Chemistry and pharmacology of benzodioxanes

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ABSTRACT

Benzodioxane represents a series of synthetic and natural compounds of considerable medicinal importance. Compounds containing dioxane ring systems exhibited different biological activities such as antihapatotoxic, \( \alpha \)-adrenergic blocking agent, neuroleptic, anti-inflammatory, hypolipidemic and D\(_2\) antagonist/5-HT\(_{1A}\) partial agonist activity. The literature concerning chemistry of benzodioxanes chemistry is scattered and has not been reviewed so far. The present article covers the various methods of preparing 1, 3-and 1, 4-benzodioxane ring system, different chemical reactions, and their different biological activities.

INTRODUCTION

Benzodioxane represent a series of synthetic and natural compounds of considerable medicinal importance and the literature concerning benzodioxane chemistry has been seldom reviewed. This article covers the various methods of preparing 1, 3-and 1, 4-benzodioxane ring system and which have resulted in the availability of many substituted benzodioxane and consequently have been instrumental in the advancement of benzodioxanes chemistry. The review also includes the reactions of the benzodioxanes, which have been developed in the past; some of them have been applied in the synthesis of biologically active compounds.

A framework of benzodioxane has been found in biologically active lignans, silybin and americanin, which are antihapatotoxic, and haedoxan posses insecticidal activity. Ahmed et al was first to report that 1, 4-benzodioxane ring plays an important role in exhibiting a significant antihapatotoxic activity of silybin, a naturally occurring flavanolignan isolated from *Silybum marianum*. The seeds contain the flavanolignans silybin(1, 2, 3, 4), silydianin and silychristin, which are isomers and lumped together under the collective designation silymarin. Ahmed et al has established that out of these isomers, silybin contains 1, 4-dioxane ring sys-

KEYWORDS

Benzodioxan; 1, 3-Benzodioxane; 1, 4-Benzodioxane; Flavanolignans; Silybin antihapatotoxic.

\[
\text{Silybin (1, 2, 3, 4) } \quad \text{Y=7'' (for 1 & 2) } \quad \text{7'' (for 3 & 4) } \quad \text{8'' (for 1 & 2) } \quad \text{8'' (for 3 & 4) } \\
\]

Silybin-a\(_1\) (1): \( R_1=9''-\text{CH}_2\text{OH}; R_2=R_3=R_4=\text{H}; R_5=\text{C}_6\text{H}_3 \) (3''-OMe, 4''-OH); Silybin-b\(_1\) (2): \( R_1=R_2=\text{H}; R_3=R_4=\text{H}; R_5=\text{C}_6\text{H}_3 \) (3''-OMe, 4''-OH); Silybin-a\(_2\) (3): \( R_1=R_2=\text{H}; R_3=\text{H}; R_4=\text{C}_6\text{H}_3 \) (3''-OMe, 4''-OH); R\(_5=9''-\text{CH}_2\text{OH} \)
tem and has found to be most active antihepatotoxic compound, and consequently concluded that 1, 4-dioxane ring system plays a significant role in elucidating the hepatoprotective activity. Whereas, other two isomers do not contain 1, 4-dioxane ring, and thus do not possess a significant activity. Thus, they have prepared a number of heterocyclic compounds containing 1, 4-dioxane ring system, which have exhibited a significant antihepatotoxic activity. Moreover, many other biological activities namely anti-inflammatory, α-adrenergic blocking, antidepressant, hypolipidemic activity, antagonistic to histamine and diagnostic agent for the detection of adrenaline producing tumors have also been reported. The compounds containing dioxane rings are also of interest for the introduction of a variety of substituents into common skeleton, novel transformations, and can provide new and general routes to a variety of organic molecules. They could also be used as suitable intermediates for the syntheses of enantiomerically pure compounds. A literature survey revealed that a very little work has been done so far in the field of dioxane ring possessing compounds. There are two important characteristics of these compounds namely 1): readily opening to alkylethenes either under thermal or photochemical conditions, and 2): the C–C double bond, if present in the dioxane ring, acts as the enol form of masked acylacetic acids, which are important building blocks in organic syntheses. Hence, these compounds are versatile intermediates in the synthesis of a variety of organic compounds.

In the present article, we have reviewed the work done on 1, 3-and 1, 4-benzodioxene compounds with special emphasis on chemical and pharmacological aspects scattered in the literature.

