ADVANCES IN CHEMISTRY IN THE BENZO-1,4-DIOXANE SERIES

(REVIEW)

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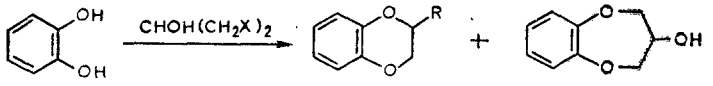
The literature data on methods for the preparation of benzo-1,4-dioxane derivatives and their chemical and physical properties, spectral characteristics, and biological activity are correlated.

Benzodioxane [1, 2] and some of its derivatives [2-4] have been known since the last century, but interest in derivatives of this heterocyclic system increased only after the publication in 1933 of papers by Fourneau and Bovet, who found that 2-alkylaminomethylbenzodioxanes have adrenoblocking properties [5, 6].

Syntheses of Benzodioxane Derivatives

Practically all of the methods for the preparation of benzodioxanes are based on the construction of the heteroring from pyrocatechol or o-quinone. The reaction of pyrocatechol (I) with 1,2-dibromoethane in alkaline media gives benzodioxane (II, R = H) in 30-50% yield when the reaction is carried out in aqueous alkali solution [1, 7, 8] or in alcohol solutions of alkoxides [2, 9, 10] and in 60-75% yield when the reaction is carried out in glycol or glycerol in the presence of sodium or potassium carbonates [11-15] (sometimes with the use of a copper catalyst [12]). Dibromoethane can be replaced by dichloroethane [16]. Aromatic-ring-substituted benzodioxanes – acyl [2, 10, 17-21], carboxy [3, 22, 23], hydroxy [4, 10, 24-26], alkoxy [26-28], halo [19, 23, 29], nitro [30, 31], alkyl [32], and other derivatives [33-35] – have been obtained from the appropriate pyrocatechols, whereas heterocyclic-ring-substituted benzodioxanes have been obtained by the use of other 1,2-dihalides – 1,2-dibromopropane [33], esters [36-50] or nitriles [51-54] of α,β- or β,γ-dibromo-substituted acids, α,β-dibromo ketones [43, 47, 51, 55-60], and others [61] – in place of 1,2-dibromoethane.

Glycerol dihalohydrins react with pyrocatechol in alkaline media to give 2-hydroxymethylbenzodioxane (II, R = CH_2OH) in 56% yield and a small amount of a benzodioxepine derivative (III) [2, 62]:



I II III

X = Cl, Br; R = CH_2OH

Alcohol II (R = CH_2OH) was also obtained in 70% yield by reaction of pyrocatechol with epichlorohydrin in aqueous potassium hydroxide solution [5, 63, 64]. A mixture of isomers is usually formed from substituted pyrocatechols [65-76], but methods that make it possible to obtain individual compounds are also known [67, 77-81].

Benzodioxane is obtained in quantitative yield by reaction of aqueous alkali on pyrocatechol β-bromoethyl ether (the kinetics of the cyclization have been studied) [82], but the cyclization of pyrocatechol bis-(chloromethyl) ether under the influence of sodium metal gives benzodioxane in only 32% yield [83].

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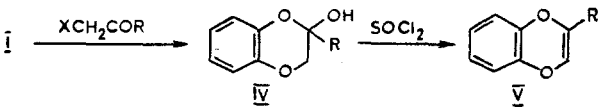
Pyrocatechol β-hydroxyethyl ethers are cyclized to benzodioxanes in the presence of phosphoric anhydride [84] or oxalic acid [85] (the yields are up to 60%) [84]:

R = H, Alk, C_6H_5

5,6,7,8-Tetrafluorobenzodioxane is formed in 45% yield by refluxing a solution of β-hydroxyethoxypentafluorobenzene in dimethylformamide (DMF) with potassium carbonate [86].

