1,4-DIAZABICYCLO[2.2.2]OCTANES (REVIEW)

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The literature data and our own experimental data on the synthesis and physical and chemical properties of 1,4-diazabicyclo[2.2.2]octanes as compared with their 4-deaza analogs (quinuclidines) are correlated. Methods for the practical utilization of the diazabicyclic systems are examined.

The systematic investigations of quinuclidine (1-azabicyclo[2.2.2]octane) derivatives carried out in the last decades mainly in the USSR [1, 2] have made it possible to expose the features of their chemical behavior to find the general principles of the relationship between structure and pharmacological activity in this series [4], and to create effective medicinal preparations – atseklidin [5], oksilidin [6], kvalidil [7], temekhin [8], imekhin [9], phenkarol [10], etc. – which have been incorporated in medical practice.

The features of the chemical and biological behavior of quinuclidine compounds are intimately associated with the rigidly fixed character of this bicyclic system. which is incapable of significant conformational changes, with the properties of the spatially deshielded nodal nitrogen atom. and with the highly reactive free electron pair, which is characterized by definite stereospecificity with respect to the bicyclic system [3].

The features of the structure and reactivities of quinuclidines should also be retained to a considerable degree in the case of their 4-aza analogs – 1,4-diazabicyclo[2.2.2]octane derivatives. However, the appearance of a second nodal nitrogen atom creates an additional reaction center and changes the character of the bicyclic system. It should be noted that, in contrast to quinuclidine compounds. 1,4-diazabicyclo[2.2.2]octanes are not found among natural products.

In the present review we correlate the literature data and our own data on methods for the preparation of 1,4-diazabicyclo[2.2.2]octanes and the features of their chemical properties by drawing a parallel with the methods for the synthesis of quinuclidine derivatives and their properties.

Methods for the Synthesis of 1,4-Diazabicyclo[2.2.2]octanes

Of the two most general groups of methods for the construction of 1-azabicyclic systems that are used extensively in the chemistry of quinuclidines [1, 2] – intramolecular acylation (Dieckmann condensation) and intramolecular alkylation – the first group of methods is fundamentally unsuitable for the synthesis of 1,4-diazabicyclo[2.2.2]octanes. On passing from 1-carbalkoxymethyl-4-carbalkoxypiperidines to their piperazine analogs, the presence of a second nitrogen atom changes the character of the carbalkoxy residue in the 4 position. converting it from an ester function to a urethane function. and the hypothetical final products of the synthesis. 4-aza-2-quinuclidones. like other 2-quinuclidones [11, 12], should be extremely unstable, and their generation under the conditions of the Dieckmann cyclization is unlikely. In 1922 an attempt to introduce an ethylene bridge between the nitrogen atoms of the piperazine ring starting from 1,4-bis(chloromethyl)-2,5-diketopiperazine was unsuccessful [13].

In this connection, methods involving exclusively intramolecular and intermolecular alkylation are used for the synthesis of 1,4-diazabicyclo[2.2.2]octanes.

Syntheses of 1,4-Diazabicyclo[2.2.2]octanes from Acyclic Compounds. An unsubstituted diazabicyclooctane was obtained for the first time by heating dibromoethane with ammonia [14].

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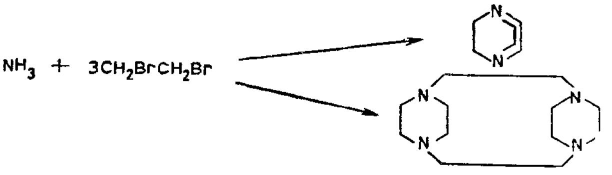
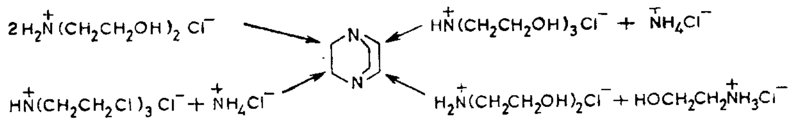


However, a subsequent attempt to reproduce this synthesis did not give positive results – the principal reaction product in all cases was hexaethylenetetramine, and 1,4-diazabicyclo[2.2.2]octane was obtained again only in 1942 [15] in 1% yield by heating diethanolamine hydrochloride at 200-210°.

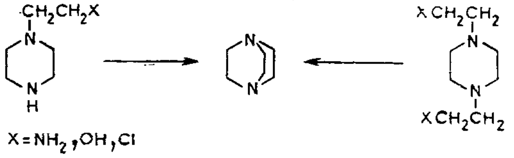


This bicyclic compound was obtained in higher yield (~2%) by heating triethanolamine hydrochloride with ammonium chloride at 220° [15] and also by hydrolysis of a mixture of mono- and diethanolamine hydrochloride or a mixture of tris(β-chloroethyl)amine hydrochloride with ammonium chloride [16]. 1,4-Diazabicyclo[2.2.2]-octane methylchloride hydrochloride was obtained by reaction of tris(β-chloroethyl)amine with dimethylamine in methanol [17]; also obtained were a number of piperazine derivatives, of which only 1-methyl-4-(β-chloroethyl)piperazine methylchloride proved to be capable of undergoing conversion to a diazabicyclic compound.