Nomenclature

Ortho condensation of 1, 3-and 1, 4-dioxane to benzene results in the two possible benzodioxanes, represented by (5) and (6). The numbering system adopted by Chemical Abstracts for the benzodioxanes is indicated in (5) and (6). Thus, (5) is 1, 3-benzodioxane, and (6) is 1, 4-benzodioxane. 1, 3-Benzodioxane (5) is also called the methylene ether of 2-hydroxybenzyl alcohol; 1, 4-benzodioxane is sometimes called 1, 2-ethylenedioxybenzene or pyrocatechol ethylene ether (6a). In the present discussion the convention adopted by Chemical Abstracts will be used.

1, 3-Benzodioxanes

The parent substance (9) was first prepared in 1928 by Chattaway and Calvet[1] by the following scheme. Since the direct condensation of formaldehyde and phenol does not lead to 1,3-benzodioxane; 6-nitro-1,3-benzodioxane (7) was prepared by condensation of p-nitrophenol and formaldehyde according to Borsche and Berkhout[2]. Elimination of the nitro group in (7) by reduction to 6-aminod 1,3-benzodioxane (8) followed by diazotization, and reduction by conventional methods yielded 1,3-benzodioxane. It is colorless, highly refracting oil and is practically insoluble in water[3] but readily soluble in all organic solvents.

The cyclic formal was later prepared by Baker[3] by cyclic etherification of saligenin in presence of methylene sulfate and alkali and by Buehler[4] directly by reacting saligenin and formaldehyde in the presence of acid.

Derivatives of 1, 3-benzodioxane

![Diagram of benzodioxane derivatives](image-url)
The commonest method for preparing substituted 1, 3-benzodioxanes is that of Borsche and Berkhout\[2\] involving the condensation of phenols and aldehydes by acids, generally represented by formulas (10-12). These substituted 1, 3-benzodioxanes (where \(R_4\) = H) as well as 1, 3 benzodioxane itself are easily oxidized to the corresponding 4-keto derivatives by potassium permanganate in acetic acid or by chromic acid. A typical example is the proof of structure of 6-nitro-7-methyl-1, 3-benzodioxane \[13\], which on oxidation with chromic acid gave 4-keto-6 nitro-7-methyl 1, 3-benzodioxane \[14\]. On alkaline hydrolysis \[14\] yielded 4-methyl-5-nitrosalicylic acid \[15\], which was identical with the substance obtained by direct nitration of 4-methylsalicylic acid \[16\]. 1, 3-benzodioxane can be prepared by condensation of \(p\)-substituted phenol with substituent in the ortho position to the phenolic hydroxyl group hinder the formation of 1, 3-benzodioxan ring whereas substituent in the meta position have little or no effect. Chattaway and Goepp\[17\] and Laskelberg and Lavie\[25\] have shown that different products have been obtained by condensation of \(p\)-nitrophenol and formaldehyde depending on the conditions, with excess \(p\)-nitrophenol, \[17\] resulted; with a 2:1 molar ratio of aldehyde to phenol at 80\(^\circ\)C \[18\] resulted; with excess formaldehyde \[19\] was the main product. The structure of the dioxane was demonstrated by degradation and by an alternate synthesis. The following mechanism has been suggested by Chattaway\[9\] for the condensation of \(p\)-nitrophenol and chloral.

In comparing this scheme with the \(o\)-hydroxymethylation of \(p\)-nitroanisole under similar conditions with formaldehyde, Calvet and Majuto\[21\] as well as Ziegler and Simmler\[8\] regarded the \(ortho\) shift from \[20\] to \[21\] as unnecessary and postulate the direct formation of \[21\] as the intermediate which then condenses with more aldehyde to yield the cyclic formal, \[22\] 6, 8-dichloro-1, 3-benzodioxane by the condensation of 2, 4-dichlorophenol with formaldehyde.