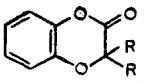
Benzodioxane was obtained in 59% yield by alkylation of pyrocatechol ethylenesulfate in aqueous alkali [87], but the yield of benzodioxane did not exceed 1% in the reaction of 1,2-bisdiazoethane with pyrocatechol in ether [88]. [The yield of II ($R=COOC_2H_5$) is also low in the ring expansion of benzodioxol with diazoacetic ester [38].] The preparation of benzodioxane II ($R=OC_2H_5$) by reaction of pyrocatechol with chloroacetaldehyde ethylacetal has been described [89]. Hydroxy derivatives IV are formed in 40-47% yields in the reaction of pyrocatechol with halomethyl ketones in alkaline media and are dehydrated under the influence of thionyl chloride to V [89]:



X = Cl, Br; R = CH_3, C_6H_5

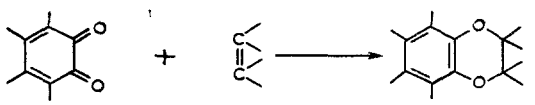
Compound V ($R=C_6H_5$) is also obtained by vacuum distillation of 1-hydroxy-2-phenacyloxybenzene [90]. 2-Alkoxy-2-vinylbenzodioxanes are formed in 42-50% yields by heating pyrocatechol with 1,4-dichloro-2-butyne and potassium carbonate in alcohol solutions, but the mechanism of the reaction has not been accurately established [91].

2-Ketobenzodioxane derivative VI ($R=C_6H_5$) was obtained in 25% yield by reaction of pyrocatechol with diphenylchloroacetyl chloride and potassium carbonate in acetone [92] or with benzylic acid [92, 93]. Compound VI (R = H) was obtained by cyclization of o-hydroxyphenoxyacetic acid [12, 85]. A similar method was also used to synthesize a number of its derivatives [94-96], whereas reaction of pyrocatechol with oxalyl chloride or oxalic acid esters gives 2,3-diketobenzodioxane [12, 97].

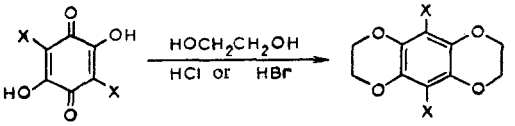


VI

The reaction of o-quinones (tetrahalo-substituted compounds have been most frequently used) with unsaturated compounds containing an activated multiple bond – styrene [98], stilbene [98-100], 1,1-diphenylethylene [99], 1,4-dimethyl- [101], 2,3-dimethyl- [102], or 1,4-diphenylbutadiene [99], tetramethylethylene [102], 1,2-diphenylacetylene [99], allenes [103], ketenes [92, 104, 104], vinyl ethers [98, 99], and other compounds [106] – usually give benzodioxane derivatives in high yields when solutions of the starting materials in inert solvents are heated or irradiated with UV light. α-Diazo ketones, which form ketenes during thermolysis or photolysis, can be used [104, 105, 107].



Closing of the benzodioxane ring is also observed when dihalodihydroxy-p-quinones are heated with ethylene glycol in the presence of acids [108]:



X = Cl, Br

Chemical and Physical Properties and Spectral Characteristics of Benzodioxane Derivatives

Properties of the Heterocyclic Fragment. The C—O bond in benzodioxanes is stronger than the ether bond in the methoxy group, and 4,5-ethylenedihydroxy-o-quinone is therefore formed when VIII (R = R' = OCH_3) is oxidized with nitric acid, whereas heating methoxy derivatives with aluminum chloride [109], hydrobromic acid [26, 27, 110, 111], or pyridine hydrochloride [110, 112] serves as a preparative method for the synthesis of hydroxybenzodioxanes. However, cleavage of the dioxane ring of 5,6,7,8-tetrafluorobenzodioxane by aluminum chloride [86] and of 5,6,7-trinitrobenzodioxane by ammonia [113, 114] has been described.

The 2-substituted benzodioxane ring is opened relatively easily. Thus, derivative II (R = CH_2OH) is converted to 1-methoxy-2-acetonyloxybenzene [94] when it is refluxed in acetone in the presence of dimethyl sulfate and potassium carbonate.

The ring of 2-ketobenzodioxanes is cleaved by alkylmagnesium halides [85], $LiAlH_4$ [94], and, in some cases, by refluxing with water [96], but the reduction of derivative VI (R = H) by means of $LiAlH_4$ to IV (R = H) in yields higher than 50% has nevertheless been described [85].

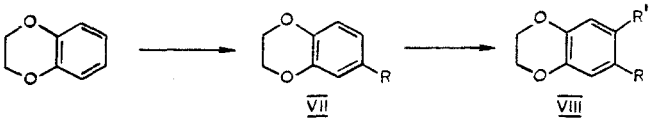
The chlorine atom in 2-chloro-2-methylbenzodioxane is distinguished by the exceptional lability typical of α-halo ethers. It is hydrolyzed instantaneously by water and is readily exchanged by a methoxy or amino group; the latter is readily hydrolyzed by water [115].