The application of oxide alumosilicates [18, 19], aluminum oxide activated by thorium oxide or phosphorus pentoxide [20], copper, nickel, cobalt, platinum, palladium, and rhenium or their oxides, chromium, molybdenum, manganese and other oxides [21] raises the yield of 1,4-diazabicyclo[2.2.2]octane during high-temperature cyclization of ethylene polyamines. Diazabicyclooctane was obtained in 21% yield by heating a mixture of high-boiling polyalkylene polyamines with ammonia chloride to 270° [22]. Metal phosphate catalysts facilitate the cyclization somewhat, and 4-azaquinuclidine was obtained from monoethanolamine or ethylene oxide and ammonia by means of alumosilicates and rare-earth exchange zeolites [23].

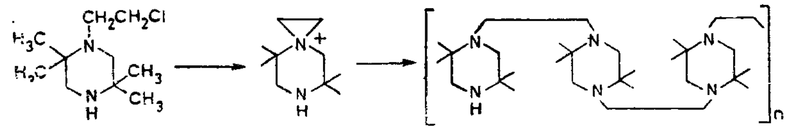
The relatively low yields of 1,4-diazabicyclic systems from aliphatic amine derivatives, in which the reaction apparently proceeds through a step involving piperazine compounds, can be explained not only by the unexpected course of the reaction but also by the inability of many piperazine derivatives to undergo conversion to the corresponding 1,4-diazabicyclic systems [17, 24]. In this connection, methods for the synthesis of 1,4-diazabicyclo[2.2.2]octanes on the basis of previously prepared piperazine derivatives that are capable of subsequent cyclization are of considerably great preparative interest.

Syntheses of 1,4-Diazabicyclo[2.2.2]octanes from Piperazine Derivatives. N-Mono- and N,N'-di(β-amino-, halo-, and hydroxyethyl)piperazines are most often used as starting compounds for the preparation of diazabicyclooctanes:

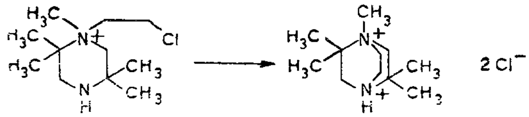


The cyclization is facilitated in the presence of oxide alumosilicates [25] (including those modified with tungsten oxide [26]), aluminum oxide [27, 28], alkali or alkaline-earth salts of organic acids [29], various phosphates [30, 32], and metal alkoxides, for example, magnesium methoxide [33]. The highest yield (60%) of 1,4-diazabicyclo[2.2.2]octane was obtained in the presence of phosphate catalysts at 300-400° [30, 32]. Cyclization proceeds at low temperatures (35°) when dichlorophenylphosphine is used, and the diazabicyclooctanes are obtained in 30-40% yields [34]. The same conditions are suitable for the synthesis of other 1-azabicyclic systems, including quinuclidine [34]. Inasmuch as all of the above-indicated methods lead to the formation of a mixture of cyclization products, fractional distillation, precipitation of the crystal hydrates from alkaline solutions after removal of the low-boiling products by distillation [35], or crystallization of the diazabicyclic compounds from lower alcohols [36] are used for the isolation of pure 1,4-diazabicyclo[2.2.2]octane. The latter method (crystallization) makes it possible to get rid of piperazine derivative impurities in the simplest manner.

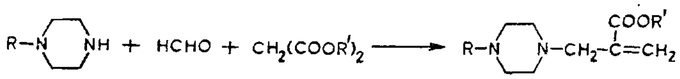
The above-examined methods for the synthesis of 1,4-diazabicyclo[2.2.2]octane have also been used for the preparation of its C-mono-, C-di-, and C-trialkyl-substituted derivatives [30, 37, 38]. However, 1-(β-haloethyl)- and 1,4-di(β-hydroxyethyl-2,2,5,5-tetramethylpiperazines do not undergo cyclization [39]: this is explained by steric hindrance to conversion of the tetramethylpiperazine to the boat form necessary for closing of the bicyclic system. The reaction in this case is directed mainly to favor the formation of an ethyleneimmonium cation, which is readily polymerized [40].



Closing of the bicyclic system to give 2,2,5,5-tetramethyl-1,4-diazabicyclo[2.2.2]octane methylchloride hydrochloride occurs only after quaternization of the starting chloroethylpiperazine and stabilization of the conformation with the substituent attached to the N' atom and the free electron pair attached to the secondary nitrogen atom of the piperazine ring drawn together [41]. The same principle has also been used for the preparation of 1,4-diazabicyclo[2.2.2]octane methylchloride hydrochloride [42].

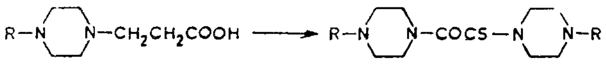


In analogy with known methods for the preparation of quinuclidine-2-carboxylic acid [43, 44], in the synthesis of functional derivatives of the diazabicyclic system unusual transformations occurred in the step involving the synthesis of 1-(β,β-dicarbalkoxyethyl)piperazines and 1-(β-carbalkoxy-β-bromoethyl)piperazines. In the Mannich reaction of piperazines with formaldehyde and malonic acid or malonic ester, instead of the normal process [45] one observes decarboxylation or decarbalkoxylation accompanied by subsequent condensation to give unsaturated compounds [46].

