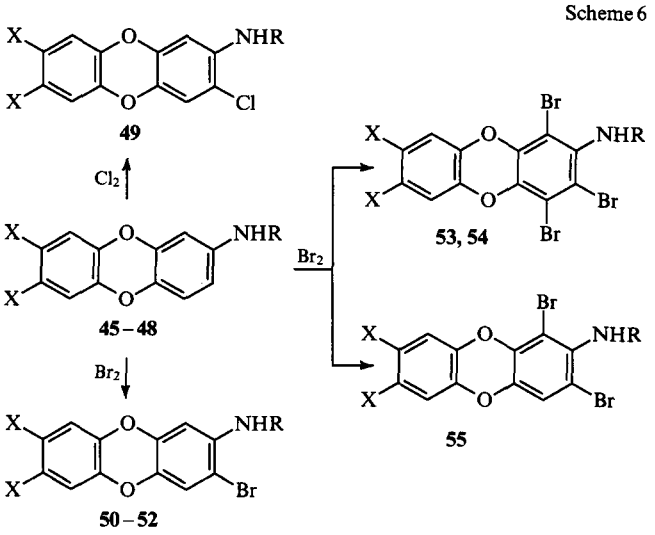


39–41 **42–44**

X = Y = Br (**39, 42**), F (**40, 43**); X = H, Y = NO_2 (**41, 44**).

Conversely, the amino group activates dibenzo-*p*-dioxin. For example, bromination of amino- or acetamido-derivatives **45–48** occurs fairly readily[121,123] and substitution involves the ring containing the amino-group (Scheme 6, compounds **50–55**). Unlike bromination, the chlorination of the amino-derivatives **45** and **47** is accompanied by the resinification of the reaction mixture.[121] The corresponding acetyl-derivatives **46** and **48** are susceptible to resinification to a lesser degree. For example, the chlorination of 2-acetamido-7,8-dichlorodibenzo-*p*-dioxin **46** gave 2-acetamido-3,7,8-trichlorodibenzo-*p*-dioxin **49** in good yield.[121,123]

Scheme 6



X = Cl, R = H (**45**), Ac (**46, 49, 50, 53**);

X = Br, R = H (**47, 51, 55**), Ac (**48, 52, 54**).

The influence of various catalysts on the process of chlorination of dibenzo-*p*-dioxins has been described.[122] The authors found that among the catalysts studied, namely I_2, $FeCl_3 + I_2$ and 18-crown-6, the last named is the most active. The chlorination pattern in all these cases is the same. In particular, irrespective of the nature of the catalyst, the chlorination of dibenzo-*p*-dioxin **1** affords a mixture of products in which, in addition to TCDD **21**, 2,3,7-trichloro- (**35**) and 1,2,3,7,8-pentachlorodibenzo-*p*-dioxins (**36**), have been detected.

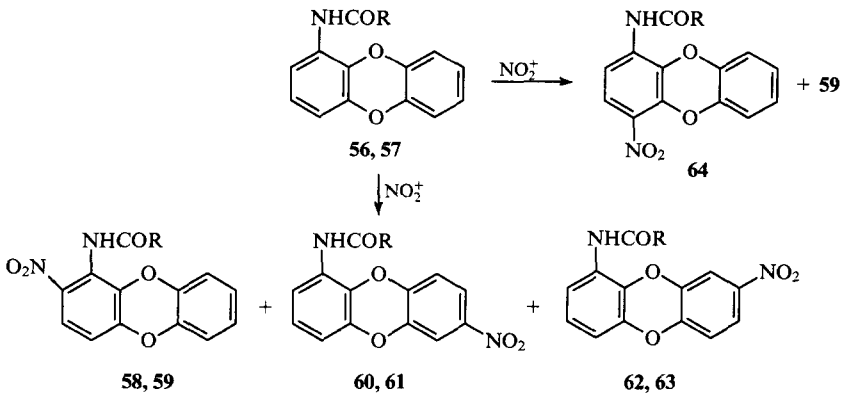
It is likely that the presence of catalysts can result in more extensive bromination. For example, the bromination of dibenzo-*p*-dioxin in the presence of $FeCl_3$ gave[119] a mixture of compounds containing, in addition to 2,3,7,8-tetrabromodioxin, the products of its further bromination. Therefore, while brominating compound **1** by bromine in the presence of a catalyst, one should take into account the possibility of the formation of polybrominated compounds.