The reaction of chloro ketone II (R = $COCH_2Cl$) with sodium acetate in acetic acid, with alcohols in the presence of alkoxides [116], or with sodium formate and ethylene glycol gives the acetate or ethers of 2-hydroxy-2-acetylbenzodioxane and, respectively, its ethyleneketal [117]. Other 2-haloacyl derivatives also react similarly [57, 118].

2-Vinylbenzodioxol is formed from iodide II [R = $CH_2\overset{+}{N}(CH_3)_3$] by Hofmann cleavage (as a result of contraction of the heterocyclic ring) [89, 119]. The action of alkaline agents on II (R = CH_2Cl, CH_2, Br, and $CH_2OSO_2C_6H_4CH_3$-p) gives 2-methylenebenzodioxane, which can be isomerized to derivative V (R = CH_3) [89, 94, 119].

According to the NMR spectral data, the heterocyclic fragment of many 2-substituted benzodioxanes (II) has a pseudochair conformation, and the substituent in the 2 position has primarily a pseudoaxial orientation [52, 119, 120].

Substitution Reactions in the Aromatic Ring. Facile electrophilic substitution reactions are characteristic for benzodioxane. Thus acid deuteration [9, 121], halogenation [12, 29, 49, 90, 109, 122, 123], chloromethylation [14, 15, 124-126], acylation [7, 8, 10, 32, 67, 77, 78, 81, 127-147], nitration [1, 2, 11, 13, 29, 87, 122, 148-151], and sulfonation [148] give 6-substituted derivatives VII, which contain only a slight amount of 5-substituted isomers IX [20, 142, 145, 149], and the second substituent enters the 7 position regardless of the types of the first (R) and second (R') substituents [12, 13, 15, 19, 29, 30, 32, 33, 48, 109, 114, 121, 131, 135, 142, 147-149, 152-159]:



VII VIII

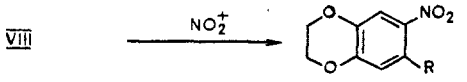
The sulfo group enters the 8 position only in the sulfonation of VII (R = NO_2) [31, 148], whereas nitro derivative VII (R = NO_2) is formed in the nitration of sulfonic acid VII (R = SO_3H) [148], and this probably can be explained by the reversibility of the sulfonation reaction.

In the reaction of trifluoroacetic acid with 5- or 6-tritio derivatives IX and VII (R = T) the tritium atom replaces the proton, and the reaction rate is higher for the 6-substituted isomer (VII) [160].

The −I and, respectively, +M effects of the ethylenedioxy group are evidently responsible for the deactivation of the 5 and 8 positions and the activation of the 6 and 7 positions of the benzodioxane ring with respect to electrophilic reagents [121, 160].*

*Only isomer IX (R = Li) is formed by the action of butyllithium on benzodioxane [160].

Further substitution in 6,7-disubstituted benzodioxanes VIII cannot always be accomplished. Thus deuteration of compounds of the VIII (R = R' = D, CH_3 [121]) type, and their chlorination (R = R' = Cl [99]), bromination (R = R' = Br [29, 99], C_2H_5 [152]), acetylation (R = R' = C_2H_5 [142]), and nitration (R = R' = Cl [29], Br [23, 29], NO_2 [12, 13, 114]; R = NO_2, R' = Br [29], $NHCOCH_3$ [30], and C_2H_5 [149]) give their 5-, 8-, or 5,8-substituted derivatives, but in other cases the 7 (or 6) substituents (R') are replaced by a nitro group during nitration [149, 158]:



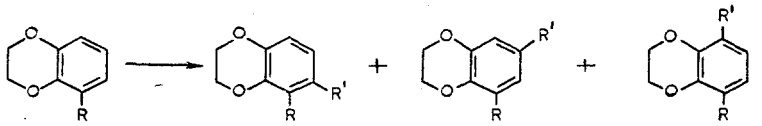
VIII

a R = Br, NO_2; R' = COOH[149]

b R = C_2H_5; R' = Br, C_2H_5, $COCH_3$, COOH[158]

ω-Nitro derivative VIII (R = NO_2, R' = $COCH_2NO_2$) is formed in the nitration of nitro ketone VIII (R = NO_2, R' = $COCH_3$) with a mixture of nitric, sulfuric, and acetic acids [149].