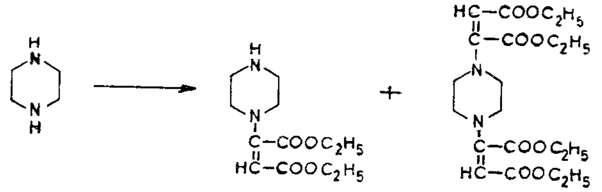


The reduction of 1-(β,β-dicarbalkoxyethylene)piperazines catalytically or with complex metal hydrides leads to fragmentation with cleavage of the C–N bond [47].

Heating 1-(β-carboxyethyl)-4-methylpiperazine with thionyl chloride and subsequent treatment with bromine gives a mixture, from which monothiooxalic acid bis(4-methylpiperazide) was isolated [48].



1-Mono- and 1,4-bis(α,β-carbethoxyethylene)piperazines were obtained from the reaction of piperazine with diethyl acetylenedicarboxylates [49].

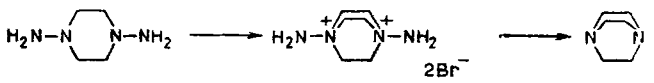


Intermolecular alkylation methods open up considerably greater possibilities. Thus, for example, the reaction of 1,4-dimethylpiperazine with 1,2-dibromoethane with subsequent dequaternization of the bis(methylbromide) of this diazabicyclic system is currently the most acceptable method for the preparation of unsubstituted 1,4-diazabicyclo[2.2.2]octane under laboratory conditions. An increase in the polarity of the solvent raises the yield of the 1,4-diazabicyclic derivative [50]. Steric factors and, particularly, the peculiarities of the conformation of the 1,4-disubstituted piperazines play a considerable role in the condensation of 1,4-disubstituted piperazines with 1,2-dibromoethane. The introduction of two alkyl substituents in the 1 and 4 positions of the piperazine ring increases the stability of the conformer having a boat form with drawn-together nitrogen atoms, and this facilitates cyclization. In the case of piperazine itself, where the boat conformation is less favorable by 3.8 kcal/mole [51], this sort of cyclization cannot be realized [62]. 1,4-Diazabicyclo[2.2.2]octane bis(ethylbromide) is formed readily in the reaction of 1,2-dibromoethane with 1,4-diethylpiperazine. However, cyclization does not occur on passing to bulkier substituents attached to the nitrogen atom (for example, 1,4-dibenzylpiperazine), and the principal reaction product is the dihydrobromide of the starting piperazine [39].

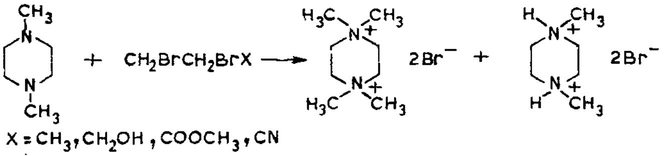
Attempts to construct an ethylene bridge in 1,4-dicarbethoxy-2,2,5,5-tetramethylpiperazine by means of 1,2-dibromoethane were also unsuccessful [39].

The introduction of a phenyl ring condensed with 1,4-dimethylpiperazine, by decreasing the conformational lability of the heterocyclic portion of the molecule, hinders closing of a diazabicyclic system by means of 1,2-dibromoethane [53]. Nevertheless, the use of optimum conditions for the construction of 1,4-diazabicyclic compounds has made it possible to realize the synthesis of benzo[b]-1,4-diazabicyclo[2.2.2]octane from 1,4-dimethyltetrahydroquinoxaline [50], but cyclization with 1,2-dibromoethane cannot be carried out [50] in the case of 5,10-dimethyl-5,10-dihydrophenazine, in which 1,4-dimethylpiperazine is condensed with two phenyl rings and its conformational lability is even more hindered.

1,4-Diazabicyclo[2.2.2]octane was obtained in 75% yield by reduction (catalytically or with iron in hydrochloric acid [54]) of 1,4-diamino-1,4-diazoniabicyclo[2.2.2]octane dibromide, synthesized by reaction of 1,4-diaminopiperazine with 1,2-dibromoethane [55].

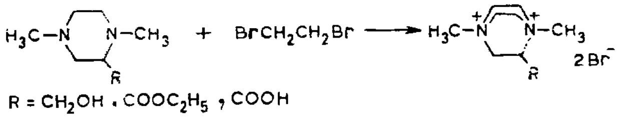


In contrast to 1,2-dibromoethane, other substituted 1,2-dibromoalkanes – 1,2-dibromopropane, 1,2-dibromo-3-propanol, methyl α,β-dibromopropionitrile – react with 1,4-dimethylpiperazine to give 1,4-dimethylpiperazine bis(methylbromide) and dihydrobromide rather than diazabicyclooctane derivatives [56].



It was demonstrated by control experiments that 1,4-dimethylpiperazine bis(methylbromide) is not formed through disproportionation of the starting 1,4-dimethylpiperazine or its dihydrobromide. Quaternization apparently occurs in the reaction of 1,4-dimethylpiperazine with substituted dibromoalkanes, but subsequent cyclization of the resulting quaternary derivatives is sterically hindered, and they are stabilized by splitting out of methyl bromide and the formation of polymerization products; the methyl bromide split out during the reaction reacts with the starting piperazine to give its bisquaternary salt [56].