This in fact Buehler et al.\[7\] isolated 2-hydroxy-3, 5-dichlorobenzyl chloride \[24\] as a by-product till the preparation of is in agreement with the proposed intermediate \[21\], the benzyl alcohol being converted into benzyl chloride in hydrochloric acid. Ziegler and Simmler\[8\] have demonstrated that 2-hydroxy-3, 5-dichlorobenzyl alcohol reacts with formaldehyde to yield \[23\] in the presence of hydrochloric acid. Several patents\[26\] have used the reaction of phenol, formaldehyde, and hydrochloric acid to prepare 6, 8-dichloromethyl-1, 3-benzodioxane.
Saligenin, 2-hydroxybenzyl alcohol, and substituted saligenins (25) have been condensed with various aldehydes to form 1, 3-benzodioxanes in a manner similar to the above reactions. These 1, 3-benzodioxane derivatives are substituted only in the 2-position or possibly carry different substituent in the 2- and 4-positions, which is not so in the direct condensation of phenols and aldehydes by acids. In their work, on the structure and mode of formation of disalicyl aldehyde, dibenzo-2,6,9-bisdioxane (26a) (Ring Index No. 2682 or 6,12-epoxy-6,12-dibenzo [b, f] [1,5] dioxocin). Adams, Fogler, and Kreger[27] have condensed benzaldehyde with saligenin to obtain 2-phenyl-1,3-benzodioxane (26, X=Y=H, R=C_6H_5) according to the general equation given above. In a later study of this condensation;

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{CH}_2\text{OH} \\
\text{OH} & \quad \text{CH}_2\text{OH} \\
\text{HO} & \quad \text{CH}_2\text{OH} \\
\text{CO} & \quad \text{COOH}
\end{align*}
\]

(27)

Adams, Sloan, and Taylor[28] have shown that certain substituted benzaldehydes condense with saligenin and substituted saligenins. The reaction was shown to be quite general and the acid catalyst necessary for the saligenin-benzaldehyde condensation was not necessary with the substituted compounds. Cinnamic aldehyde condenses like aromatic aldehydes, but simple aliphatic aldehydes do not condense with saligenin to give 1, 3-benzodioxanes under the same conditions. The 2-aryl-1, 3-benzodioxanes have been prepared in good yields (60-95%). Ziegler[29] used this reaction with hydrochloric acid as catalyst to prepare 2-phenyl-6-methyl-8-hydroxymethyl-1, 3-benzodioxane ((26), R=C_6H_5, Y=CH_2OH), as well as the corresponding compounds, where X=cyclohexyl, chloro, and tert-butyl. With stronger hydrochloric acid the corresponding chloromethyl-1,3-benzodioxanes have resulted. Condensation of bis-(3,5-bishydroxymethyl-4-hydroxy phenyl)-methane (27) with benzaldehyde gave bis-6-(2-phenyl-8-hydroxymethyl-1, 3-benzodioxanyl) methan (28) in the presence of 1N hydrochloric acid. Other methods have been reported in the literature for preparing 1, 3-benzodioxanes. Firstly the intermediate substituted 2-hydroxybenzyl alcohol or benzyl chloride was prepared by condensing various para-substituted phenols and formaldehyde with alkali or acid, which was then condensed with formaldehyde or trioxymethylene to give the cyclic formals. A similar set of reactions involving the condensation of p-nitrophenol and methyl alcohol in presence of hydrochloric acid was employed by Mehta and Ayyar[20] and by Buehler, Deebel, and Evans[32] to give 2-hydroxy-6-nitrobenzyl chloride, which on further condensation with formalin, hydrochloric acid, heating at 100°C gave 5-nitro-1, 3-benzodioxane.

Other methods involving salicylic acid are reported by DuPont[33] and by Mowry, Yanko and Ringwald[34]. The dupont method involved the reaction of disodium salicylate with phosgene and may be looked upon as displacement of chloride ion by phenoxide and benzoate anions, yielding 2, 4-diketo-1, 3-benzodioxane(29). Reaction of (29) with methyl alcohol yielded (30)[35].

\[
\begin{align*}
\text{ONa} & \quad \text{Cl} \\
\text{COONa} & \quad \text{Cl} \\
\text{O} & \quad \text{ROH} \\
\text{O} & \quad \text{OCOOCH}_3 \\
\text{O} & \quad \text{COOH}
\end{align*}
\]

(29) (30)

Mowry, Yanko and Ringwald[34] have shown that 2-methyl-4-keto-1, 3-benzodioxanes (32) were the products of the reaction of salicylic acids (31) and vinyl
acetate in the presence of mercuric acetate, where \(X=H, NO_2, Cl, Br,\) and \(Y=H, OCH_3\) and \(CH_3\).