The direction of the substitution reactions of isomers IX depends on the substituent already present (R) and the entering substituent (R'):



IX X XI XII

Halogenation [45, 111, 161, 162] or acylation [110, 111] or 5-hydroxy(alkoxy or acyloxy)derivative IX gives mixtures of 6- and 8-substituted compounds (X, XII), in which isomers XII predominate in the case of 5-alkoxy derivatives [110, 111]. In the bromination of phenol IX (R = OH), both reaction products (X, XII: R = OH, R' = Br) are formed in a ratio of 1 : 1, whereas in the case of IX (R = $OCOCH_3$) the 6-bromo-substituted compound (X, R' = Br) predominates [162]. The nitration of 5-alkoxy derivatives (IX) gives 7-nitro-substituted XI (R' = NO_2), which contains only a very small amount of isomers X [111, 163], whereas, on the other hand, more of isomer X than of XI is formed in the case of nitration of IX (R = $OCOCH_3$) [162, 163]. The nitration of IX (R = NO_2) gives a mixture of dinitro derivatives X, XI, and XII in a ratio of 3 : 2 : 1 [149].

The regularities found experimentally are explained by the overall effect of electronic, steric, and kinetic factors by assuming that in the case of substitution of derivatives of the IX (R = $OCOCH_3$, NO_2) type the electrophilic agent initially adds to the nucleophilic center of the 5-substituent (R) and only then migrates to the nearest (i.e., 6) position of the aromatic ring [162, 164].

Claisen and Fries Rearrangements and the Kolbe-Schmitt Reaction. A mixture of X and XII (R = OH, R' = C_3H_5) in a ratio of 9 : 1 is obtained by heating allyl ether IX (R = OC_3H_5) [165, 166], whereas ether VII (R = OC_3H_5) gives a mixture of VIII (R = OH, R' = C_3H_5) and X (R = C_3H_5, R' = OH) in a ratio of 1 : 1 [153].

o-Hydroxy ketones X (R = OH, R' = acyl) containing only a very small amount (and only in the case of the simplest acyl groupings and when the reaction is carried out at low temperatures) of p-hydroxy ketones XII (R = OH, R' = acyl) are formed in the rearrangement of 5-acyloxy derivatives IX in the presence of aluminum chloride [165, 167-170]. The rearrangement of 6-acyloxy derivatives VII gives o-hydroxy ketones VIII (R = OH, R' = acyl) [109, 171, 172].

Heating the sodium or potassium salt of phenol IX (R = OH) with CO_2 under pressure gives hydroxy acid X (R = OH, R' = COOH) [173].

Physical Properties. The 5-substituted derivatives have higher refractive indexes and densities than 6-substituted isomers VII, whereas the magnitudes of the exaltation of the molecular refraction are approximately identical for the halo, alkoxy, and alkyl derivatives of both types and amount to 0.6-1.5 ml/mole [136] from calculations via the Eisenlor scheme.

The UV absorption bands of 6-substituted derivatives VII are more intense and are shifted to longer wavelengths as compared with the corresponding bands of 5-substituted isomers IX. An exception to this is observed only in the case of derivatives containing a carbonyl or nitrile group conjugated with the aromatic ring. Thus the long-wave absorption bands of these two types of compounds are shifted to longer wavelengths for IX, although the band of isomers VII remains more intense [152, 174].

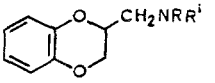
The electronic structures [153, 175, 176], the nature of the UV bands and their relationship to the chemical structure [32, 94, 174-182], and the luminescence [178, 183, 184], Raman [181, 185, 186], and IR [94, 177, 181, 187-190] spectra of benzodioxanes are discussed in a number of papers. The effect of solvents and hydrogen bonding on their UV [174, 176, 191], IR [174, 192-194], and PMR [195, 196] spectra have been examined. The dipole moments of benzodioxane and its derivatives [197] are presented in [197], and the ionization constants (in 50% ethanol) of amino derivatives of benzodioxane are given in [198, 199].

