1,5-BENZODIAZEPINES

(REVIEW)

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UDC 547.892

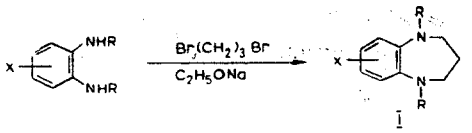
Methods for the synthesis of and the most important properties of 1,5-benzodiazepines are examined. The specifications of models of pharmacological significance are briefly given.

The discovery of elenium and its analogs has promoted the intensive study of the chemistry of 1,4-benzodiazepines (see reviews [1, 2]). Less study has been devoted to the isomeric 1,5-benzodiazepines, although they have become of ever-increasing interest to investigators, inasmuch as among them are found tranquilizers [3-7], substances that lower blood pressure [8,.9], analgetics [10], sedative agents [11-13], and substances that relieve coughing more effectively than codeine [14, 15]. Compounds with anticonvulsive action are observed among the dioxo derivatives [16-20]. Several problems of the stereochemistry, tautomerism, and chromaticity of structures of this sort have begun to be solved simultaneously (for example, see [21, 22]). The available reviews [1, 22-28] touch upon these models only indirectly with the presentation of selective information.

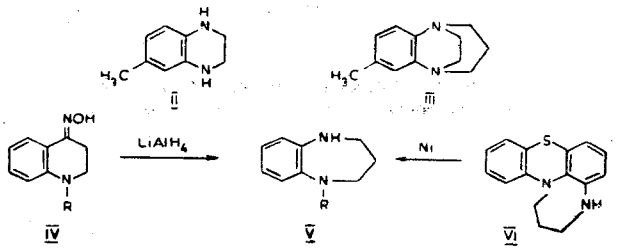
According to the rules of the International Union of Chemists, 1,5-benzodiazepines would have to be called benzo[b]-1,4-diazepines [29, 30], but this leads to a certain amount of confusion. In the last two decades, in analogy with 1,4-benzodiazepines, they have been called 1,5-benzodiazepines, considering the condensed structure to be a single system [31]. The "oxa, aza" system was used in early papers, and these compounds were called 2,3-benzo-1,4-diazacycloheptenes or benzoheptadiazines (for example, see [32, 33].

2,3,4,5-Tetrahydro-1H-1,5-benzodiazepines (1)

These compounds are formed by aklylation of diphenylsulfonyl-o-phenylenediamines with 1,3-dibromopropane and subsequent hydrolysis [34-37].

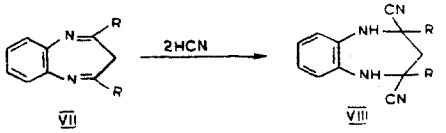


1-Phenyl-5-tosyl-2,3,4,5-tetrahydro-1,5-benzodiazepine was similarly obtained [10, 38]. The conversion of 6-methyltetrahydroquinoxaline (II) to 1,5-endoethylenetetrahydro-1,5-diazepine (III) by heating with 1,3-dibromopropane [39] has been described. However, the product has a doubled molecular weight and forms colored salts, and this allows one to have some doubts about structure III.



M. V. Lomonosov Moscow State University. Dnepropetrovsk State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1443-1463, November, 1975. Original article submitted September 16, 1974.

Ring expansion, which leads to tetrahydrobenzodiazepines V [40], may occur in the reduction of 4-quinolone oximes (IV). If the ring nitrogen atom of oxime IV is tosylated, only the tetrahydroquinoline derivative is formed [41]. 1-Phenyltetrahydrobenzodiazepine V ($R = C_6H_5$) was also obtained by desulfuration of diazepinophenothiazine VI [37]. Some tetrahydro-1,5-benzodiazepines are obtained from the corresponding 1,5-benzodiazepines (VII) by addition of HCN [42, 43], catalytic hydrogenation [37, 44-46], or reduction with sodium borohydride [47]. However, diazepine VII could not be reduced with lithium aluminum hydride in tetrahydrofuran (THF) [48], although 2,3,4,5-tetrahydrobenzo-2-diazepinone is readily converted to tetrahydrobenzodiazepine under these conditions [11, 36]. Examples of the reduction of both oxo groups in tetrahydrobenzodiazepine-2,4-diones are known [37]; these reactions proceed nonstereo-specifically [42, 45]. All of the tetrahydro compounds reduce an ammonia solution of silver oxide, change the color of a ferric chloride solution to bright-violet, are readily nitrosated to give dinitroso derivatives, and undergo acylation [35, 49].



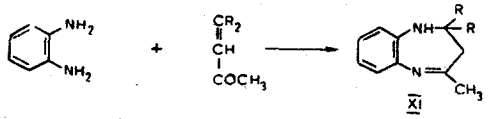
VII VIII

2,2,4-Trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (XI)

This compound was obtained for the first time from mesityl oxide and o-phenylenediamine [50, 51], but it was assigned dihydroquinoxaline structure IX. Later, Elderfield and co-workers [52, 53] considered benzimidazoline X structure to be more probable.

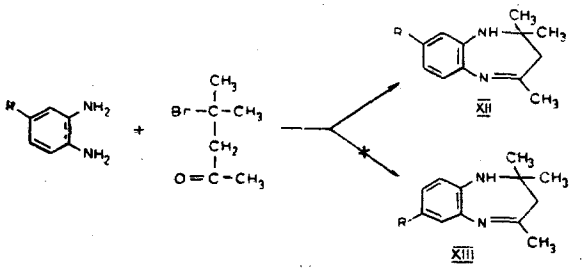
X

Structure XI was proved in studies by L. K. Mushkalo and co-workers [46, 54-57]. Other unsaturated ketones or β-halo ketones react similarly [58-69].