The reaction is assumed to proceed in two steps: first the formation of acetoxethyl salicylate, and second the cyclization of the intermediate with elimination of acetic acid. They have also shown that the intermediate alpha-acetoxethyl salicylate, prepared from sodium salicylate and \(\alpha\)-chloroethyl acetate, cyclized in good yield to give 2-methyl-4-keto-1, 3-benzodioxane. The reaction of sodium salicylate and chloromethyl acetate gives acetoxymethyl salicylate, which on cyclization yielded 4-keto-1, 3-benzodioxane. The reaction has been extended by the substitution of isopropenyl acetate for vinyl acetate with the subsequent formation of 2, 2-dimethyl-4-keto-1, 3-benzodioxanes, although the yields are poor. A similar reaction had been reported by Wallach[36] and Boeseken[37] who found that the chloralide of salicylic acid, 2-trichloromethyl-4-keto-1, 3-benzodioxane, was obtained in poor yields by heating salicylic acid with excess of chloral. Hexahydro-1, 3-benzodioxane was reported by Mikeska and Arundale[38] to be the product of a process involving the condensation of cyclohexene and formaldehyde at 60-80°C under pressure in the presence of sulfuric acid.

Reactions and properties of 1, 3-benzodioxane

Transformations of substituents on the benzene ring of 1, 3-benzodioxanes have been carried out by conventional methods. The 6-nitro derivative was reduced to the 6-amino derivative with sodium and acetic anhydride, zinc and hydrochloric acid, iron and hydrochloric acid[10], tin and hydrochloric acid. 6-Amino-1,3-benzodioxane can be diazotized in the usual way and reduced to 1,3-benzodioxane (5) coupled with various phenols with formation of various azo dyes, or the amino group may be replaced by a halogen or nitrile group by the Sandmeyer reaction[10]. The 6-sulfonic acid has been transformed to the sulfonyl chloride and the sulfonamide by conventional methods[19].

Substitution in the aromatic ring of 1, 3-benzodioxanes have shown the relative stability of its heterocyclic ring and occurred in the 6 position; disubstitution has led to 6, 8 derivatives. Nitration of 1, 3-benzodioxane was found[41] to yield 6-nitro- and 6,8-dinitro-1, 3-benzodioxane as well as some picric acid, fuming nitric acid or nitric acid with urea nitrate[40] gives the 6,8-dinitro compound. On nitration the 6-nitro derivative or the 6-sulfonic acid yielded the 6,8-dinitro compound. Chlorination or bromination of 6-nitro-1, 3-benzodioxane[17] yielded 6-nitro-8-chloro- or 8-bromo-1, 3-benzodioxane. Bromination of 1, 3-benzodioxane itself yields 6-bromo-1, 3-benzodioxane.

The 2-aryl-1, 3-benzodioxanes[28] are very stable toward alkali but unstable toward acid, yielding 2-hydroxybenzyl alcohol and aldehydes. Other 1,3-benzodioxanes containing electron-attracting substituents such as NO_2, COOH, or SO_3H in the 6 and/or 8 positions[14,22] are susceptible to alkaline fission of the heterocyclic ring. This was explained by nucleophilic attack of the base on the 9-carbon atom, which was rendered sufficiently, cationoid by the electron-attracting substituents. The presence of electron-donating groups (X=NH_2, OH, OCH_3) rendered the 9-carbon atom anionoid, and the heterocyclic ring was thus made resistant toward anionic attack. For example, the action of alcoholic potassium hydroxide on 6-amino-2, 4-bistrichloromethyl-1, 3-benzodioxane (33) yielded 6-amino-2, 4-bis dichloromethylene-1, 3-benzodioxane (34) with the elimination of two molecules of hydrogen chloride.

An azo group conferred similar stability. The action of potassium cyanide, sodium hydroxide, or sodium acetate on 6-nitro-2, 4-bistrichloromethyl-1, 3-benzodioxane resulted in the formation of 6-nitro-2-chloromethyl-4-dichloromethylene-1,3-benzodioxide. It was not possible to remove a second molecule of hydrogen chloride, since the 2-hydrogen atom was not sufficiently activated. Reduction of the benzodioxide ring by zinc and acetic acid was demonstrated by
Meldrum and Tata\cite{16,44} who reduced 6-substituted 2, 4-bistrichloromethyl-1,3-benzodioxanes to the corresponding 5-substituted hydroxy (β,β-dichloroethyl) benzene. In all the 2, 4-bistrichloromethyl-1, 3-benzodioxanes mentioned above, cis-trans isomeric forms are possible, but these have not been isolated. In the case of 6, 6'-di-(2,4-bistrichloromethyl)-1,3-benzodioxanyl sulfone obtained by condensation of 4,4'-dihydroxy diphenylsulfone and chloral in the presence of sulfuric acid\cite{45}, wherefrom three of the six possible cis-trans isomerides have been isolated by fractional crystallization. They are described as being well crystallized compounds closely resembling each other in their properties, except that they melt at 215°C, 240°C and 248°C respectively. Each depresses the melting point of the other two. These isomerides have been designated as α-, β- and γ-6, 6'-di-(2, 4-bistrichloromethylene)-1, 3-benzodioxanyl sulfone in the order of increasing melting point. Each isomeride was converted into the same 6, 6'-di-(2, 4-bisdichloromethylene) 1, 3-benzodioxanyl sulfone, by the theoretical amount of alcoholic potassium hydroxide. When α-, β- or γ-isomerides are reacted with dilute alcoholic potassium hydroxide have resulted in the corresponding isomeric α-, β- and γ-6, 6', 2-trichloromethyl-4-dichloromethylene)-1, 3-benzodioxanyl sulfones, melting at 241 and 250°C respectively.