Comparative Study of the Reactivities, Spectral Characteristics, and Structures of Benzodioxane and Its Structural Analogs. Studies of the kinetics of acid deuteration [9, 121], deuterium [121] or tritium [160] exchange by hydrogen, bromination [123, 182], and alcoholysis of chloromethyl derivatives [182] and the determination of the compositions of the products of Claisen rearrangement of allyloxy derivatives [153], products of substitution [159] or oxidation [128] reactions of hydroxy derivatives, and products of the direct iodination [109] of benzodioxane, benzodioxol, veratrole, and other analogs, despite the certain contradictory character of the results [121, 160, 182, 197], nevertheless indicate that in all cases the reactivity is lower in the ortho position (relative to the oxygen atoms) of the aromatic ring than in the para positions, and this difference is a maximum in the case of benzodioxol. The reactivities in the para positions of the aromatic rings of benzodioxane and veratrole are approximately identical, but the reactivity is lower in the ortho positions of the latter [121, 160] (because of steric shielding of the methoxy groups, which was proved by a study of the basicities of this series of compounds with respect to CH_3OD [121] by means of IR spectra and by other methods [153]). The deactivation in the ortho positions and the activation in the para positions of benzodioxol as compared with benzodioxane and veratrole are explained by the quasi-aromatic character of the heterocyclic fragment of benzodioxol [121, 160]. The bands of the UV spectra of benzodioxol are shifted to the longwave region and have increased intensity as compared with the corresponding bands of benzodioxane and veratrole, whereas in the case of 3,4-dihydro-2H-benzodioxepine they are shifted to the shortwave region and have reduced intensities [32, 182]; this is explained by the differences in the degree of conjugation of the unshared pairs of the oxygen atoms with the electrons of the aromatic ring caused by the geometry of the molecule [32]. The UV spectra of benzodioxane [178, 181] and veratrole [200] differ only slightly.

The data from the PMR spectra and conformational analysis of benzodioxane and its analogs are presented in [32].

Benzodioxane Derivatives Having Biological Activity

Derivatives Containing Substituents in the Heteroring. 2-Alkylaminomethylbenzodioxanes (XIII) have received the greatest amount of pharmacological study. They are synthesized by the action of amines [5, 63, 89, 94, 200-222] (or hydrazines in the case of the synthesis of the hydrazino analogs [222-224]) on derivatives of the II ($R = CH_2Cl$, CH_2Br, CH_2I, $CH_2OSO_2CH_3$, and $CH_2OSO_2C_6H_4CH_3$-p) type,* and also by reduction of the alkylamides [221, 222, 225, 226] or nitrile [53, 227] of acid II ($R = COOH$) by means of $LiAlH_4$.



XIII

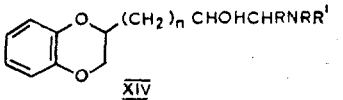
Compounds of the XIII type substituted in the aromatic [43-45, 55, 65-70, 72, 73, 76-81, 122, 139, 140, 151, 228-230] or heterocyclic [15, 40, 41, 46, 47, 231] portions of the molecule are obtained by the same methods, whereas derivatives that are alkyl- or aryl-substituted in the side chain are synthesized from ketones II (R = acyl) by means of the Leuckart reaction [59] or by reduction of oximes [47, 55, 232]. A number of investigations have been devoted to N-alkylation of amines XIII (R, R' = H) [233-239]. Guanidino derivatives are obtained by the action of guanidine on compounds of the II ($R = CH_2OSO_2C_6H_4CH_3$-p) type in 60% yields [240] and also by reaction of amines XIII ($R = R' = H$) with S-methylisothiourea (in 85% yields) [64, 241] or with cyanamide [55]. The synthesis (and metabolism) of XIII ($R = H$, $R' = C_4H_9$) [24] and its 8-ethoxy derivative [242] labeled with ^{14}C in the butyl or ethoxy grouping has been described.