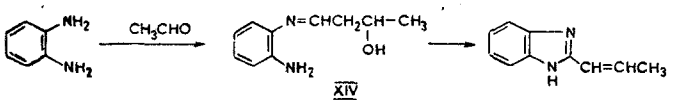
XI

One might have expected the formation of isomeric 1,5-benzodiazepines from unsymmetrical o-diamines, but only one substance, to which structure XII was assigned on the basis of a study of the absorption spectra of styryls and cyanine dyes [54, 64, 65], was isolated in each case.



XII XIII

The reaction of o-phenylenediamine with acrolein gives polymerization products or 2-vinylbenzimidazole. Schiff base XIV, from which benzodiazepine derivatives could not be obtained even on fusion with dehydrating agents for many hours, is formed in the reaction of acetaldehyde with o-phenylenediamine in refluxing benzene. Polyphosphoric acid (PPA) brings about cyclization of imine XIV to 2-propenylbenzimidazole.

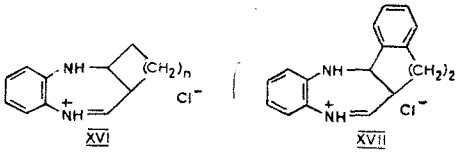


XIV

Benzylideneacetone and benzylideneacetophenone [46] add an amino group to the carbon–carbon double bond to give β-amino ketone XV. heating of which to 200°C with splitting out of acetone (or aceto-

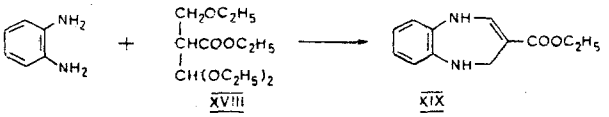
R = CH_3, C_6H_5 XV

phenone) gives 2-phenylbenzimidazole. N-cinnamylidene-o-phenylenediamine is formed with cinnamaldehyde, i.e., the condensation proceeds only at the aldehyde group. A seven-membered ring is formed quite smoothly in the case of β-chlorovinyl aldehydes [70]. This method was used to obtain a number of condensed diazepines in the form of colored hydrochlorides of the XVI or XVII type [71, 72].



XVI XVII

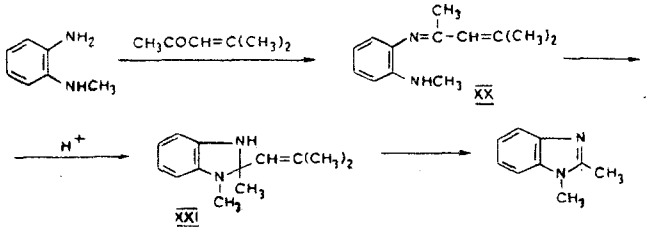
Several cases in which acetals have been used are known [47]. Thus benzodiazepines of the XIX type are formed in the condensation of o-phenylenediamine or its ring-substituted derivatives with 2-ethoxymethyl-3,3-diethoxypropionate (XVIII) [7].



XVIII XIX

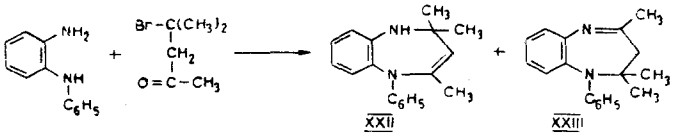
A number of dihydro-1,5-benzodiazepines were obtained from diamines and β-amino ketones [68, 73-76] or β-ethoxyacetals [47].

In the case of N-methyl-o-phenylenediamine, in which methylated amino group has a higher basicity than the unmethylated amino group, steric factors hinder addition to the carbon–carbon double bond of mesityl oxide, but protonation of the carbonyl group renders it sufficiently reactive. As a result, instead of a seven-membered ring one observes the formation of ketimine XX, which on heating is converted to 1, 2-dimethylbenzimidazole [77], probable through a step involving benzimidazoline XXI.



XX XXI

If the substituent attached to the amino group is an aryl group rather than an alkyl group, the basicity of the amino group changes in the reverse direction. Consequently, benzodiazepine XXII containing an isomeric substance, which was assigned structure XXIII [61], is formed from N-phenyl-o-phenylenediamine and methyl β-bromoisobutyl ketone.



XXII XXIII

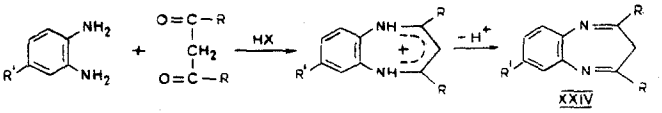
Dihydrobenzodiazepines are converted by catalytic hydrogenation to the corresponding tetrahydrobenzodiazepines [11, 42, 46, 47, 68]. Dinitroso derivatives are formed with nitrous acid, but the position of the second nitroso group has not been proved [46]. Dihydro-1,5-benzodiazepines are preferably acylated at the tertiary (with migration of the double bond) nitrogen atom rather than at the secondary nitrogen atom [64, 65]; this is in conformity with the higher basicity of the tertiary nitrogen atom. However, in compounds with an alkylated nitrogen atom the methylene group reacts with aryl isocyantes [78]. Polymethine dyes (styryls and carbocyanines) have been obtained from recommended dyeing polyacrylic fibers [80]. Tranquilizers [81] and substances that have sedative activity [75, 78] are found among 2,3-dihydro-1,5-benzodiazepines.

3H-1,5-Benzodiazepines

It was previously assumed [82-87] that 1,5-benzodiazepines are formed in the reaction of aromatic aldehydes with diamines. Later [88,89] it was found that 2-aryl-1,3-dibenzylbenzimidazolines are formed under these conditions. A seven-membered ring could not be obtained in the condensation of malonaldehyde with o-phenylenediamine [90], but its bisacetal forms 1,5-benzodiazepine [48]. However, for 1,3-dioxo

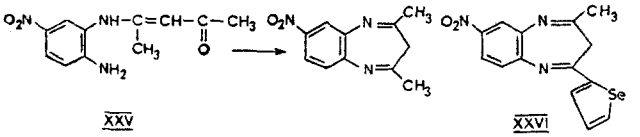
compounds the reaction usually proceeds quite smoothly with the formation of colored salts, from which colorless bases XXIV are isolated [91, 92].