b. Nitration of dibenzo-*p*-dioxin and its derivatives

Dibenzo-*p*-dioxin **1** can be nitrated by conventional nitration reagents such as nitric acid or nitric acid in concentrated sulfuric acid.[16,124–130] Depending on the reaction conditions, a series of successive substitution products are formed, and the order in which substitution occurs follows the rules which govern halogenation. Owing to the strong deactivating effect of nitro-groups, nitration proceeds only until 2,3,7,8-tetranitrodibenzo-*p*-dioxin is formed.[130]

The influence of various substituents and various nitrating agents on the nitration process has been studied.[124,125,128,131,132] For example, depending on the reaction conditions, the first substitution in the nitration of 1-acyldibenzo-*p*-dioxins[128] (**56** and **57**) may involve either the ring containing the functional group or the unsubstituted ring as well, as shown in Scheme 7. The ratio between the isomers obtained and their quantity depends on the nature of the substituent and the nitrating agent. When an excess of the latter is used, 2-, 7-, or 8-nitro-derivatives (compounds **58–63**) are formed. However, in some cases, this order of nitration may be violated. For example, when compound **57** is nitrated by the $NH_4NO_3-(CF_3CO)_2O-THF$ mixture, substitution involves only the ring containing the functional group and mostly the 4-position of this ring (compound **64**).[129] Some instances where the acetyl group is replaced by the nitro-group during nitration have also been reported.[125] Dibenzo-*p*-dioxins incorporating methyl or methoxy groups are readily nitrated by nitric acid in either sulfuric or acetic acid.[124,131,132]

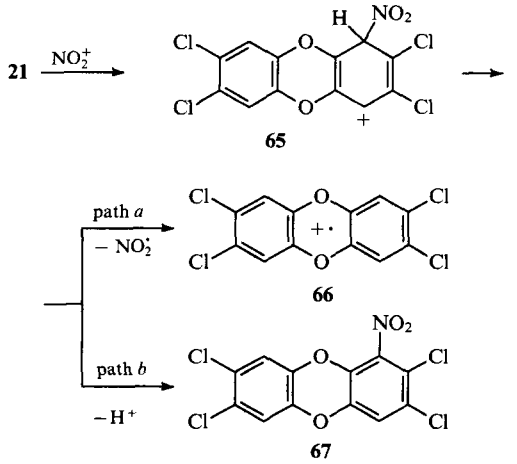
Scheme 7



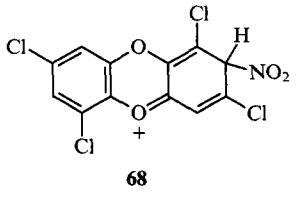
R = Me (**56**, **58**, **60**, **62**), CF_3 (**57**, **59**, **61**, **63**, **64**).

The nitration of halogen-containing dibenzo-*p*-dioxins presents certain difficulties associated with the deactivating effect of the halogens. For example, it has been noted that 1,6-dibromodibenzo-*p*-dioxin **15** does not undergo nitration with nitric acid in concentrated sulfuric acid.[124] This task can be accomplished by using fuming nitric acid in acetic acid at $T = 70$ °C;[131] this nitrating agent can also be used successfully in other cases, for example, to nitrate mono- and dihalo-substituted dibenzo-*p*-dioxins.[121,123,130,133] Good results have also been obtained in the nitration by this mixture of polyhalogenated dibenzo-*p*-dioxins containing halogens in one ring, in particular, of 1,2,3,4-tetrachlorodibenzo-*p*-dioxin.[121,123,133] The nitro group goes to the unsubstituted ring. 2,3,7-Trihalo-substituted derivatives are also nitrated under these conditions to give the mono-substitution product.[133]

Tetrahalo-derivatives are more stable. The most stable are isomers with a lateral arrangement of the halogens. In particular, TCDD **21** does not react with a mixture of nitric and acetic acids[128] and is destroyed on treatment with fuming nitric acid in sulfuric acid.[95] This behaviour can be explained, on the one hand, by the low stability of the σ-complex **65** arising in the course of the reaction (which is due to the fact that the positive charge in this complex cannot be delocalised owing to the electron pairs of the oxygen atoms) and, on the other hand, by the decomposition of the σ-complex **65** via pathway *a* to the radical-cation **66** and the $NO_2^{\cdot}$ radical.[134] Under these conditions, oxidation processes leading to the destruction of the dioxin nucleus prevail. In the case where complex **65** decomposes via pathway *b*, nitration affording compound **67** takes place.[133]