Methods for the synthesis of 1,4-diazabicyclo[2.2.2]octane derivatives with various functional substituents have been developed on the basis of C-substituted 1,4-dimethylpiperazines and 1,2-dibromoethane [50, 57]:



Properties of 1,4-Diazabicyclo[2.2.2]octanes

The physical and chemical properties of 1,4-diazabicyclo[2.2.2]octane, which is obtained as colorless, volatile, hygroscopic crystals with mp 158-159.5°, bp 174°, and vapor tensions of 4 mm at 50° and 58 mm at 100°, have been studied in greatest detail (see reviews [15, 58-63]). The introduction of C-alkyl substituents disrupts the symmetry of the molecule and, as in the case of quinuclidine compounds, lowers the melting point: for example, 2-methyl-1,4-diazabicyclo[2.2.2]octane exists as a liquid at room temperature and is considerably less volatile than the unsubstituted bicyclic compounds.

Two maxima at 7.52 and 9.65 eV, which are due to a second-order interaction between the free electron pairs of the nodal nitrogen atoms that is realized primarily via a type of hyperconjugation through the carbon atoms rather than through space, appear in the photoelectronic spectra of 1,4-diazabicyclo[2.2.2]octane. This conclusion is in agreement with theoretical calculations of the spectra [64-66]. A comparison of the photoelectronic spectra of bicyclo[2.2.2]octane, quinuclidine, and 1,4-diazabicyclo[2.2.]octane [63] shows that successive replacement of the nodal carbon atoms by nitrogen atoms leads to a shift of the first band of the σ bond in the spectrum to higher ionization potentials (by 0.65 eV for quinuclidine, and 1.4 eV for diazabicyclooctane).

The UV spectrum of 1,4-diazabicyclo[2.2.2]octane in the gas phase [66] has two intense bands at 165-250 nm, which are related to a Rydberg n→p transition, and weaker absorption at 265-270 nm. In the case of quinuclidine similar bands appear at 165-230 and 230-250 nm [67]. A study of the IR and Raman spectra in vapors, solutions, and the solid phase has made it possible to establish that 1,4-diazabicyclo[2.2.2]octane molecules have a globular rigidly fixed symmetrical structure with a D_{3h}-6m2 point group in which each pair of CH_2 groups is in a shielded conformation [68]. Bands at 2945, 2937, 2870, 1464, 775, and 755 cm^{-1} and at 1100-1400 cm^{-1}, which are due to various types of methylene group vibrations [58, 71], appear in the IR spectra in the gas phase and in solution.

The principal parameters of the molecule are as follows: $\angle$C—C—N 110°53′; $\angle$C—N—C 108°1′, and bond lengths C—C 1.59 Å, C—N 1.477 Å, and C—H 0.96 Å [70, 72]. At low temperatures (up to 353°K) the 1,4-diazabicyclo[2.2.2]octane molecules are densely packed in a hexagonal crystal lattice with space group C_{6h}^{2}-$P_{6_3/m}$ (z = 2). The phase transition (353°K) [70, 73] to the so-called "plastic crystal" state is accompanied by a considerable increase in entropy (7.19 cal/mole · deg) as compared with the entropy increment for fusion (4.11 cal/mole · deg) [74, 75]. In this case the molecule acquires certain orientational, rotational, or even "translational" freedom, and this reduces the point group symmetry to D_{3-32} [71]. As in the case of quinuclidine or bicyclo[2.2.2]octane, the low-temperature modification (from 353°K to the melting point) has a disordered face-centered cubic structure, which was found by comparison of the IR spectral data, x-ray diffraction analysis data [72, 76], and data from the Raman spectra [71, 73].

The IR spectra of the diazabicyclic system differ from the spectra of quinuclidine [77] with respect to the higher intensities of the bands and the presence of a "red" shift due to an $n \rightarrow \sigma^*$ transition [71, 78]. Excitation of the 1,4-diazabicyclo[2.2.2]octane molecules with radiation at 2507 Å at 25° causes fluorescence at a wavelength of 2850-3700 Å with a lifetime of 1040 nsec and a quantitative yield of 0.9 due to an $N \rightarrow V$ transition [79].

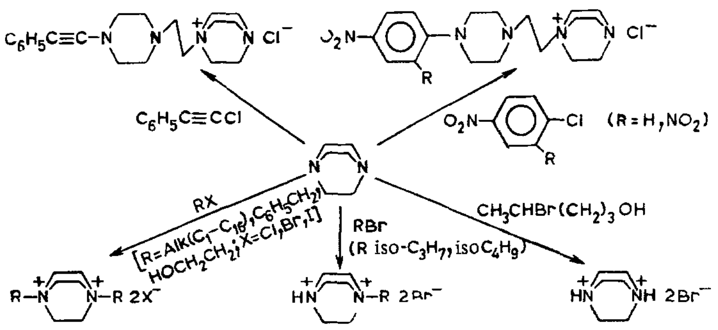
The signal (2.72 ppm) of 12 equivalent protons is observed in the PMR spectrum of 1,4-diazabicyclo[2.2.2]octane in D_2O. A nuclear quadrupole resonance (NQR) study [80] showed restricted rotation of the molecule about the hexagonal (N—N) axis in the low-temperature phase; this gives rise to a line in the spectrum that is contracted at 190°K and to axial reorientation in the "plastic" phase, the activation for which is 8.17 kcal/mole [81, 82]. A minimum spin—lattice relaxation time is most characteristic at 140-320°K because of modulation of the N—H dipole interaction [83]. Rotation of the bicyclic molecule in the solid state was also confirmed by neutron spectroscopy [84].