This reaction has even been proposed for the calorimetric determination of acetylacetones [93]. The closing of the seven-membered ring depends on the pH of the medium [49, 94]. The maximum yield is achieved at pH 4,5-8; benzodiazepine is not formed above pH 8.



XXIV

In alkaline media the seven-membered ring is apparently opened to give a monoanil [95]. Correspondingly, 4-nitro-o-phenylenediamine reacts with acetylacetone in acetic acid to give monoanil XXV, which is cyclized on heating with hydrochloric acid to give 2,4-dimethyl-7-nitro-1,5-benzodiazepine [96-98].



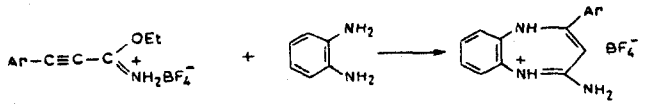
XXV XXVI

The synthesis, by this method, of benzodiazepines with various substituents in the benzene [45, 48, 98] or seven-membered [99-102] ring has been described. Benzoylacetone [91], dibenzoylmethane [79, 92, 103, 104], 2-hydroxymethylene ketones (i.e., keto aldehydes [71, 105, 269]), nitromalonic dialdehyde [106], and diketo thioacetals [107] have been used as dioxo compounds. Triacylmethanes from 3-acyl-1,5-benzodiazepines, although the 3-acyl group is simultaneously eliminated in aqueous media. 2-Acylcyclohexane-1,3-diones and 2-acylindane-1,3-diones react similarly [92, 108, 109]. Their functional derivatives have been used in place of β-diketones [110].

If the dicarbonyl compound has yet another carbon–carbon double bond, the reaction proceeds ambiguously. Thus 3-benzylindenepentanedione reacts with o-phenylenediamine in glacial acetic acid to give 2-phenylbenzimidazole, whereas in the presence of piperidine it gives 2,4-dimethyl-1,5-benzodiazepine [46]. Under these conditions, benzylindenepyruvic acid is converted to quinoxaline derivatives [111].

A heterocyclic residue can be introduced by means of β-diketones [112, 113]; for example, the condensation of acetylacetoselenophene with o-phenylenediamine gave 1,5-benzodiazepine XXVI [112].

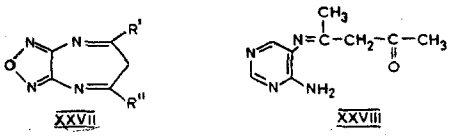
Acetylenic ketones [114, 115] or arylpropiolimidate tetrafluoroborates [116] have also been used in place of diketones.



Arylethynylglyoxylic esters have been used for the synthesis of 1,5-benzodiazepines containing a carbalkoxy group [117, 118].

o-Nitroanilines have been used in place of o-diamines; the o-nitroanilines were reduced with hydrazine in the presence of Raney nickel and used, without isolation, for the condensation [48], or the products of the reaction of o-nitroaniline with 1,3-dicarbonyl compounds were subjected to reductive cyclization [119]. The reductive cyclization of 3-(2-aminoanilino)acrylonitrile has been described [120].

Under severe conditions, particularly for N-substituted diamines, benzimidazole derivatives rather than benzodiazepines are formed competitively in the reaction with 1,3-diketones [56, 78, 92]. Thus naphthimidazole was obtained from 2,3-naphthalenediamine and acetylacetone but naphthodiazepine derivatives were isolated for the isomeric 1,2-naphthalenediamine [56]. Diamines of the heterocyclic series react like o-phenylenediamine [121-123, 270]. For example, furazanodiazepines XXVII were obtained from diaminofurazan [121].

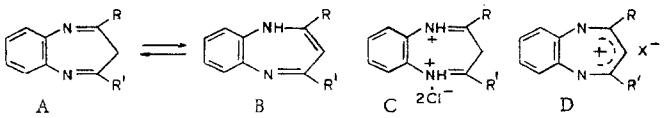


XXVII XXVIII

Ketimine XXVIII was isolated in the reaction of 2,3-diaminopyrimidine with acetylacetone [122].

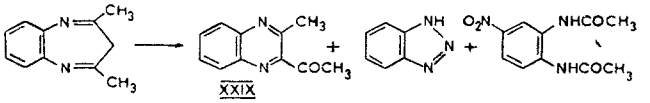
Two isomeric structures (A and B) are possible for 1,5-benzodiazepines. According to the data from the IR [92, 103], UV (92, 102], and PMR [45, 124-128, 271] spectra, if substituents R are alkyl or aryl groups, the substance has structure A, although structure B is evidently formed intermediately when salts D are made alkaline [95]. Quantum-chemical calculations have been made in [272, 273].

The bases and dihydrochlorides (C) of 1,5-benzodiazepines are colorless substances, while the monohydrochlorides (D) have intense blue or dark-violet colors as a consequence of the formation of a conjugated system [48]. In analogy with the 1,4-isomers one may assume that structure A is nonplanar, but it may become flattened on protonation.



The chemical properties of 1,5-benzodiazepines were elucidated in [23], and we will therefore discuss only publications of recent years. The seven-membered ring undergoes opening under the influence of aqueous solutions of acids and recyclization on heating, with simultaneous aromatization and the formation of benzimidazole derivatives [48, 91, 92, 112]. The opening of the seven-membered ring under the influence of phenylhydrazine has also been described [91, 92, 129].