The amino-1, 3-benzodioxanes may be converted into the greenish blue dyes of the anthraquinone series as described by Lubs and Johnson\cite{46}. Debromination of 6-hydroxymethyl-8-bromo-1, 3-benzodioxane-5-carboxylic acid lactone\cite{47} as shown to proceed in alcoholic solution by Busch’s method\cite{48} with hydrazine hydrate, aqueous potassium hydroxide, and palladium on calcium carbonate catalyst, producing 6-hydroxymethyl 1, 3-benzodioxane-5-carboxylic acid lactone. The dechlorination of 6-hydroxymethyl-8-chloro-1, 3-benzodioxan-7-carboxylic acid lactone was accomplished by a modification of Busch and Stove’s method\cite{49} with alcoholic potassium hydroxide, hydrogen at 50 pounds pressure and palladium on calcium carbonate catalyst.

1, 4-Benzodioxanes

The parent substance (36) was first prepared by Vorlander\cite{50} from pyrocatechol and ethylene bromide in the presence of sodium methoxide or potassium hydroxide.

This was repeated by Gattermann\cite{51} who showed that 1, 4-benzodioxane underwent the Gattermann reaction, yielding the 1, 4-Benzodioxane-6-aldehyde and by Moureu\cite{52} who increased the yield by working under a hydrogen atmosphere. In 1965 Ghosh\cite{53} improved the method further by using potassium carbonate, copper bronze, and glycerol heated at 190-200°C to obtain a 66% yield of 1,4-benzodioxane, as compared to the 33% yield of Vorlander. By the Wurtz reaction pyrocatechol dichloromethyl ether in benzene, Sabetay and Sandulesco\cite{54} obtained 1, 4-benzodioxane in 32% yield.

Becker and Barthell prepared the intermediate β-hydroxyethyl-2-hydroxyphenyl ether from pyrocatechol, ethylene oxide, and sodium hydroxide at 8°C. This on distillation with phosphorus pentoxide cyclized to 1, 4-benzodioxane. 1, 4-benzodioxane is a heavy liquid distilling at 216°C, have a very persistent aromatic odour. It is insoluble in water but soluble in most organic solvents.

Derivatives of 1, 4-benzodioxane

The first derivative of 1, 4-benzodioxane, (6-carboxyl-1, 4-benzodioxane) was prepared by Fittig and Macalpine\cite{56} from 4-carboxy pyrocatechol, ethylene bromide and potassium hydroxide. By using this reaction Maggati\cite{57} later prepared 5-hydroxy 1, 4-benzodioxane from pyrrogallol and ethylene bromide. 2,3-diketo-1,4-benzodioxane was prepared by Ghosh\cite{58} by the reaction of pyrocatechol and oxalyl chloride in pyridine in almost quantitative yield, although dehydrating agents such as phosphorylchloride, orthophosphoric acid and acetic anhydride were unsuccessful in condensing pyrocatechol and oxalic acid. Bischoff and Hedenstrom\cite{58} obtained 2, 3-diketo 1, 4-benzodioxane from ethyl oxalyl chloride and the monosodium salt of catechol. 2-Keto 1, 4-dioxane was also prepared by Ghosh\cite{58} by cyclizing ethyl α-(2-hydroxyphenoxo) acetate with boiling concentrated hydrochloric acid. 2-
Hydroxymethyl-1, 4-benzodioxane was prepared by Moureu by the Vorlander method from pyrocatechol and dibromohydrin in the presence of sodium ethoxide. From the reaction of pyrocatechol and epichlorohydrin with potassium hydroxide, Fourneau, Maderni, and de Lestrangé obtained 2-hydroxymethyl-1, 4-benzodioxane, which with thionyl chloride gave 2-chloromethyl-1, 4-benzodioxane. Further reaction of the chloro derivative with primary or secondary amines resulted in various amines which possesses a paralyzing action on the sympathetic nervous system. Geigy, Grun, and de strange have applied the same reactions to various other substituted pyrocatechols. Jean-Robert Labrosse has shown that catechol reacts with various propargylic carbonates in the presence of a palladium catalyst and a chiral atropoisomeric diphosphine to give 2-alkylidene-3-alkyl-1, 4-benzodioxanes in good yields and 59-67% enantiomeric excess.