In the nitration of 2,3,7,8-tetrachloro-derivative **21**, satisfactory results have been obtained[135] by using nitronium tetrafluoroborate in sulfolane at $T = 125$ °C. This reaction yields a disubstitution product. Compound **21** can also be nitrated by an $NH_4NO_3-(CF_3CO)_2O-MeNO_2$ mixture. In this case, substitution involves the 1-position and gives compound **67** (yield 1%–2%).[137] The tetrahalo-derivatives in which the arrangement of halogen atoms is other than lateral form the more stable σ-complexes **68**. Therefore, 1,3,6,8-tetrachloro- and 1,3,7,8-tetrachloro-dibenzo-*p*-dioxins are readily nitrated by the $NH_4NO_3-(CF_3CO)_2O-MeNO_2$ mixture.[87,136]

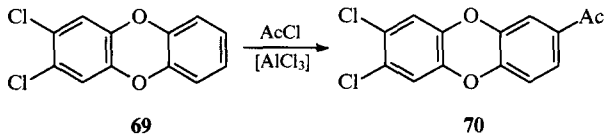


68

c. Acylation and alkylation of dibenzo-*p*-dioxin and its derivatives

Dibenzo-*p*-dioxins are fairly smoothly acylated by acyl chlorides in the presence of aluminium chloride (or bromide).[15,22,27,125,129,137–145] The reaction is most frequently carried out in carbon disulfide. The hydrogen atoms in the 2- and 7-positions are substituted preferentially. If these positions are occupied, substitution involves the 3-position. For example, acylation of 2,7-dihalodibenzo-*p*-dioxins by acetyl chloride gives the corresponding 2-acetyl-3,8-dihalodibenzo-*p*-dioxins.[145] If the 1-position is occupied by a substituent, the reaction may involve the 4- and 9-positions.[142]

The third halogen atom deactivates the nucleus to such an extent that, for example, 2,3,7-trichlorodibenzo-*p*-dioxin **35** cannot be acylated by acetyl chloride even in the presence of aluminium chloride.[133] Compound **21** also does not undergo acylation. In the case where the halogen atoms are located in one ring, the unsubstituted ring is acylated. For example, by acylating 2,3-dichlorodibenzo-*p*-dioxin **69** by acetyl chloride, one can obtain 2-acetyl-7,8-dichlorodibenzo-*p*-dioxin **70**.[133]



69 **70**

The alkylation of dibenzo-*p*-dioxin **1** has been studied in detail[19] and has some peculiarities. In particular, it was found that in the alkylation of compound **1** by isopropyl chloride, the second substitution in the resulting 2-isopropyldibenzo-*p*-dioxin involves the 3-position, in contrast to halogenation, nitration, or acylation. After that, the 7-position is substituted. Exhaustive alkylation is not observed even when an excess of isopropyl chloride is employed. Under these conditions, the authors cited isolated

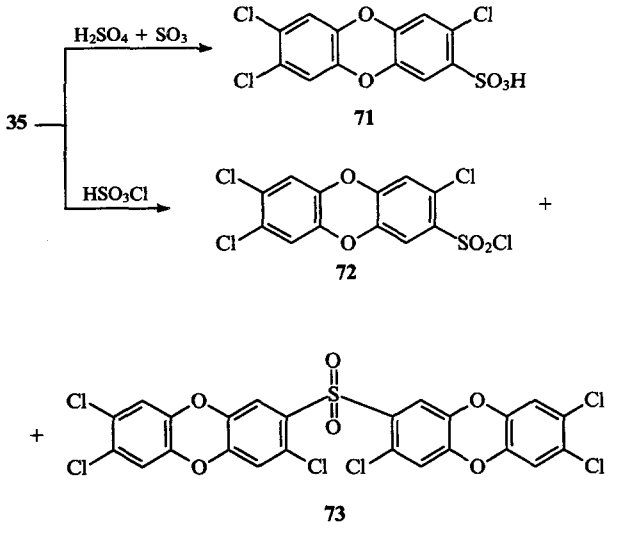
one of the possible hexaisopropyl derivatives. If there is steric hindrance, for example if the alkylation is carried out with *tert*-butyl chloride, only a disubstitution product is formed, the second substitution involving the 7- or 8-position.