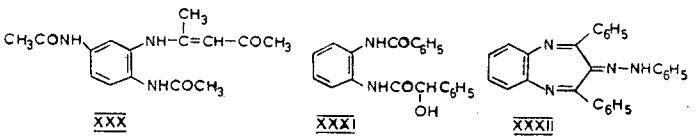
If the benzene ring contains electron-donor groups, the molecule is relatively stable; however, if a nitro group is introduced, the seven-membered ring is easily opened [124]. Nitration of 2,4-dimethyl-1,5-benzodiazepine gives a mixture of 2-acetyl-3-methylquinoxaline (XXIX), benzotriazole, and 4-nitro-N,N'-diacetyl-o-phenylenediamine [130].



Substances of this type are tosylated at the ring imino group [133]. The Vilsmeier reaction with acid amides (in the presence of phosphorus oxychloride) proceeds, on the other hand, with participation of 3-C, and this makes it possible to synthesize 3-acyl derivatives [104].

2,4-Dimethyl-7-amino-1,5-benzodiazepine is acetylated at the 7-amino group with an equimolar amount of acetic anhydride, but the C=N bond undergoes simultaneous acetolysis to give 1,2,4-triacetamidobenzene under the influence of excess reagent. Schiff base XXX was also obtained in the presence of 2 moles of acylating agent [131].

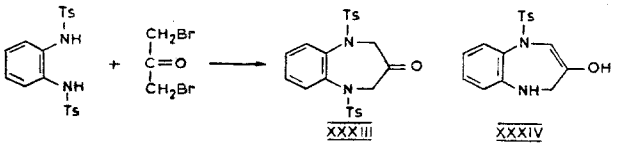
The chief product in the oxidation of 2,4-dialkyl-1,5-benzodiazepines with peracetic acid [132] was amide XXXI. Oxidation with monopersulfuric acid [92, 133] or photooxidation [134, 135] leads to acylquinoxalines. 1,5-Benzodiazepines are capable of adding hydrocyanic acid to the carbon–nitrogen double bond [42]. The reaction of 2,4-diphenyl-1,5-benzodiazepine with diazo compounds gives arylhydrazones XXXII.



Benzodiazepines readily form complexes with cadmium, cobalt, mercury, and other metal salts [135, 136]. Some derivatives have antitumorigenic activity [137-139].

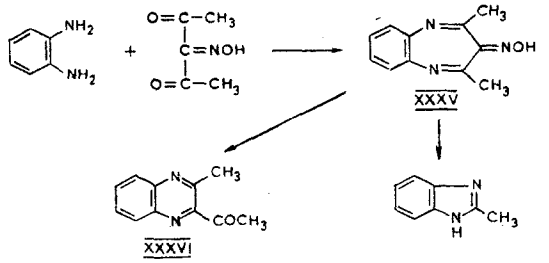
1,5-Benzo-3-diazepinones

These compounds have received the least study in this series. 1,2,4,5-Tetrahydro-3H-1,5-benzodiazepinone (XXXIII) was obtained by heating ditosyl-o-phenylenediamine with 1,3-dibromoacetone [133].



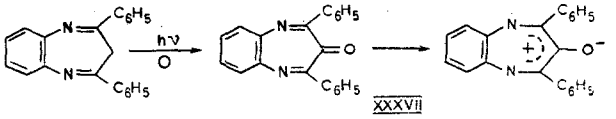
Treatment of this compound with sodium or potassium alkoxide gives a red substance, to which enol anion structure XXXIV was assigned on the basis of the IR and PMR spectra [133, 140]. Information on 3-hydroxy-benzodiazepine is also contained in [276].

The synthesis of 3H-1,5-benzo-3-diazepinone has been attempted by oxidation of 1,5-benzodiazepinones [129] or by condensation of 2,3,4-trioxopentane with o-phenylenediamine [141-144]. However, 2-acetyl-3-methylquinoxaline was isolated in both cases. It was found that it is possible to obtain 2,4-dimethyl-1,5-benzo-3-diazepinone oxime (XXXV) from 3-hydroxyiminoacetylacetone and o-phenylenediamine in benzene [92, 129]. However, if the oximation is carried out under conditions capable of inducing hydrolysis, for example, in the presence of ferric chloride, the ring undergoes contraction, and XXXV is converted to quinoxaline XXXVI. Cleavage of the seven-membered ring to give 2-methylbenzimidazole occurs in alkaline media.



Recylization is also observed on treatment of oxime XXXV with acyl-, thioacyl-, or arylhydrazines in the presence of acids even at room temperature [145] (although a substituted benzodiazepine structure was previously ascribed to the reaction products [146]). Oxime XXXV reacts with hydrazine to give 2,3-diaminophenazine and 3,5-dimethyl-4-nitrosopyrazole.

However, it was found that it is possible to obtain benzo-3-diazepinones by photooxidation of 1,5-benzodiazepines [147]. Thus, unstable 2,4-diphenyl-1,5-benzo-3-diazepinone (XXXVII) is formed on irradiation of a 4% benzene solution of 2,4-diphenylbenzodiazepine.



The maximum peaks in the mass spectrum of ketone XXXVII are the molecular ion peaks (m/e 310) and a peak with m/e 282 (M − CO). In the presence of acids ketone XXXVII is readily converted to 2,3-diphenylquinoxaline. Thus, benzodiazepinone and its derivative are considerably less stable than 3-benzotropolone.