Many XIII compounds display α-adrenoblocking activity and some have been proposed for treatment of disorders of the peripheral circulation [6, 243]. Their quaternary salts are inactive [202, 244], whereas the levorotatory isomers are considerably more active and not substantially more toxic than the dextro-

*These compounds were obtained by the action of $SOCl_2$ [5, 36, 63, 221], PBr_3 [64, 222, 253], or sulfonyl chlorides [89, 119, 215-217] on alcohol II ($R = CH_2OH$ and by other methods [80, 254]).

rotatory isomers [245, 246]. Monoalkylamines XIII (R = H; R' = C_4H_9, C_5H_{11} [247], $CH_2CH_2CH_2OCH_3$ [248], and others [205, 219]), which have not only peripheral but also central adrenoblocking activity, also display psychosedative properties. The guanidino derivative has local anesthetic activity and not only blocks the adrenoreceptors but also hinders isolation of adrenalin from the postganglion sympathetic nerve endings [249]. The introduction of various substituents in the ring or side chain of compounds of the XIII type reduces their adrenoblocking activity; however, the introduction of hydrocarbon groupings in the heteroring or side chain imparts local anesthetic properties to them [79, 139]. The introduction of alkoxy groups in the 8 position of XIII (R = H, R' = C_4H_9) intensifies its psychosedative properties [250], whereas introduction of a chlorine atom in the 5 position prolongs this effect [251]. Separation of the diethylamino or piperidino group from the heterocyclic ring by two or three methylene groups does not reduce the adrenoblocking activity of XIII [252]. Compounds of the latter type are obtained by reduction of nitrile II (R = CH_2CN) [53, 227, 253, 254 and subsequent N-alkylation either of alkylamides [227, 253-255] of acids II (R = CH_2COOH, CH_2CH_2COOH), synthesized by reaction of their chlorides [54, 253-255], or of their esters [37] with amines [39-41, 43-45, 55, 221, 222, 230, 252, 253, 256-262].

Stimulators [261] and depressants [262] of the central nervous system (CNS) are found among the alkylamides mentioned above, but the investigated alkylaminoalkyl esters of these same acids II (R = COOH, CH_2COOH) are less active. The latter are synthesized by the action of dialkylamino alcohols on acid chlorides [36, 222, 263, 264], transesterification of methyl esters of acids of amino alcohols, or reactions of acids with ω-chloroalkyldialkylamines [265].



XIV

n = 0, 1 ; R = H, CH_3

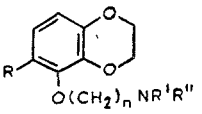
More complex derivatives of 2-(ω-aminoalkyl)benzodioxanes that have different forms of biological activity have been obtained [227, 266-269]. In particular, compounds XIV, which depress [270, 271] or stimulate [272, 273] the CNS or act as β-adrenoblocking agents [50], were synthesized through α-haloketones [49, 50, 270-276] obtained by the action of diazoalkanes on acid chlorides II (R = COCl, CH_2COCl) [49, 50, 271-275, 277, 278] or by bromination of ketones II (R = acyl) [49, 50, 279, 280]. Another method for the synthesis is the action of amines and $NaBH_4$ on keto aldehyde II (R = COCHO) [49, 50, 281], which is the product of oxidation of ketone II (R = $COCH_3$) by means of selenium dioxide [50, 282].

The reaction of alkyl mercaptides with chloride II (R = CH_2Cl) gives sulfides II (R = CH_2SAlk) [283-285], the oxidation products of which – sulfoxides – have depressive activity but do not have adrenoblocking activity [284, 285]. Hydrazino derivative II [R = $CH_2N(NH_2)CH_2C_6H_5$] inhibits monoamine oxidase [286], nitrate II (R = CH_2ONO_2) has hypotensive activity [287], and alcohol II [R = $C(CH_3)_2OH$] [277, 288] weakens the musculature. Other alcohols of this type [289] and their carbamates [290-293], including the active myorelaxant II [R = $CHOHCH_2OCONHCH(CH_3)_2$], have also been synthesized. Compounds of the II (R = $CH_2OCH_2CH_2NR'CH_2CH_2Cl$, R' = CH_3, $CH_2C_6H_5$) type have high adrenoblocking activity [222].