X. Jing et al. have synthesized a number of benzodioxane compounds using the palladium-catalyzed etherification of aryl halides by employing triphenylphosphine ligands. This method was used as key step in the synthesis of two natural products isoamericanol-A and isoamericanin-A. 1, 2-Ethanediol and o-dibromobenzene are difficult to be coupled to get benzodioxane in the presence of CS2 CO3 and catalyzed amount of PdCl2, but in the presence of triphenylphosphine, the yield of benzodioxane had improved significantly.

Ethyl-1, 4-benzodioxan-2-carboxylate was prepared by condensation of ethyl 2, 3 dibromopropanoate with catechol in the presence of anhydrous potassium carbonate.

Similarly ethyl-3-methyl-1, 4-benzodioxan-2-carboxylate was prepared by condensation of ethyl-2, 3-dibromobutyrate, with catechol in the presence of anhydrous potassium carbonate. The ester was saponified to give benzodioxancarboxylic acid which on treatment with thionyl chloride afforded the acid chloride.

N-Hydroxyureas based on the 1,4 benzodioxane template were prepared by Yoshitaka Satoh from appropriately substituted 1, 4-benzodioxane-2-
methanols as the key intermediates. Regiocontrolled
synthesis of 7-substituted 1,4-benzodioxan-2-
methanols (45) was carried out using 5-substituted sali-
cylaldehyde (43) as the starting materials. Alkylation of
(43) with epibromohydrin and subsequent Baeyer-
Villiger oxidation with m-CPBA yielded the formyloxy
derivative (44). Treatment of (44) with hydroxide re-
sulted in hydrolysis of the formate and concomitant clean,
regioselective intramolecular epoxide opening to their 1,4-
benzodioxane derivative (45). When MMPP was used
in the oxidation step, free phenols instead of their for-
mates were isolated upon workup, compound (45)
was converted to the corresponding N-hydroxyurea
(47). It should be noted that the condensation of the hydroxy-
lamine (46) with methyl isocyanate yielded N-hydrox-
yurea derivative (47), uncontaminated with the bis-
adduct, under the same conditions, the regioisomeric
benzodioxane (47) was prepared from the same inter-
mediate (43). Thus (43) was first protected with benzyl
bromide and subjected to Bayer-Villiger oxidation with
hydrogen peroxide. The phenol thus formed was treated
with epibromohydrin to give tris ether (48). CATAL-
ytic hydrogenation of (43) with palladium hydroxide (atm.
H₂ in ethyl acetate) gave the debenzylated phenol, which
cyclizes upon treatment with aq. base to yield (49).
Compound (49) was transformed into the N-hydroxy
ureas (50).

α-Halo Michael acceptors react with catechol in
aprotic solvents in the presence of potassium carbon-
ate to form 2-substituted-1, 4-benzodioxanes[72]. Cis
β-alkyl and β-acyclic α-halo Michael acceptors yield
primarily cis 2, 3-disubstituted 1, 4-benzodioxanes,
whereas trans 2, 3-disubstituted isomers predominate
when catechol is treated with trans β-alkyl α-halo
Michael acceptors. It is therefore inferred that the re-
action proceeds via a cis Michael addition of catechol
monooanion, followed by intramolecular nucleophilic
displacement of halide from the newly generated sp³ α-
carbon by the remaining catechol oxygen. Ethyl 1, 4-
bromobut-2-enoate, formed by isomerization of ethyl
2-bromobut-2-enoate during the course of the reac-
tion of the latter with catechol, is believed to be the
source of the isomeric ethyl 1, 4-benzodioxanyl-2-ac-
etate (51) isolated as a minor product.