2,3,4,5-Tetrahydro-1H-1,5-benzo-2-diazepinone

This compound was obtained by condensation of o-phenylenediamine with acrylic acid in acidic media [148]. However, this method is not always satisfactorily reproducible. Replacement of the acid by its esters sometimes lowers the yields. It is preparatively more convenient to use acrylamide [149]. Tetrahydrobenzodiazepinones are also obtained from crotonic acid and substituted o-phenylenediamines [32, 33, 36]. Methyl groups in the benzene ring , which increase the basicities of the amino groups, usually raise the yields [33]. The condensation of o-phenylenediamine with vinylacetic acid gives 2-propenylbenzimidazole rather than a seven-membered system [150] (but the reaction does not give 2-allylbenzimidazole, which, if it is formed, undergoes isomerization). 4-Methyl-2,3,4,5-tetrahydro-1H-naphtho[2,3b]-1,4-diazepin-2-one was obtained by fusing 2,3-naphthalenediamine with crotonic acid or with 3-bromobutyric acid at 100° [56]. The reaction with 1,2-naphthalenediamine proceeds similarly (isomeric substances were not detected) [33, 56].

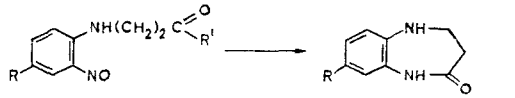
The synthesis of tetrahydrobenzodiazepinones containing a phenyl group in the 1 position by cyclization of acylated diphenylamine derivatives has been patented [151-157]. The products have anticonvulsive and sedative action [151, 152, 154, 155].

Tetrahydrobenzodiazepinones containing a phenyl group in the 4 position and various substituents in both phenyl rings have been described [158]. They are obtained by fusing cinnamic acid with o-diamines or their hydrochlorides. However, there is a report that o-phenylenediamine forms exclusively 2-styrylbenzimidazole with cinnamic acid [32, 159]. 4-Benzyltetrahydrobenzodiazepine was obtained by catalytic

hydrogenation of 4-benzyl-1,2-dihydro-1,5-benzo-2-diazepinone [160], which was synthesized from o-phenylenediamine and γ-phenylacetoacetic ester.

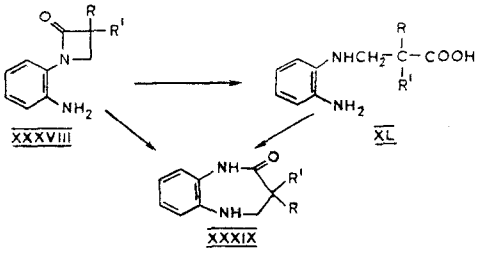
The reaction of esters of 2,6-disubstituted 4-piperidonedicarboxylic acids with o-phenylenediamine in refluxing xylene is accompanied by opening of the piperidine ring and gives 2-carbalkoxymethylene-2,3,4,5-tetrahydro-1H-1,5-benzo-4-diazepinone [161, 162].

Tetrahydrobenzo-2-diazepinones were also obtained by reductive cyclization of 2-nitro-4-alkylacetoacetanilides [48, 163] and N-(o-nitrophenyl)-β-amino acids [149, 164, 165]. (Sexton [163] has erroneously assigned a benzimidazole derivative structure to the compounds obtained by this method.)

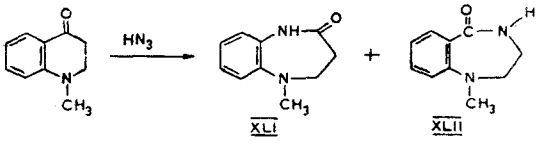


R = H, CH_3, Br, OCH_3, NO_2; R' = OH, NH_2, OCH_3, $NHNH_2$

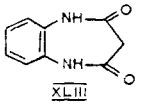
A third method for the preparation of tetrahydrobenzo-2-diazepinones involves intramolecular rearrangements with ring expansion. 1-(o-Aminophenyl)-2-azetidinones (XXXVIII) [166, 167] are converted to 3,3-disubstituted tetrahydro-1,5-benzo-2-diazepinones (XXXIX) and amino acids XL in weakly acidic media. Amino acids XL can be cyclized by heating with dicyclohexylcarbodiimide.



Ring expansion leading to 1-alkyltetrahydro-1,5-benzo-2-diazepinone (XLI) and 1,4-benzodiazepine XLII occurs during the action of hydrazoic acids on 1-alkyl-4-oxo-1,2,3,4-tetrahydroquinoline [168-170]. The ratio of XLI and XLII depends on the character of the substituent attached to the nitrogen atom of quinolone.



Ring opening to give aromatic diamines occurs on prolonged heating of tetrahydrobenzodiazepinones with strong acids or alkalis [162]. Tetrahydro-1,5-benzodiazepinones are alkylated primarily in the 1 position [151, 171, 172]. 1-Aryl derivatives are obtained under the conditions of the Ullmann reaction [173, 174]. Acylation gives 5-acetyl derivatives [5, 7, 32, 166, 175, 176]. There are patent data that indicate that the latter have a tranquilizing effect and are also myorelaxants and anticonvulsants [177-181]. 1-Ureido- and 1,5-diureido-1,5-tetrahydrobenzodiazepinones, which have sedative and hypotensive activity [12, 166, 182], are obtained by heating compounds of the XLI type with urea. Nitrous acid gives N-nitroso compounds, the reduction of which gives the corresponding hydrazines [32, 166]. Substances having mutagenic activity have been obtained from them [176]. Potassium permanganate and chromium and manganese oxides [157] oxidize tetrahydro-1,5-benzodiazepines to tetrahydro-1,5-benzodiazepinediones (this same process has been carried out enzymatically [274]), whereas ferric chloride oxidizes them to dihydro derivatives [166]. The reaction of tetrahydrobenzodiazepinones with P_2S_5 in pyridine gives tetrahydro-1,5-benzodiazepinethiones [79].