No examples of the alkylation of halogenated dibenzo-*p*-dioxins have been reported. However, from general considerations, it may be suggested that this process would be substantially hampered owing to the deactivating effect of the halogens.

d. Sulfonation (sulfochlorination) of dibenzo-*p*-dioxin and its derivatives

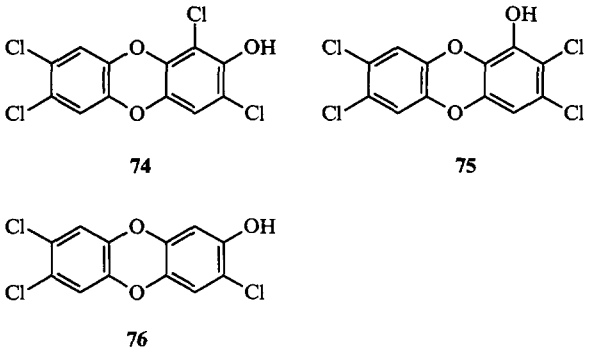
Sulfonation of dibenzo-*p*-dioxin **1** by sulfuric acid or oleum gives the 2,7-disulfonic acid.[146] When chlorosulfonic acid is used, the 2-chlorosulfonyl chloride is formed.[32] Halodibenzo-*p*-dioxins are sulfonated under similar conditions.[133] For example, when the sulfonation of 2,3,7-trichlorodibenzo-*p*-dioxin **35** is carried out with oleum at room temperature, the hydrogen atom in a lateral position is replaced by the sulfo group and the reaction yields the sulfonic acid **71** (Scheme 8). Sulfochlorination of dioxin **35** gives[133] 2-chlorosulfonyl-3,7,8-trichlorodibenzo-*p*-dioxin **72**; the sulfone **73** is formed as a side product.

Scheme 8



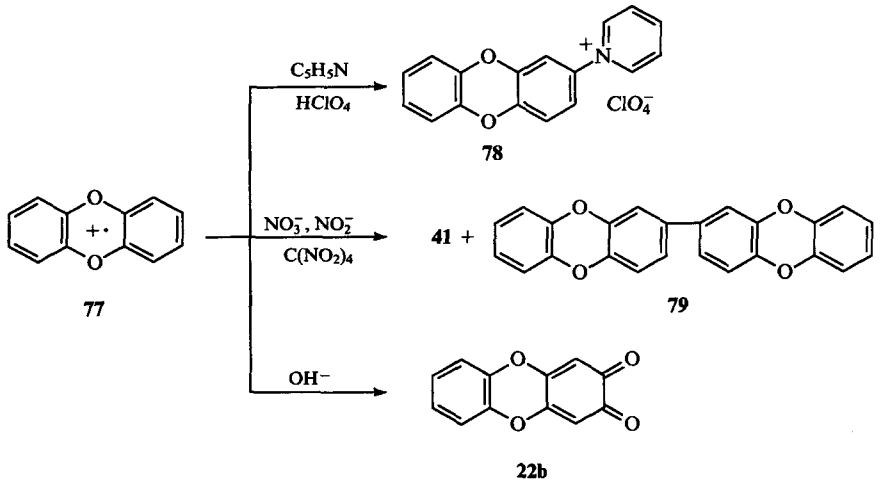
2. Reactions involving nucleophiles

Despite the fact that nucleophilic substitution plays a significant role in the chemistry of dibenzo-*p*-dioxins, this problem has not been adequately addressed in the literature. Methods based on the nucleophilic substitution of hydroxy groups for chlorine atoms on treatment with potassium hydroxide[2,147] or potassium carbonate and hydrogen peroxide[148] have been suggested for the practical removal of PCDD from the gas phase. It is believed that, among all the chemical methods recommended for the detoxification of PCDD-containing waste, the alkaline dehydrochlorination technology, applicable to both liquid and solid waste, is the most promising.[149] In addition, nucleophilic species are known to participate directly or indirectly in many processes involving PCDD and occurring in the environment and in the organs of mammals.[4,150] For example, it has been found that ring hydroxylation is the dominant route in the metabolism of chlorinated dibenzo-*p*-dioxins.[151,152] It was found that the metabolism of dioxin **21** involves hydroxylation in lateral positions with migration of chlorine to the 1-position and gives 2-hydroxy-1,3,7,8-tetrachlorodibenzo-*p*-dioxin[151] **74**. 1-Hydroxy-2,3,7,8-tetrachlorodibenzo-*p*-dioxin **75** and 2-hydroxy-3,7,8-trichlorodibenzo-*p*-dioxin **76** are also metabolites of TCDD. Dibenzo-*p*-dioxins chlorinated to lesser degrees are converted into 2- and 3-hydroxy-derivatives.[153] The metabolism in dogs and rats may involve the cleavage of the dioxin nucleus to give bis(dichlorohydroxyphenyl) ether[151] and 4,5-dichlorocatechol.[154]