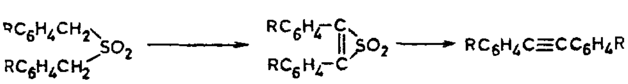
The thermodynamic properties of 1,4-diazabicyclo[2.2.2]octane have been investigated by Trowbridge and Westrum [85] and Suga and co-workers [86]. The standard enthalpy at 298.15°K was found to be −970.8 kcal/mole, and the standard formation values are $\Delta H_f^0 = -3.2 \pm 2.2$ kcal/mole, $\Delta F_f^0 = 57.4 \pm 22$ kcal/mole, and $\Delta S_f^0 = 203.5 \pm 0.3$ kcal/mole · deg [87]. The good agreement between the calculated and experimental values indicates relatively small internal stress in the diazabicyclooctane molecule. Nevertheless, this sort of stress does exist because of repulsion of nonbonded hydrogen atoms in the bridges, which somewhat destabilizes the molecule. This sort of stress has also been demonstrated for bicyclo[2.2.2]octane and quinuclidine [88, 89].

The presence of free electron pairs attached to the sterically unhindered nitrogen atoms determines the basic properties of 1,4-diazabicyclo[2.2.2]octane, which, however, is a weaker base than quinuclidine or triethylamine [90]. The ionization constants of the monoprotonated and diprotonated diazabicyclic system [91, 92] in aqueous solution at 25° are pK_{a_1} 8.60 and pK_{a_2} 2.95. The diazabicyclic system is ~100% unprotonated at pH 12, is 99.7% monoprotonated at pH 5.7-5.9, and almost completely diprotonated at a H^+ concentration above 1.2 moles/liter [93]. Owing to the +I effect, the introduction of C-alkyl substituents increases the basicity of the bicyclic system. Thus, for example, pK_{a_1} is 8.86 and pK_{a_2} is 3.15 for 2-methyl-1,4-diazabicyclo[2.2.2]octane [60].

Protonation distorts the solvation layer surrounding the amine molecule, disrupts the partial molar volume of the aqueous solution [94], changes the chemical shift of the water protons [93], and reduces the ground-state relaxation time of water by 48% [95]. A study of the solvation effects in the protonation of 1,4-diazabicyclo[2.2.2]octane in other solvents, particularly in acetonitrile [96] and benzene [97], showed that, as in the case of other ammonium cations, the free energy of solvation in these solvents for protonated diazabicyclooctane is lower than in water. The protonation of 1,4-diazabicyclo[2.2.2]octane was also studied in detail by PMR spectroscopy [98]. This method has been used for the study of complexes of the diazabicyclic system with chloroform [99]. A characteristic band of $\sigma_{\overset{+}{N}}$H deformation vibrations is observed at 1380 cm^{-1} in the IR spectrum of the protonated diazabicyclic system [100].

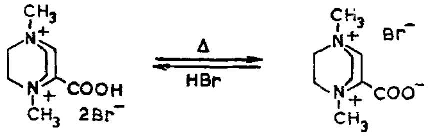
Like other ditertiary amines, 1,4-diazabicyclo[2.2.2]octane forms two series of salts [15, 17, 101], as well as quaternary derivatives, which are obtained by reaction with alkyl halides in a suitable solvent (methanol, ethanol, isopropyl alcohol, etc.) [102]. Monoquaternary derivatives are formed when nonpolar solvents are used [60], and an increase in the polarity of the solvent promotes the formation of diquaternary salts. Depending of the alkyl halide used, the reactions may proceed with ring opening [103-105] to give quaternary derivatives or with splitting out of hydrogen halides from the alkyl halide molecule to give the hydrohalide salt of diazabicyclooctane.





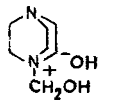
Secondary alkyl halides give only monoquaternary derivatives, whereas the principal reaction in the case of functionally substituted secondary alkyl halides is splitting out of hydrogen halide [102, 106]; p-nitrocumyl chloride forms a monoquaternary derivative [107]. Depending on the chain lengths, alkyl dihalides give various derivatives: dibromomethane gives only a monoquaternization product, 1,2-dibromoethane gives a monoquaternary derivative, which is converted to a diquaternary derivative under more severe conditions, and 1,3-dibromopropane gives polymeric compounds [108].

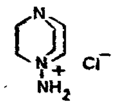
A molecule of HBr is split out when 2-carboxy-1,4-diazabicyclo[2.2.2]octane is treated with water or alcohols or when it is heated without a solvent to 135° to give an inner quaternary salt, the reprecipitation of which from hydrobromic acid by the addition of acetone gives the starting bis(methylbromide).