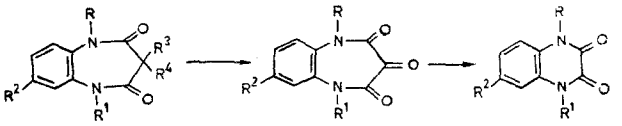


2,3,4,5-Tetrahydro-1H-1,5-benzodiazepine-2,4-diones (XLIII)

These compounds were obtained by condensation of malonic acid and its esters with o-phenylenediamine [183]. Monoaminomalonanilides, which are cyclized under more severe conditions [184], are formed simultaneously in small amounts. Malonic acid reacts with 2 moles of o-phenylenediamine to give 2,2-dibenzimidazolylmethane [185]. The structure of XLIII was established in [186, 187]. Acid chlorides [188, 189], malonic acid esters [179, 190], and alkyl- and dialkyl-substituted derivatives of these esters [191-193] have been used for the synthesis of diazepinediones.

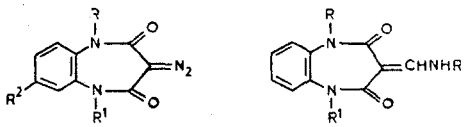
The intramolecular condensation of o-nitrodiphenylamine derivatives [17, 194, 195] or their reductive cyclization [196] is used for the preparation of 1-phenyldiazepinediones. 1,5-Benzodiazepinediones are alkylated at the 3-C atom on heating in THF in the presence of sodium hydride [197-199, 275, 277], but alkylation of the nitrogen atom and rapid conversion to the corresponding benzimidazolone occur in aqueous media [274]. When the conditions of the Ullmann reaction are used, a hydrogen atom of the amino group can be replaced by an aryl or hetaryl group [16, 200, 201]. The acylation of both diones of the XLIII type and of their sodium derivatives by the action of acid anhydrides or acid chlorides proceeds only at the imino group [202, 203]. These sodium salts on reaction with chlorine or bromine give the corresponding 3-halides. It was found to be impossible to replace the halogen of 3-chlorobenzodiazepinedione by the action of sodium methoxide or sodium acetate [19, 274]. The reaction of chloramine with diones XLIII gave 3-amino-substituted compounds, which can be completely diazotized, after which the diazo group in XLV can be replaced by a hydroxy, alkoxy, or acetoxy group [274].

Examples of the oxidation of 1,5-benzodiazepinediones with chromium oxides [204] or potassium permanganate [205] to 1,5-benzodiazepinetriones (XLIV), which are converted to tetrahydroquinoxaline-2,3-diones in acidic or alkaline media at high temperature (for example, by refluxing in xylene), have been described.



XLIV

The action of tosyl azide in the presence of sodium hydride converts diones XLIII to 3-diazo-1,5-benzodiazepinediones (XLV) [206], and diones XLIII can be converted to 3-aminomethylene derivatives (XLVI) by means of phosphorus pentachloride and aliphatic amines [207, 208].

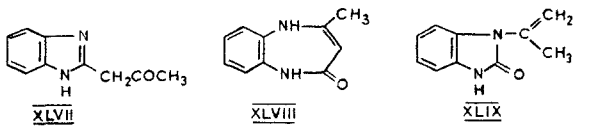


XLV XLVI

One or both oxygen atoms are replaced by sulfur atoms when 1-alkyl- or 1-alkyl-5-aryl-1,5-benzodiazepinediones are heated with phosphorus polysulfide in dry pyridine. The sodium salts of these thiones are alkylated at the sulfur atom [274, 278]. Some 1,5-benzodiazepinediones, in particular, 1-phenyl-7-trifluoromethyl-1,5-benzodiazepine-2,4-dione, have tranquilizing and anticonvulsive activity [16, 195-198, 209, 274] and have been patented as myorelaxants or sedative preparations [20, 189, 203, 274]. The presence of substituents in the 3 position does not lead to loss of psychopharmacological activity [19, 199, 204, 205, 208]. 5,7,8-Trimethyl-3H-1,5-benzodiazepine-2,4-dione has been patented as a hardener in the manufacture of polyurethanes [210].

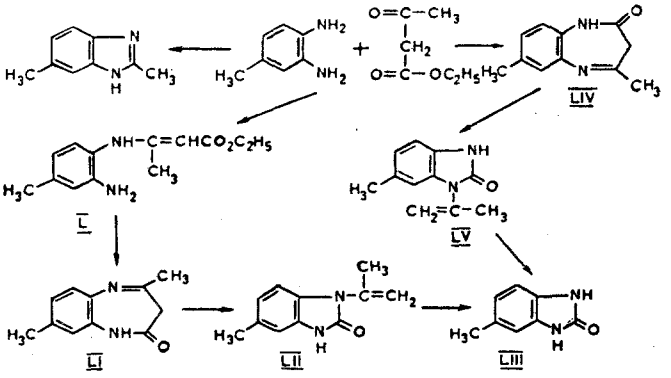
2,3-Dihydro-1H-1,5-benzo-2-diazepinones

The condensation of β-keto esters with diamines is used for the synthesis of 2,3-dihydro-1H-1,5-benzo-2-diazepinones. The chief products in the reaction of o-phenylenediamine or substituted phenylenediamines with acetoacetic ester at room temperature in the presence of catalytic amounts of acid are 3-(2-aminoarylamino)crotonic acid esters [36, 163, 211-214]; It has been reported that o-aminoacetoacetanilide is formed on heating in the presence of pyridine [215], but this was not confirmed later [36]. Sexton [163] isolated two substances, to which he assigned 4-methyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (XLVII) and 2-acetonylbenzimidazole (XLVIII) structures, when he refluxed o-phenylenediamine with acetoacetic ester in xylene.