Dibenzo-*p*-dioxins are capable of forming radical cations when treated with strong oxidising agents in combination with photoirradiation.[155,156] The radical-cations of functionally substituted dibenzo-*p*-dioxins are generated, for example, on treatment with concentrated sulfuric acid in the presence of potassium nitrate,[56] nitric acid, potassium perchlorate, manganese dioxide, hydrogen peroxide,[58] or antimony pentachloride[157] and also during electrochemical oxidation.[54,158–160] The chemical and physical properties and the EPR spectra of the radical-cation derived from compound **1** and a large number of its substituted derivatives have been studied.[57,58,157,161–166] It was shown that the dibenzo-*p*-dioxin radical-cation **77** (Scheme 9), stabilised by an anion, possesses a certain stability. For example, stable acetonitrile solutions of the tetrafluoroborate of the radical-cation **77** have been obtained by treating compound **1** with $NO^+BF_4^-$.[167]

Scheme 9



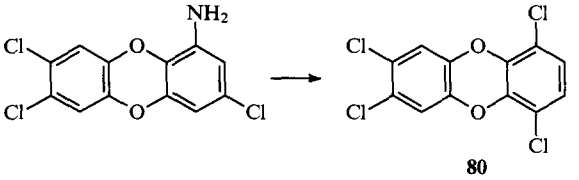
In another study,[158] the perchlorate of the radical-cation **77** was isolated and its reactivity was studied. The radical-cation **77** was found to react with pyridine giving *N*-(2-dibenzo-*p*-dioxinyl)pyridinium perchlorate **78**. The nitrite anion reacts with the radical-cation as a nucleophilic agent to form 2-nitrodibenzo-*p*-dioxin **41**. The nitro compound **41** was also obtained when the radical-cation **77** was treated with nitrate anions or with tetranitromethane. In addition to the perchlorate of the radical-cation **77** the dimer of dibenzo-*p*-dioxin **79** was isolated,[158] however, its structure was not discussed. Taking into account the melting point of the compound obtained, one may suggest that it is 2,2'-bis(dibenzo-*p*-dioxin), which was described previously.[127] It has also been found[54,159] that the perchlorate of the radical-cation **77** in solution reacts with water to give dibenzo-*p*-dioxin-2,3-quinone **22b**.

Apart from the reaction products, the initial dibenzo-*p*-dioxin **1** has been recovered in all cases. Reactions with other nitrogen-containing nucleophiles (CH, NH_3, RNH_2) led only to the recovery of compound **1**. It is believed[158] that, for nucleophilic substitution to occur, a stronger nucleophile is required.

3. Reactions of functional groups

Among the functionally substituted dibenzo-*p*-dioxins, the nitro- and amino-derivatives are of prime interest and have been the most thoroughly studied.[47,128,136,168–170] These compounds are more frequently encountered than is believed.[168] They present a severe hazard to mammals and are environmental pollutants.[123] Aminodibenzo-*p*-dioxins have found application in the development of a radio-immune method for the assay of PCDD.[171,172]

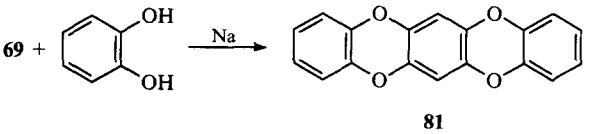
No data have been published that would make it possible to speak of any influence of the dioxin nucleus on the reactivity of nitro- and amino-derivatives. In some studies, the Sandmeyer reaction has been used to prepare halogenated dibenzo-*p*-dioxins from the corresponding amino-derivatives.[95,104,136,173] It was noted that in some cases the reaction is complicated by a rearrangement and consequently may give unexpected products, for example, compound **80**.[104]