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whereas trans 2, 3-disubstituted isomers predominate

Equimolar amounts of catechol and methyl 4-chlorobutynoate in boiling anhydrous acetone in the presence of anhydrous potassium carbonate or in cold N,N-dimethylformamide in the presence of sodium hydride yielded three 1, 4-benzodioxinic products[74] E(56) and Z(57) isomers and the endo isomer (60). They are easily isolated in pure form from the reaction mixture by column chromatography in the 2:1:1 ratio. Under the same experimental conditions (acetone, potassium carbonate, reflux) catechol reacts with (59) to yield only the expected ester (60).

**Reactions of 1, 4-benzodioxane**

Nitration of 1, 4-benzodioxane was first carried out by Vorlander[50] who obtained 6-nitro-1, 4-benzodioxane. Ghosh[53] has shown that 1, 4-benzodioxane may be dinitrated directly by sulfuric acid and nitric acids, or by further nitration of the mononitro derivative with the same nitrating mixture or with nitric acid alone[75] to 6, 7-dinitro-1, 4-benzodioxane. The 6, 7, 8-trinitro derivative was obtained by nitration of 1, 4-benzodioxane with mixtures of acetic, nitric, and sulfuric acids[53] or by further nitration of the dinitro derivative with sulfuric and nitric acid[67]. Each step proceeded in good yield. Heertjes, Dahmen, and Wierda[76] repeated this work and have shown that 5, 6, 7, 8-tetranitro-1, 4-benzodioxane was also formed. 6-Methyl-1, 4-benzodioxane was less readily nitrated than the corresponding dimethyl or diethyl ethers of 4-nitrocatechol. Heertjes and co-workers have studied the substitution reactions of a number of 1, 4-benzodioxane derivatives intensively. Transformations of the products thus obtained have made several derivatives, of the parent substance available.

Bromination of 1, 4-benzodioxane[53] with bromine in refluxing acetic acid has given 6-bromo-1, 4-benzodioxane, and with excess bromine the 6, 8-dibromo derivative is formed. The Blanc chloromethylation re-
benzodioxane-6-carboxylic acid.

Other Friedel-Craft reactions with 1, 4-benzodioxane have been reported by Tomita.[81] Phthalimidoacetyl chloride and aluminum chloride in carbon disulfide gave 6-phthalimidoacetyl-1, 4-benzodioxane, which on hydrolysis resulted in the formation of 6-aminoacetyl-1, 4-benzodioxane. The position of the acetyl group was shown by oxidation of the aminoacetyl-1, 4-benzodioxane to 1, 4-benzodioxane 6-carboxylic acid. From hippuryl chloride under the same conditions 6-benzoylaminoacetyl-1, 4-benzodioxane was obtained. Reduction of 6-nitro-1, 4-benzodioxane to the 6-amino derivative by tin and hydrochloric acid,[52], by stannous chloride and hydrochloric acid[82] in water, acetone, or chloroform, or by hydrogen sulfide, or sodium hydrosulfate in alkaline solutions all gave poor results. Stannouschloride and hydrochloric acid reduction followed by electrolytic removal of the stannic ions gave better results, and the best method, direct cathodic reduction gave 65% yields of 6- amino-1, 4-benzodioxane. The free amine is clear, colorless, thick oil that readily oxidizes in contact with air. Its hydrochloride was easily diazotized and coupled by the usual method to produce azo dyes with good levelling properties and which dyes in brilliant clear colors. Reaction of 5-cyano-1, 4-benzodioxane[83] with ethylmagnesium bromide and subsequent hydrolysis gave 5-propionyl-1, 4-benzodioxane. In a study of the cleavage of the heterocyclic ring of 1, 4-benzodioxane derivatives Robinson and Robinson[61] found that 3, 5-dinitro-2, 4-diamino-β-

trinitro-1, 4-benzodioxane was treated with ammonia. The 1, 4-benzodioxane ring was cleaved on boiling with hydriodic acid and is stable in hot aqueous or alcoholic ammonia.

S.S.Mochalov[83] has shown that bromination of 6-cyclopropyl-1, 4-benzodioxane (62) occurs with concerted orientation of the ethylenedioxy group and the cyclopropyl radical for the least sterically hindered position of the aromatic ring. Nitration of 6-bromo-7-cyclopropyl-1, 4-benzodioxane did not lead to products of substitution of the hydrogen atom in the 5 or 8 position of the 1, 4-benzodioxane, but rather to the nitrodebrimation product: 7-nitro-6-cyclopropyl-1, 4-benzodioxane. The anomalous behavior of the bromo-substituted benzodioxane was explained by the predisposition of the carbon atom bonded to the bromine toward ipso attack by an electrophile.