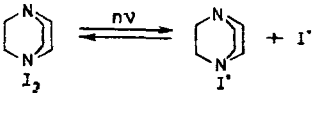
1,4-Diazabicyclo[2.2.2]octane is less reactive than quinuclidine in the nucleophilic reactions peculiar to tertiary amines [109]. The decisive factors here are not so much the differences in the pK_a values of the compounds as the magnitudes of the Brönsted coefficient (β). In reactions with p-nitrophenyl acetate and Malachite Green, for which $\beta = 0.83$ and 0.41, quinuclidine reacts faster by factors of 135 and 71 than diazabicyclooctane, and the difference in the rate reaches a factor of 2.5 when β is reduced to 0.1 (reaction with methyl p-toluenesulfonate); in the case of 2,4-dinitrophenyl phosphate the rate of reaction of diazabicyclooctane is even higher by a factor of three than the rate observed for quinuclidine. The latter "anomaly" was explained within the framework of molecular orbital theory by interaction of the σ^* orbital of the reagent with the n_1 and n_2 orbitals of the diazabicyclic system and was associated with the higher energic stability of the occupied (symmetrical) orbital in this molecule as compared with quinuclidine [109].

1,4-Diazabicyclo[2.2.2]octane reacts with formaldehyde to give a quaternary N-hydroxymethyl derivative [110] and undergoes chloroamination to give a quaternary monohydrazinium salt [111] but practically does not react with furoylchymotrypsin [112].





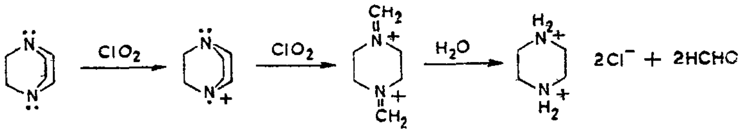
As an electron-donor agent, 1,4-diazobicyclo[2.2.2]octane forms a large number of adducts and complexes that have found practical application. In particular, adducts with one and two molecules of sulfur dioxide are used as polymerization catalysts [113], and a complex with N-bromosuccinimide (NBS) is used for the selective oxidation of sulfides to sulfoxides [114, 115]. Treatment of diazabicyclooctane with iodine or bromine gives N, N'-tetraiodo and N,N'-tetrabromo derivatives [116, 117], which are used as halogenating agents [116]. Similar iodine complexes have also been obtained for quinuclidine [117, 118]. Photolysis of the iodine complexes leads to reversible radical dissociation [119].



1,4-Diazabicyclo[2.2.2]octane forms monohydridalanes [120, 121], mono- and bishydroboranes [122, 124], and covalently bonded compounds with alcohols [125], pyrrole [126], indole [126], lithium hydride [127], 2,6-xylidinoborane dichloride [128], and chlorohydroborane [129]. The complexing ability of diazabicyclooctane was studied by measurement of the free energy of adsorption on a mercury electrode [130]. Some of its adducts have found application as hydrogen sources in the reduction of organic compounds and also in the synthesis of borohydride complexes with trialkylphosphoranes [131], and adducts with phenols and hydroquinone are used as catalysts for a variety of condensations [132]. Of no less interest are numerous monomeric and polymeric complexes with transition-metal salts and alkylmetals [133-138], which are used as organometallic reagents [139, 144], catalysts for various processes [145], solid electrolytes [146], and agents for the hydroformylation of 1-octene [147].

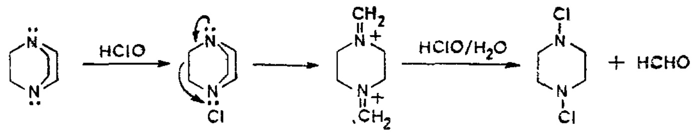
Treatment of 1,4-diazabicyclo[2.2.2]octane with hydrogen peroxide gives the mono- and dihydroperoxide, which, according to IR spectroscopic data, are hydrogen-bonded polar complexes and decompose to N-monoxides and N,N'-dioxides [148-150]. The same hydroperoxide adducts are evidently also formed with organic peroxides [151].

1,4-Diazabicyclo[2.2.2]octane is not oxidized by oxygen generated by an electrodeless radiofrequency discharge and acts as an inhibitor in the oxidation of diphenylisobenzofuran with oxygen generated in this manner [152]. The mechanism of the inhibition can be classified as "contact charge-transfer interaction" [153]. Manganese dioxide cleaves the diazabicyclooctane system to 1,4-diformylpiperazine [154]. Cleavage of the C—C bond is also observed under the influence of hypochlorites and chlorine dioxide [155-157]. In the latter case a stable cation radical, the formation of which was confirmed by ESR spectroscopy [69, 158], is generated. The cation radical subsequently undergoes fragmentation to give formaldehyde and piperazine.



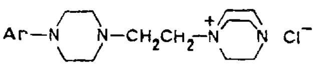
The generation of a cation radical has also been observed in a number of other chemical and electrochemical oxidations of 1,4-diazabicyclo[2.2.2]octane [69, 155, 159].

Oxidative fragmentation with hypochlorous acid proceeds via the solvolytic mechanism described for 4-bromoquinuclidine [160].