80

Nitro-derivatives can be reduced, and this reaction is the main method of synthesis of amino-containing dibenzo-*p*-dioxins. Various reducing reagents have been used,[121,130,136,173–175] however, the highest yield was achieved in the case of tin dichloride.[121] Aminodibenzo-*p*-dioxins are readily acylated,[123] enter into the Skraup reaction to form the corresponding quinoline derivatives,[176,177] and condense with quinones[178] to give phenazines. Hydroxy-derivatives are acylated in a similar way.[179]

Halogen-containing dibenzo-*p*-dioxins can condense,[102,127] affording products with enlarged structures.



81

V. Toxic properties of compounds of the dibenzo-*p*-dioxin class

1. Toxic properties

It is believed, with good reason, that PCDD are products of human technological activity.[4,180] The pathways to the formation of PCDD are known and have been fairly extensively studied, but the formation of functionally substituted dibenzo-*p*-dioxins still remains unexplored. There are data showing that halogenated nitro-derivatives of dibenzo-*p*-dioxins are formed on the fly ash from incinerators via the nitration of the corresponding dibenzo-*p*-dioxins by the nitrogen dioxide present in the exhaust gases.[168] Although the potential hazard of functionally substituted dibenzo-*p*-dioxins is quite considerable,[87,123] they have scarcely been studied.

The urgent need to study dibenzo-*p*-dioxin class compounds arises primarily from the results of toxicological studies. A large number of publications, including several detailed reviews, have been devoted to this problem.[2,181–183] Analysis of these and other data makes it possible to make some generalisations concerning the toxicology of compounds of this class.

Among dibenzo-*p*-dioxins and compounds with similar structures — polychlorinated dibenzofurans, biphenyls, and naphthalenes — those substances in whose molecules all the lateral positions are occupied by halogen atoms are the most toxic. It has been found that TCDD **21** exhibits the highest toxicity toward the most sensitive species (guinea pigs), while 2,3,7,8-tetrachloronaphthalene has the lowest toxicity. When the number of halogen atoms in the ring decreases or increases, the toxicity diminishes sharply.[2,183] Completely halogenated compounds exhibit virtually no toxicity, at least, under the conditions of an acute experiment.

The positions of the halogen atoms in the ring are significant for biological activity. For example, symmetrical derivatives are as a rule more toxic than their nonsymmetrical analogues.

TCDD possesses the highest biological activity among all the classes of compounds under consideration. It comes as no surprise that most of the published data are devoted to the toxicology of this compound.

The high toxicity of TCDD for warm blooded animals is combined with pronounced interspecific differences in sensitivity to it.[184] The coefficient of interspecific differences is as high as four orders of magnitude.[150,183–186] Another important feature of the biological action of TCDD is the presence of clear-cut individual intraspecific distinctions, which is indicated by the fact that the slopes of 'dose–effect' plots are small, compared with those for other xenobiotics.[187] Interstrain differences in the sensitivity to TCDD are fairly clear-cut (~250 for rats and ~20 for mice).[183] The presence of paradoxical behaviour in the 'dose–effect' relations should be regarded as significant evidence in support of intraspecific polymorphism in the sensitivity to TCDD and its analogues.[188]

Studies of the chronic action of small TCDD doses have demonstrated the presence of pronounced supercumulative effects,[184,189–191] which is significant for the regulation of the maximum permissible concentrations of this compound in the environment.

The most general symptoms of the TCDD poisoning of various types of warm blooded animals are liver enlargement, thymus atrophy, progressive weight loss, and a clear-cut latent period of up to 10–15 days after contact with the poison. Other clinical manifestations are fairly polymorphic. In fact, in mice, rats, and rabbits, apart from hepatomegaly, pronounced centrolobular necrosis of liver tissue, in some cases turning into hepatargia, has been observed.[183,189,192] The edematous syndrome, accompanied by intense secretion of transudate in pericardial, pleural, and abdominal cavities, is typical for chickens. In the case of guinea pigs and monkeys (rhesus, macaque), the prevailing symptoms are those indicating deep suppression of the immune system. The data concerning symptoms of the effects of TCDD on humans are less definite, because they have been obtained in relation to accidental contacts with the xenobiotic or by examining the personnel engaged in the production of 2,4,5-trichlorophenol containing TCDD as an impurity.