XLVII XLVIII XLIX

In 1960, Davoll [36] and Rossi and co-workers [31] established that the former is 1-isopropenylbenzimidazolone (XLIX) and that the latter does indeed have the XLVIII structure. The complexity of the process is best demonstrated in the case of an unsymmetrically constructed diamine. Thus ethyl 3-(2-amino-4-toluidino)crotonate (L), which is converted to 4,8-dimethyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone (LI) on heating in the presence of sodium ethoxide, is formed in the reaction of 4-methyl-o-phenylenediamine with acetoacetic ester [216, 217] in neutral media or in the presence of small amounts of acid. The thermal rearrangement of LI [218] gives 1-isopropenyl-5-methylbenzimidazolone [LII). The presence of an enamine grouping in LII explains the case of its conversion to the corresponding imidazolone (LIII([219, 220].

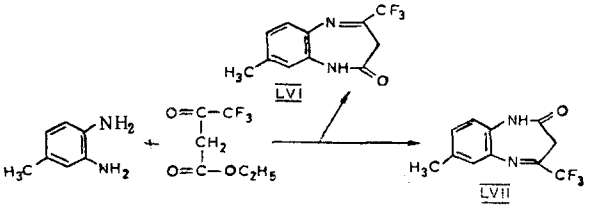


L LIV LV LI LII LIII

Substances LIV and LV are formed in refluxing xylene. Compound LIV was obtained in 80% yield in very dilute solution, whereas only traces of L were obtained. An increase in the concentration leads to a decrease in the yield of LV. Prolonged heating promotes an increase in the yield of LV. Like diazepinone LI, LIV is converted on heating to benzimidazolone LV, the acid cleavage of which gives imidazolone LIII. The synthesis of LIV from 4-methyl-o-phenylenediamine and the diketone was also described in 1970 by Japanese chemists [221]. However structure LIV was given only as a hypothetical structure.

Thus, under mild conditions, particularly under the influence of an acid catalyst, the composition of the reaction products is determined by the relative nucleophilicity of each of the donor amino groups with respect to the electrophilic keto group of acetoacetic ester. In this connection, the fastest kinetically controlled reaction is apparently the formation of the arylaminocrotonate ester, which, depending on the conditions, cyclizes to give 2,5-dimethylbenzimidazole or dihydrobenzodiazepinone. The latter is converted by heating to 1-isopropenyl-5-methyl-2-benzimidazolone. If the condensation is carried out immediately under severe conditions, thermodynamic control of the reaction plays the main role, and the arylaminocrotonate is evidently isomerized (as observed in the Conrad-Limpach synthesis) to an acetoacetamide with simultaneous (or subsequent) cyclization leading to the dihydrobenzodiazepinone and the isomeric isopropenylbenzimidazolone. Ring contraction (conversion of the benzodiazepinones to isopropenylbenzimidazolones) is used to establish the structure of the products of such reactions [218].

In contrast to [222, 223], both isomeric dihydrobenzodiazepinones (LVI and LVII) [224, 225] were isolated in the reaction of 4-methyl-o-phenylenediamine with trifluoroacetoacetic ester under severe conditions.

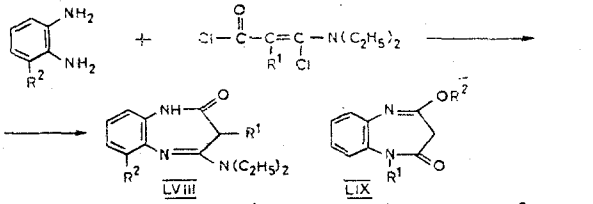


LVI LVII

The available data on the structures of the products of the reaction of chlorinated diamines with acetoacetic ester are ambiguous: the corresponding benzodiazepinones are described in [212, 226], whereas

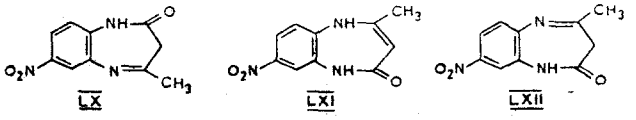
other investigators [227, 228] report that isopropenylbenzimidazolones (which have selective herbicidal activity) are formed immediately under these same conditions [228, 229]. O-phenylenediamine reacts with benzoylacetic ester to give 4-phenyl-2,3-dihydro-1H-1,5-benzo-2-diazepinone [68, 111, 218], the derivatives of which have sedative activity [230, 231]. A similar reaction of diaminonaphthalenes [33, 56, 232, 233] with various β-keto esters has been described [234-236].

The formation of benzodiazepinones cannot be practically established if some alkylated (at the methylene group) acetoacetic esters are subjected to the reaction, inasmuch as the formation of benzimidazole derivatives proceeds rapidly [279]. However, 1,5-benzo-2-diazepinones of the LVIII type containing a dialkylamino group in the seven-membered ring can be obtained from o-phenylenediamine and β-chloro-β-dialkylaminoacryloyl chlorides [237-239]. N-phenyl-o-phenylenediamine reacts with these acid chlorides to give two isomeric aminobenzodiazepinones. Compounds LIX were obtained from 1,5-benzodiazepine-2, 4-diones by reaction with trialkylboron etherate or through the 4-halo derivatives [240-241] with subsequent treatment of them with alcohols. If amines are used in place of alcohol, LVIII are formed [4, 242]. Sulfur-containing dihydro-1,5-benzodiazepines have been described [243-246].