Diazabicyclooctane is cleaved via the same mechanism under the influence of perbenzoic acid or when its N-monoxide is treated with benzoyl chloride [161]. Unsbustituted quinuclidine does not undergo oxidative fragmentation under the influence of these reagents but forms only the N-oxide with chlorine dioxide, whereas 3-oxo- and 3-hydroxyquinuclidines are readily cleaved to isonipecotic acid and formaldehyde [157]. Oxidative fragmentation also occurs when diazabicyclooctane is treated with triphenyl phosphite ozonide [162] and during photosensitized oxidation with benzophenone, Methylene Blue, or other reagents [163]. Like quinuclidine [1], diazabicyclooctane is resistant to heating with mineral acids and is not oxidized by potassium permanganate in acidic media but slowly decomposes under the influence of potassium permanganate in the presence of alkaline reagents [15].

Strong nucleophiles open the 1,4-diazabicyclic system, as is observed also for 1-azabicyclo[1.2.2]heptane [164]. When diazabicyclooctane bis(methylbromide) is treated with potassium hydroxide, fragmentation is realized due to nucleophilic attack of the hydroxide anion to give 1,4-dimethylpiperazine and acetaldehyde [165]. The bisquaternary derivatives of 2,2,5,5-tetramethyl-1,4-diazabicyclo[2.2.2]octane display considerable thermal instability [16]. Opening of the bicyclic system and subsequent polymerization are observed when diazabicyclooctane is treated with benzene sulfonic [88] or p-toluenesulfonic acid [166], Friedel—Crafts catalysts, and organometallic compounds [167]. The process is evidently realized by means of nucleophilic attack of one molecule of the bicyclic amine on a second molecule, bearing a positive charge at the nitrogen atom due to protonation, acylation, or the formation of a complex salt [88]. The character of the resulting polymers depends on the concentration of the starting diazabicyclic compound [168]. Opening of the diazabicyclic system is also observed when diazabicyclooctane is treated with several aryl halides, and quaternary derivatives of the type



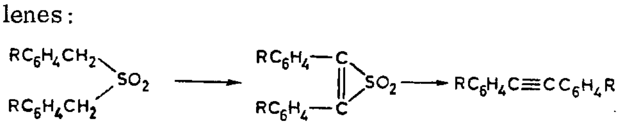
are formed [103. 104. 168-170]. Similar processes also take place in a number of quinuclidine derivatives [171].

There are individual studies devoted to the problem of the introduction of substituents in the 1,4-diazabicyclo[2.2.2]octane carbon skeleton. Attempts at direct C-alkylation with butyllithium and 1-iodopentane or 1-iodobutane did not give positive results [172, 173]. Electrolysis of diazabicyclooctane in hydrofluoric acid solution for many hours gave its perfluoro derivative, but the yield of the latter was not indicated [174]. The yield of the final product also was not presented in the case of chlorination of diazabicyclooctane with carbon tetrachloride in the presence of copper acetate, in which the reaction has radical character with subsequent ionic halogenation; the presence of the 2-chloro derivative in the reaction mixture was established only on the basis of mass-chromatographic analysis [175]. The above-described synthesis of compounds of this type from substituted piperazines [50, 57] is evidently the most efficient method for the preparation of C-substituted 1,4-diazabicyclo[2.2.2]octanes at the present time.

Practical Utilization of 1,4-Diazabicyclo[2.2.2]octanes

In the preceding section we have already noted the application of diazabicyclooctane and its derivative as chemical reagents in processes involving dehydrohalogenation, selective oxidation, halogenation, a variety of condensations, etc.

The dehydrohalogenating action of this diazabicyclic system has found further application in the induction of the Ramberg–Backlund reaction [176] and the conversion of α,α-dichlorodibenzyl sulfones to diphenylthiirene 1,1-dioxides and diphenylacetylenes:



Selective oxidation with air oxygen in the presence of diazabicyclooctane and copper acetate has been used for the conversion of 3-oxobisnor-4-cholen-22-al to progesterone [177].

The high nucleophilicity of 1,4-diazabicyclo[2.2.2]octane has been responsible for its application as a catalyst for a variety of processes involving the hydrolysis [178] and aminolysis [179, 180] of phosphoric and carbonic acid derivatives, acylation of N-lithio compounds of a number of amines, amides, and phthalimides [181], and the selective cleavage of β-keto esters [182].

According to the patent data, 1,4-diazabicyclo[2.2.2]octanes are finding extensive application in the most diverse industrial areas. Some bisquaternary salts and their polymeric analogs fasten gelatin in photographic films and are photographic fixers [183]. Quaternary salts of diazabicyclooctane – nitrates and alkylnitrates – can be used in mixtures with oxidizing agents ($HNO_3 + NClO_4$) as liquid rocket fuels; a solid fuel is obtained when alkyl chlorides are added to diazabicyclooctane in nitrobenzene [184, 185]. Diazabicyclooctane dimethylsilicate is used in the preparation of synthetic zeolites [186]; quaternary aryltriazinium salts catalyze the reaction of dyes with textile fibers [187], and the quaternary azo derivatives themselves are dyes [188]. 1,1'-Pentamethylenebis[4-aza-1-azoniabicyclo[2.2.2]octane]diiodide and its 3-methyl- and 2,5-dimethyl-substituted derivatives have found diverse application as emulsifiers, corrosion inhibitors, and antistatic agents [189]. Diazabicyclooctane bismethylnitrates stabilize anhydrous nitric acid [190]. 1,4-Diallyldiazoniabicyclo[2.2.2]octane dichloride reduced surface tension in solutions [191]. Diazabicyclooctane N,N'-tetraiodo and N,N'-tetrabromo derivatives are used as germicides and bleaches [116].