Nevertheless, it has been reported[192,193] that the TCDD intoxication in humans is manifested as skin changes (chloracne), weight loss, high susceptibility to fatigue, muscle

asthenia, insomnia, high irritability, decrease in libido, reduction of sensory functions, tendency to hepatomegaly, decrease in the concentration of serum lipids, increase in the prothrombin time, and porphyria. In addition, there are data on more severe pathologies: the people under examination suffered more frequently from soft tissue sarcoma.[191] This last fact is the reason why studies dealing with remote consequences of the action of TCDD, and, in particular, with mutagenic, carcinogenic, teratogenic, and embryotoxic effects, are urgently required.

In 1972, a mutagenic effect of solutions of TCDD was observed in bacterial test systems, and a mechanism of this phenomenon, involving the intercalation of TCDD with the DNA helix, was suggested.[193] Somewhat earlier, Courtney and Moore,[194] who carried out experiments with various strains of mice and rats, discovered embryotoxic and teratogenic effects of TCDD: the cleaving of the hard palate and defects in kidney embryogenesis. Discussions concerning the character of the carcinogenic effect of TCDD still continue.[195] The authors of another study [196] are apt to regard TCDD as a pronounced promoter of carcinogenesis, at least in rodents. In conformity with their data, the tumour-stimulating effect of PCDD is comparable with that of aflatoxin B_1. According to other data,[197] at concentrations that can occur in an organism, TCDD is neither a classical carcinogen nor a mutagen. One may speak only of its promoting effect with respect to some carcinogens, such as nitrosamines.

2. The mechanism of action

To explain the mechanism of the toxic action of TCDD, several hypotheses have been put forward.

1. The toxic effect of TCDD arises through bonding to the highly specific cytosol Ah-receptor. The complex is then translocated to the nucleus and expresses the DNA sections, responsible for the synthesis of pools and the RNA initiating the synthesis of cytochrome P-450 (or 448)-dependent monooxygenases.[183,198] This hypothesis adequately explains the extraordinarily high degrees of induction of microsomal monooxygenases.

2. TCDD exhibits a thyroxine-like action, which is indicated by a number of hyperthyroid symptoms, enhancement of the catabolism of lipids and biopolymers, weight loss, additivity of the toxic effects of TCDD and thyroid hormones.[183,199]

3. The toxic action of TCDD is due to the relative deficiency of carotinoids.[183,200] This hypothesis was based on the sharp decrease in the concentration of carotinoids, in particular vitamin A, in the liver of rats exposed to TCDD. This approach is supported by the syndrome (skin changes, hyperkeratosis, lesion of the sclera and the cornea, etc.) in laboratory animals poisoned by TCDD.

Among other attempts to explain the mechanism of the toxic action of TCDD, the assumption that disturbance of the flavin metabolism, in particular the metabolism of riboflavin, whose structure is similar to that of TCDD, plays the key role in the pathogenesis of TCDD intoxication deserves attention.[201] The above structural similarity accounts for the fairly successful use of riboflavin preparations in the experimental therapy of TCDD poisoning. It should be noted that none of these hypotheses concerning the pathogenesis of TCDD toxification can explain fully by itself the whole diversity of the clinical pattern of the poisoning and especially the very pronounced inter- and intraspecific differences in the sensitivity to this xenobiotic.

At the same time, there is the noteworthy possibility that all the above approaches can be interpreted in terms of the disturbance of the equilibrium between the pro- and antioxidant systems in an organism. In fact, the hypothesis of the leading role of the Ah-locus accounts for the activation of prooxidant processes. Thyroid hormones also exert an indirect prooxidant effect. Carotinoids as well as tocopherols are obligatory constituents of the antioxidant protection of an organism.

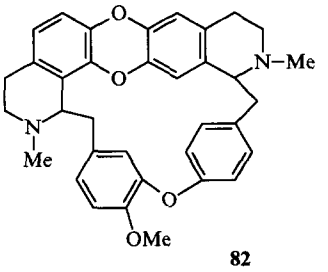
We believe that all the above hypotheses could be accommodated within the framework of a unified theory of the pathogenesis of the intoxication by polychlorinated polyaromatic hydrocarbons, which would be based on the assessment of the degree of prooxidant action and on the determination of the actual balance between the pro- and antioxidant systems, especially since the intensification of the peroxide oxidation of lipids and the enhancement of the generation of active oxygen forms in an organism under the influence of TCDD (i.e. the existence of prooxidant action) are established facts.[202] Such activity is manifested by the characteristic features of the functioning of pro- and antioxidant systems in various species.