Aminoalkyl Ethers of 5- and 6-Hydroxybenzodioxanes. Amino ethers [XV (R = H, n = 2] of 5-hydroxybenzodioxane [27, 295-297] or their 6-substituted isomers [298] and their chloro- [161], nitro- [163], alkyl- [166-170, 172], or acyl-substituted derivatives [110, 112, 229] in the aromatic ring are synthesized by reaction of amines with halo ethers of the IX and VII (R = OCH_2CH_2X, X = Cl, Br) type and, respectively, with their derivatives obtained by reaction of hydroxybenzodioxane with 1,2-dihaloalkanes [27, 110, 112, 161, 163, 166-170, 296, 297, 299, 300] or β-chloroethyl tosylate [110, 112, 172, 295, 298, 299] in alkaline media. The same method is also used for the preparation of other ω-alkylaminoalkyl [168, 296, 297] and β-(β'-alkylaminoethoxy)ethyl [25] ethers of 5-hydroxybenzodioxane. Bromo ethers IX [R = $O(CH_2)_nBr$, n = 2-5] react with diethylamine in ethanol more rapidly than isomers VII, the reaction rate of which does not differ from that for the corresponding phenol ethers [300, 301]. The increase in the rate of the S_N2 reaction in the case of isomers IX is explained by the effect of the field of the oxygen atom of the ethylenedioxy group, which promotes cleavage of the C–Br bond [301]. The rate of reaction of bromo ethers with diethylamine is minimal when n = 2, maximal when n = 3, and gradually decreases as n increases [300, 301]. The introduction of nitro [163], acetyl [110], or benzoyl groups [112] in the 6 position of bromo ethers IX (R = OCH_2CH_2Br) somewhat decreases their reaction rates, whereas the introduction of n-alkyl groups has practically no effect [300].

Another method for the synthesis of β-dialkylamino ethyl ethers – the reaction of hydroxybenzodioxanes with β-chloroethyldialkylamines in acetone in the presence of potassium carbonate – has been used

less frequently [161, 166, 295, 296]. Amino ethers of the same type but with a methyl or phenyl group in the β position of the ethoxy group have been synthesized by means of the Leuckart reaction from formamide or N-methylformamide and keto ethers VII or IX (R = OCH_2COR, R = CH_3, C_6H_5) obtained by reaction of hydroxy derivatives VII, IX (R = OH) with bromoacetone [302-303] or phenacyl bromide [303] in acetone in the presence of potassium carbonate. Products of N-alkylation of amino ethers have also been obtained [302-304].



XV

Amino ethers XV (R = H, n = 2), like XIII, display hypotensive and α-adrenoblocking activity, but the activity is somewhat inferior to that of XIII. The butylamino derivative (R' = H, R" = C_4H_9) also has a depressive effect on the CNS, whereas the quaternary salts do not have adrenoblocking activity but behave like curarines [305]. The introduction of various substituents in the aromatic ring or with the ethoxy group, an increase in the number of methylene groups to three or four [306-308], transfer of the aminoethoxy group to the 6 position [305], or opening of the dioxane ring (conversion to 2,3-dimethoxyphenol amino ethers) [308, 309] lead to a decrease in the adrenoblocking activity. (Opening of the dioxane ring of XIII also leads to guaiacol β-aminoethyl ethers, which have reduced adrenoblocking activity [308].) Consequently, for the manifestation of high adrenoblocking activity by compounds of the phenol β-aminoethyl ether type it is necessary that their amino ether group be found in the ortho position relative to the ethylenedioxy group (XV, R = H, n = 2) or that it be incorporated in it (XIII); the second variant can be considered to be a special case of the first variant.

Amino ethers XV (R = H, n = 2) and their 6-substituted isomers display local anesthetic activity when a phenyl group is introduced in the β position of the aminoethoxy group [303]. Amino ethers XV (R = alkyl, R' = H, R" = CH_3, n = 2) are even more active [310, 311]. Thus the activity of the most active representative of this series (R = C_4H_9) exceeds the activity of tetracaine by a factor of 12 under terminal anesthesia conditions [311]. Transfer of the 6-alkyl group (R) to the 8 position, the introduction of a second alkyl group in the aromatic ring [310], an increase in the number of methylene groups, and opening of the dioxane ring [168] lead to a sharp decrease in the activity. Consequently, for the manifestation by XIII and XV of local anesthetic activity their molecules should contain a certain "mass" of hydrocarbon groups, the formation of which can be attained by the combination of hydrocarbon groups of the appropriate length in their alkylamino and alkoxy groups and in their aromatic and heterocyclic rings.

The reaction of hydroxybenzodioxanes with epichlorohydrin in alkali solution gives their β,γ-epoxypropyl ethers (in 60-70% yields), which are converted to γ-alkylamino-β-hydroxypropyl ethers on heating with amines [312-314]. The isopropylamino derivatives of this series have β-adrenoblocking activity [313, 314]. The malate of amino ether IX [R = $OCH_2CHOHCH_2NHCH(CH_3)_2$] – benzoral, benzodixine – is recommended for the treatment of cardiac arrhythmia [315].