Diazabicyclooctane and its homologs and derivatives have found wide application as catalysts for the production of polyurethane foams. As compared with triethylamine, 1,4-dimethylpiperazine, and N-ethylmorpholine, these catalysts have activities that are higher by factors of 4.3, 5.3, and 17.3 [192]: in addition, they are capable of creating a balance between an increase in the chain and foam formation. The mechanism of the catalysis involved the formation of intermediate complexes of the $R-N=C(O^-)\overset{+}{N}R_3$ type [193, 194].

The use of diazabicyclooctane in the quantitative determination of water in carbon dioxide [195] is based on its catalytic effect in the reactions of isocyanates with water. Diazabicyclooctane is also a catalyst in the manufacture of plastics [196] and resins [197] and in the vulcanization of epihalohydrin and chloroprene rubbers [198]. In the latter case, complexes of the unsubstituted bicyclic system with chlorohydroborane [124, 128] are used along with the unsubstituted system itself.

Considerably less study has been devoted to the biological activity of 1,4-diazabicyclo[2.2.2]octane derivatives. An exception to this is the unsubstituted diazabicyclic system itself, the extensive and diverse practical utilization of which has stimulated quite detailed studies of its pharmacological and toxicological properties. It has been shown that unsubstituted diazabicyclooctane does not display anabolic, androgenic, diuretic, analgesic, and narcotic activity, does not suppress cholinesterase [199, 200], does not, in contrast to piperazine, have anthelmintic activity [17], and displays a pressor effect and cholinomimetic properties only in large (sublethal) doses. The LD_{50} value of this compound in experiments with mice proved to be 200 mg/kg [58]. In contrast to unsubstituted diazabicyclooctane, 1,4-bis(hydroxypropyl)- and 1,4-bis(hydroxybutyl)-1,4-diazoniabicyclo[2.2.2]octane hydroxides are capable of suppressing the growth and vitality of a number of plants and microorganisms [201]. Some of the tested quaternary mono- and bisphenacylium derivatives [202, 203] and compounds that contain steroid residues attached to the quaternary nitrogen atoms [23, 204] have displayed a depressive or stimulating effect on the central nervous system and antimicrobial activity. 1,4-Bis(3α, 17α-dihydroxy-11,20-dioxo-5β-pregnan-21-yl)-1,4-diazoniabicyclo[2.2.2]octane dibromide has proved to be the most active compound with respect to a number of microorganisms in vivo experiments (in LD_{50} doses up to 5 mg/kg intraperitoneally) [204]. According to the results of experiments with rabbits, the 1,4-diazabicyclo[2.2.2]octane complex with cobalt iodide reduces the cholesterol concentration in the blood and hinders the deposition of lipids in the walls of the aorta [205].

The synthesis and pharmacological study of 1,4-diazabicyclo[2.2.2]octane analogs of medicinal preparations of the quinuclidine series are obviously of considerable interest.

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δ-ETHOXYDIVINYLPYRYLIUM SALTS

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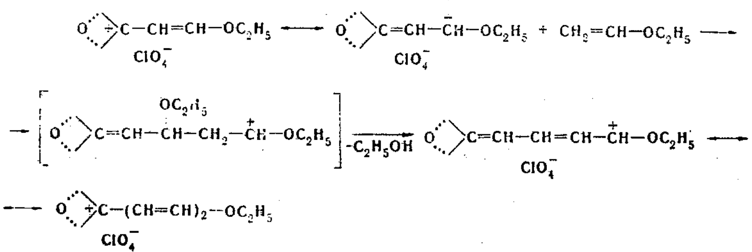
The previously unknown δ-ethoxydivinylpyrylium salts were obtained by reaction of β-ethoxyvinylpyrylium salts with ethyl vinyl ether. Their high reactivities with respect to nucleophilic compounds are demonstrated.

The reaction of alkyl vinyl ethers with acetals proceeds through carboxonium cations [1] that are generated by the action of acid catalysts on acetals. β-Ethoxyvinylpyrylium salts are an extremely convenient model of such carboxonium cations, and one therefore might have expected that 2- and 4-β-ethoxyvinylpyrylium salts would react with alkyl vinyl ethers. In the case of ethyl vinyl ether we were able to show that this reaction actually takes place when the components are heated in acetic acid and gives the previously unknown δ-ethoxydivinylpyrylium salts (I).



I

A bathochromic shift of 20-35 nm as compared with β-ethoxyvinylpyrylium salts is noted in the UV spectra of salts I: this is in conformity with lengthening of the conjugation chain of the chromophore by one double bond.

Salts I react with many nucleophiles, although their reactivities, as one can judge from the yields of the final products, are somewhat lower than the reactivities of β-ethoxyvinylpyrylium salts. Reaction with aromatic amines gives δ-aminodivinylpyrylium salts (II).

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