VI. Formation and occurrence in nature

The causes of the formation of technogenic PHDD and the pathways by which they arrive in the environment have been studied quite extensively.[4,180,181,185] However, dibenzo-*p*-dioxins of natural origin have scarcely been studied. At the same time, the presence of a large number of hydroxy-derivatives of benzene in plants makes it possible to infer that the compounds under consideration are not rarities.[203] The oxidation of hydroxy-compounds is most probably the main pathway to the formation of the tricyclic dibenzo-*p*-dioxin system in plants. For example, dibenzo-*p*-dioxin is known to be formed on oxidation of *p*-benzoquinone,[110] catechol,[106,108] and certain pyrogallol derivatives.[109,204] It has been established [205–208] that such oxidation can occur in plants through the action of certain enzymes. In fact, an enzyme that oxidises catechol to dibenzo-*p*-dioxin-2,3-quinone [208] with a high specificity has been isolated from an extract of *Tecoma stans* leaves. In another study,[207] this quinone was isolated in a pure state after the oxidation of catechol by polyphenol oxidase, and its structure was confirmed by an alternative synthesis.

In a study of keto-derivatives of inositol,[111] it was found that the acetylation of these compounds in the presence of an acid catalyst yields completely hydroxylated dibenzo-*p*-dioxin. It was suggested that dibenzo-*p*-dioxin derivatives may be synthesised via this route in nature.

The discovery of the alkaloid trilobine and the determination of its structure served as direct confirmation of the formation of dibenzo-*p*-dioxin in nature. In 1924, Kondo and Nakasato studied an extract from the roots of cocculus (*Cocculus trilobus DC*) and isolated an alkaloid which was called trilobine.[209] Eight years later, Kondo and Tomita found that the trilobine structure is based on the heterocyclic system of dibenzo-*p*-dioxin.[210] In 1942, Tomita and Tani [211,212] published the full formula of trilobine **82**.



82

The alkaloid micranthine, isolated from the plant *Daphnandra micrantha*,[213] as well as the alkaloids tiliaresine, tiliacorine, and tiliacorinine, obtained from the plant *Tiliacora racemosa*,[214–216] have structures similar to that of trilobine.

VII. Conclusion

The data presented in this review indicate that studies devoted to dibenzo-*p*-dioxins are progressing vigorously. The methods of synthesis of compounds of this class are being improved, and insight is being gained into processes occurring in nature and in the organs of animals involving halo-derivatives of dibenzo-*p*-dioxins. However, the knowledge accumulated does not yet make it possible to speak of an ultimate solution of the problem of dioxin-like xenobiotics. Although the latter have mostly been created by human activity, one should keep in mind that the

dibenzo-*p*-dioxin structure has been invented by nature. From this viewpoint, this class of compounds remains poorly investigated. For this reason, humankind has probably been deprived of many useful things, ranging from medicines to various materials. However, in recent years some studies dealing with this problem have been published. These were mostly attempts to develop new medicines.[217]

Comprehensive investigation of halogenated dibenzo-*p*-dioxins has been the dominant factor in the development of the chemistry of dibenzo-*p*-dioxins. One significant property of these compounds that has not yet received the due attention of scientists is noteworthy, namely that, in some cases, it is expedient to treat dibenzo-*p*-dioxin (and its halo-derivatives) as a crown ether (dibenzo-6-crown-2). Some of the properties of PCDD, including their toxic properties may be associated with the ionophoric and complex-forming capacities of these compounds. In any case, the toxicity of octabromodibenzo-18-crown-6 is comparable with that of 2,3,7,8-tetrabromodibenzo-*p*-dioxin.[102] In addition, TCDD exhibits a growth-stimulating activity with respect to herbaceous plants, typical of crown ethers.[218]

The complex-forming capacity of dibenzeo-*p*-dioxins forms the basis of a photometric determination of PCDD.[219]

Thus, the data considered in the present review indicate that careful study of the properties of dibenzo-*p*-dioxins may lead to new possibilities in the investigation of the physiological activity of compounds of this sort.

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