The reaction of $SOCl_2$ with dialkylaminohydroxy ethers gives β-chloro-γ-dialkylaminopropyl ethers, which react with secondary amines to give β,γ-bisdialkylaminopropyl ethers that have hypotensive activity [296].

Other Derivatives Containing Substituents in the Aromatic Ring. Bromination of 5- [21] and 6-acylbenzodioxanes [134, 137, 141, 143, 316-318] (IX, VII, R = acyl) and their derivatives [135, 154, 316] (VIII, R = acyl, R' = alkyl) gives α-bromo ketones, which on reaction with amines are converted to α-alkylamino ketones [134, 135, 137, 141, 143, 154, 317-319]. The corresponding β-dialkylamino ketones are synthesized from acylbenzodioxanes by means of the Mannich reaction [21, 76, 133-135, 137, 141, 154, 299, 320, 321]. Amino ketone VII (R = $COCH_2NH_2$) was obtained by acid hydrolysis of its N-acyl derivatives, synthesized by acylation of benzodioxane with N-acylglycine chlorides in the presence of $AlCl_3$ [138].

Adrenomimetic activity is characteristic of many α-amino ketones, whereas adrenoblocking [141, 321-323] and antispastic [133] activity is peculiar to β-amino ketones. 6-[β-(3-Phenylpyrrolidino)propionyl]benzodioxane hydrochloride (pyrroxan) has been approved for use in hypertonic and diencephalic crises and states associated with hypersympacticotonia [321].

Amino alcohols [134, 135, 137, 143, 154, 317-319], including β-adrenoblocking agent VII [R = $CHOCH_2NHCH(CH_3)_2$] [317, 318], are obtained by reduction of amino ketones by means of $NaBH_4$ or $LiAlH_4$.

Other methods for the synthesis of amino alcohols of this type are reaction of amines with $NaBH_4$ and keto aldehyde VII (R = COCHO) [318] and the action of amines on chloro alcohol VII ($R = CHOHCH_2Cl$) obtained by reduction of the chloro ketone with KBH_4 [324]. Acid VII (R = COOH) is conveniently obtained by oxidation of ketone VII ($R = COCH_3$) with hypohalites [131, 132, 324] or $KMnO_4$ [147]. β-Dialkylaminoethyl esters [325] or amides [326] of acids, respectively, are obtained by the action of 1-hydroxy(or amino)-2-dialkylaminoethanes on acid chlorides VII and IX (R = COCl).

Amine XI ($R = OCH_3$, $R' = CH_2CHNH_2CH_3$) is a hallucinogen [327]. Related amines (VII, R = β-aminoalkyl) are synthesized by reduction with $LiAlH_4$ [18, 328, 329] of unsaturated nitro compounds obtained from the corresponding aldehyde VII (R = CHO) and nitroalkanes in alkaline media or by other methods [8, 129, 329]. Adrenoblocking agents are found among the N-alkyl derivatives of these compounds [330].

6-Alkylaminomethylbenzodioxanes, some of which dilate blood vessels and bronchi [331], are synthesized by reaction of amines with chloromethyl derivatives VII ($R = CH_2Cl$) [124, 126, 320, 331].

The reaction of ω-chloroalkyldialkylamines [23, 332, 333] with amines VII and IX ($R = NH_2$) or their derivatives gives diamines, the N-arylsulfonyl derivatives of which have hypotensive and adrenoblocking activity [334-336] and the N-nitroso derivatives of which have immunodepressive activity [337]. N-substituted derivatives of amine VII ($R = NH_2$) and other types of amines [338] and N-(β-alkylaminoethyl)amides of sulfonic acid VII ($R = SO_3H$) [339] have been synthesized.

The reduction of nitro compound VII ($R = NO_2$) with iron and hydrochloric acid [148, 332] or catalytic reduction [156, 338] (yields above 80%) are better methods for the preparation of amine VII ($R = NH_2$). Other reductive methods give lower yields [2, 89, 147, 334, 340, 341]. Amine IX ($R = NH_2$) is synthesized in 30% yield by heating acid IX (R = COOH) with hydroxylamine and polyphosphoric acid [23].

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