S.S.Mochalov[83] has shown that he reaction of 6-bromo-7-cyclopropyl-1, 4-benzodioxane (63) with N₂O₄ in methylene chloride does not affect cyclopropane ring and forms the nitro debrominated product (ipso-substitution).

The same reaction of 6-nitro and 5, 6-dinitro-7-cyclopropyl-1, 4-benzodioxanes afforded the products only with a modified three membered ring. The difference in the reaction paths of the studied cyclopropyl benzodioxanes with N₂O₄ explained by the different ratio of substrate to one-electron oxidant, the nitrosyl cation. The reaction of 6-cyclopropyl-1, 4-benzodioxane with N₂O₄ led to the formation of only the nitroaromatic derivative in which the cyclopropane ring was retained.

It was proposed that the different behavior of these cyclopropyl-containing reactants is related to the occurrence of processes caused by the different reactivity of the starting materials with respect to one-electron
oxidation initiated by the nitroso cation.

**Pharmacological action**

The benzodioxane derivatives have been screened for various biological activities. Some important pharmacological activities have been summarized here.

**Antihapatotoxic activity**

The flavanolignans isolated from Silybum marianum namely Silybin have been reported to possess a potent antihapatotoxic activity, which contain 1, 4-dioxan ring. Ahmed et al.[85] has thus postulated that 1, 4-dioxane ring compounds could play an important role to exhibit a significant antihapatotoxic activity. Ahmed et al.[85] have therefore, synthesized a series of 3', 4'(1'', 4''-dioxino) flavone, 3', 4' (2-hydroxymethyl, 1'', 4''-dioxino) flavone (67), 7,8 (1', 4''-dioxino) coumarin (68), 7, 8 (2'-hydroxymethyl-1', 4''-dioxino) coumarin and reported its antihapatotoxic activity.

Ahmed et al.[86] has synthesized and reported antihapatotoxic activity of chalcones containing 1,4-dioxane ring system (69) and found 2-hydroxy-4-methoxy-3', 4'-(2''-hydroxy methyl-1'' , 4''-dioxino) chalcone and 2-hydroxy-3', 4-dimethoxy-3', 4'-(2''-hydroxy methyl-1'' 4''-dioxino) chalcone to be the most potent compound in this series.

**5-Lipoxygenase inhibitors**

Satoh Yoshikata[71] has prepared a number of N-hydroxyurea based on the 1,4-benzodioxane template and the substituent having 7-phenoxy or 7-p-fluorophenoxy was found to be a potent 5-LOX inhibitor.

**α₂ Adrenoreceptor antagonist**

3-Aminomethyl-1, 4-benzodioxane and its N-substituted derivatives shown an inhibitory effect[88] on motor nerve centers as well as adrenaline antagonizing action[89], with the monosubstituted derivatives the toxicity rises with the molecular weight, and the adrenaline antagonizing action reaches a maximum between ethyl and propyl-N-substituted-3-aminomethyl-1, 4-benzodioxanes. In the tertiary series the diethyl derivative is the most toxic and has the greatest anti-adrenaline action. Substitution by piperidine increases the toxicity and diminishes the anti-adrenaline action. These derivatives were also found to be antagonistic to histamine[90] and they prolong the effects of paraldehyde and barbiturates[91].

**D₂ antagonist/5-HT₁A partial agonist activity**

A series of N-substituted-1-(2, 3-dihydro-1, 4-benzodioxino-2-y1) methylamine derivatives with D₂ antagonist/5-HT₁A partial agonist activity has been prepared by A.M. Birch et al.[92] as atypical antipsychotic agents.

**Anti-inflammatory activity**
Hypolipidemic activity

Aldo salimbeni and Elso Manghisi have studied the hypolipidemic activity of compounds containing benzodioxane ring system. In this connection they synthesized and evaluated ethyl (1,4-benzodioxan-2-yl) carboxylate and its 6-and 7-chloro derivatives for anti-hyperlipidemic activity and found some of these derivatives effective in lowering the triglycerides.

In addition, 2-Piperidylmethylbenzodioxane (Benodiane or Piperoxan) is used as a diagnostic agent for the detection of adrenaline producing tumors (Pheo-chromocytoma).

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