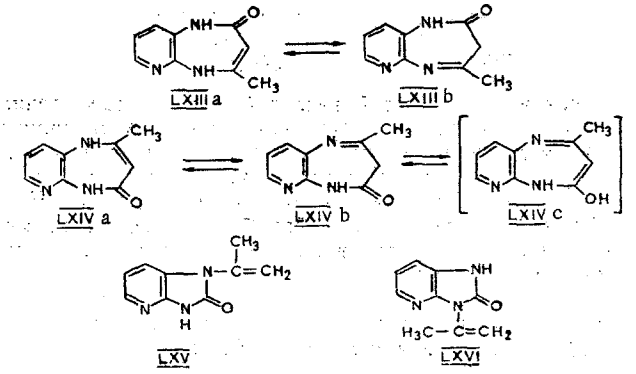
LVIII $R^1 = CH_3, C_2H_5, C_6H_5$; $R^2 = H, Cl$ LIX $R^1 = CH_3, C_2H_5$; $R^2 = C_6H_5$

In the case of 4-nitro-o-phenylenediamine, the presence of a nitro group brings about facile migration of the double bond in the crotonate [247, 248] and dihydrobenzodiazepinone [249, 250]; this facilitates isomerization to isopropenylbenzimidazolones. In this case, depending on the conditions, one can isolate three isomeric benzodiazepinones (LX-LXII), the structures of which are confirmed by hydrolytic cleavage and reduction to the corresponding tetrahydro compounds. Compounds LX and LXI (or the tautomeric LXII) differ with respect to their thermal isomerization products. Crystallization of yellow diazepinone LXI



from alcohol (but not from xylene) gives dark-red LXII. A difference in the region of the frequencies of the CO groups is clearly traced in the IR spectra of the solids, but the UV spectra of alcohol solutions of them are identical. The mass spectra of these isomers differ with respect to the intensities of the molecular and fragment ions [251]. This sort of stabilization of the tautomeric forms was not observed for compounds with other substituents in the benzene ring. The most stable structure is usually a model of the LX or LXII type, inasmuch as the signals of the methylene and imino groups are clearly seen in the PMR spectrum [128, 250, 279]. Earlier data [31, 36] require verification.

In addition to diamines of the aromatic series, 2,3-diaminopyridine [218, 245, 252-257], 3,4-diaminopyridine [258, 259], 1-acetyl-5,6-diaminoindoline [260, 261], 4,5-diaminopyrimidine [262-265], and other heterocyclic amines (for example, see [266]) have been used in reactions with β-keto esters. Condensation



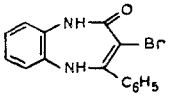
of 2,3-diaminopyrimidine with acetoacetic ester [252] gives primarily diazepines LXIII or LXIV imidazolones LXV and LXVI.

The more basic amino group of 2,3-diaminopyridine reacts with the carbonyl group of the keto ester under both mild and severe conditions [251-256]. Fusion of the reagents (180°) gives a mixture of diazepines LXIIIa and imidazole LXVI. The tautomeric forms (LXIVa and LXIVb), the structures of which were evaluated from the UV spectra, inasmuch as the PMR spectra of deuterochloroform solutions of these substances are identical because of conversion of LXIVa to LXIVb, were isolated in the case of LXIV. The presence of lactim form LXIVc was also established in the case of diazepinone LXIV.

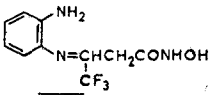
The tautomeric forms of pyridodiazepines were also obtained in the case of 3,4-diaminopyridine [258]. Here, the difference in the basicities of the amino groups is not so large as in the case of 2,3-diaminopyridine, and a mixture of isomeric compounds is therefore formed when the reagents are refluxed in xylene [258]. The condensation proceeds similarly for 4,5-diaminopyrimidine [262, 263].

The acid hydrolysis of 2,3-dihydro-1,5-benzodiazepinones under mild conditions gives 2-alkylbenzimidazoles [36, 248]. Under more severe conditions, the seven-membered ring opens to give the diamine [162]. When dihydro-1,5-benzo-2-diazepinones are heated above their melting points [218] or with sodium 2-ethoxyethoxide [36], they undergo isomerization to 1-isopropenyl-2-benzimidazolones. Dihydrobenzodiazepinones are alkylated primarily in the 1 position [3, 4, 267]. Acylation with acetic anhydride [3, 67, 175] or carboxylic acid chlorides [3, 67] in pyridine gives 1-acyl derivatives. 1-Carbomoyldihydro-1,5-benzodiazepinones have been described [3, 268]. If acylation is carried out with acid amides under the conditions of the Vilsmeier reaction, the methylene group undergoes reaction, i.e., the condensation proceeds at the 3C atom [280].

Dihydro-1,5-benzodiazepinones are reduced with hydrogen on palladium or nickel catalysts to the corresponding tetrahydro derivatives [31, 36, 44, 68, 111, 175]. Lithium aluminum hydride reduces the carbonyl group in these compounds [36, 68]. Bromination of 4-phenyl-2,3-dihydro-1,5-benzo-2-diazepinone with N-bromosuccinimide gives 3-bromodiazepinone LXVII. 4-Methyl-2,3-dihydro-1,5-benzo-2-diazepinone is nitrated in the benzene ring (in the 7 position) [176, 281].



LXVII



LXVIII

The reaction with nitrous acid and benzenediazonium chloride has been described, but the structures of the products have not been established [36]. The methyl group of compounds of the XLVIII type reacts with benzaldehyde to give 4-styryl derivatives [221]; hydroxylamine brings about cleavage of the diazepine to give hydroxyamic acid LXVIII [222].

Tranquilizers, antidepressants, substances with sedative activity, etc., have recently been found among 1,5-benzo-2-diazepinones [3-5, 8, 151, 196, 199-201, 208, 238, 239].

A number of interesting papers, the citations to which we have included only selectively, were published after the text of this review had been prepared for printing. A small review by Lloyd and Cleghorn [282] encompassing 53 publications and in which one can find data on the physicochemical study of the described models appeared in 1974. We felt it useful to supplement our text with citations to studies of the biological activity of 1,5-benzodiazepines (see [283-290]) and of several condensed structures including a 1,5-benzodiazepine fragment or a fragment of its heterocyclic analogs (see [291-306]). The authors thank Dr. K. H. Weber for sending us the text of the plenary paper that he presented in Czechoslovakia [274].

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