2-QUINAZOLINONES AND THEIR CYCLIC HOMOLOGS (REVIEW)

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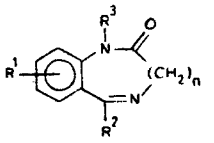
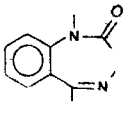
Methods for the synthesis of 2-quinazolinones, 1,2-dihydro-3H-1,4-benzodiazepin-2-ones, 1,2,3,4-tetrahydro-1,5-benzodiazocin-2-ones, and 1,2,3,4-tetrahydro-5H-1,6-benzodiazonin-2-ones are examined along with the peculiarities of their structure, their tautomerism, their chemical properties, and their biological activity.

2-Quinazolinones (I), 1,2-dihydro-3H-1,4-benzodiazepinones (II), 1,2,3,4-tetrahydro-5H-1,5-benzodiazocin-2-ones (III), and 1,2,3,4-tetrahydro-5H-1,6-benzodiazonin-2-ones (IV) are related heterocyclic systems, and their properties in some respects should be similar. At the same time, expansion of the heteroring of quinazolines leads to significant changes in the three-dimensional structures and properties of their cyclic homologs. Compounds of these series are active with respect to the central nervous system (CNS), possibly owing to the presence of the common pharmacotropic fragment V in them.



I–IV



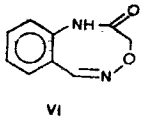
V

I $n=0$; II $n=1$, III $n=2$; IV $n=3$

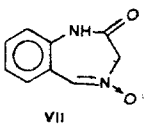
1,2-Dihydrobenzodiazepin-2-ones II, which are widely used as psychotropic agents, currently have the most practical value. The problems involved in their chemistry and pharmacology have been illuminated in reviews [1-5], in which the literature up to 1970 was used. Less study has been devoted to 2-quinazolinones [6, 7] and their eight- and 10-membered cyclic homologs. Data on the chemistry of systems I-IV up to 1976 are correlated in the present review.

2-Quinazolinones I were obtained at the end of the last century [8], but less attention was paid to them than to the isomeric 4-quinazolinones, among which fairly physiologically active substances of natural and synthetic origin were detected. However, the prospects for the search for physiologically active substances among 2-quinazolinones were in doubt in view of their low solubilities [6].

Auwers and Frese [9] were the first to obtain a compound of the II series, but they erroneously assigned benzoxadiazocine structure VI to it. It was later shown [10] that it has the 2-oxo-1,2-dihydro-3H-1,4-benzodiazepine 4-oxide structure (VII).



VI



VII

The chemistry of dihydrobenzodiazepinones II began to develop rapidly in the 1960's after the discovery of the psychotropic properties of benzodiazepinones.

Tetrahydrobenzodiazocinones III were recently described [11], whereas tetrahydrobenzodiazoninones IV were synthesized independently by us [12] and Japanese researchers [13].

Synthesis of 2-Quinazolinones and Their Cyclic Homologs

Heterocyclic systems I-IV can be obtained from o-acylanilines or their derivatives.

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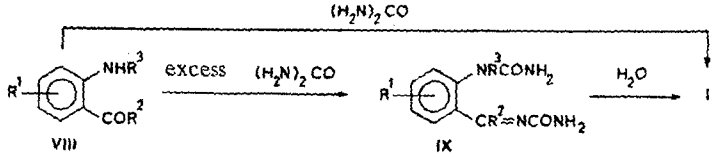
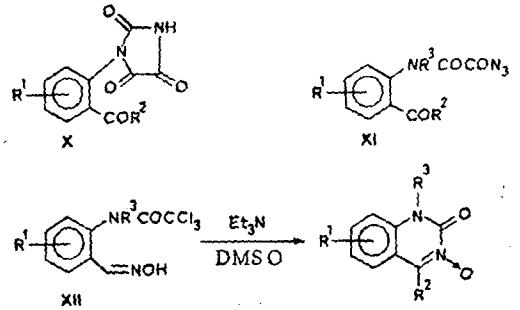
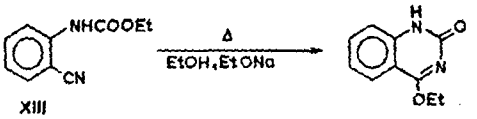
2-Quinazolinones (I) are obtained by condensation of o-acylanilines VIII with urea [8, 14-19]. I. Ya. Postovskii [19] has demonstrated that stable intermediates IX, which undergo cyclization in water to quinazolinones I, are formed when excess urea is present. The reaction of acylanilines VIII with urethane [20], cyanic acid or its salts in the presence of $ZnCl_2$ and other salts [21, 22], esters of chlorocarbonic acid, and ammonia or ammonium acetate [23, 24], as well as treatment of N-trichloracetylamino ketones VIII with an alcohol solution of ammonia [25, 26], leads to 2-quinazolinones.



The hydrolysis of imidazolidinetriones X [27] and the Curtius rearrangement of acyl azides XI [28] also proceed with the formation of compounds of the I type. The cyclization of oximes XII in the presence of bases leads to 2-quinazolinone 3-oxides [29].

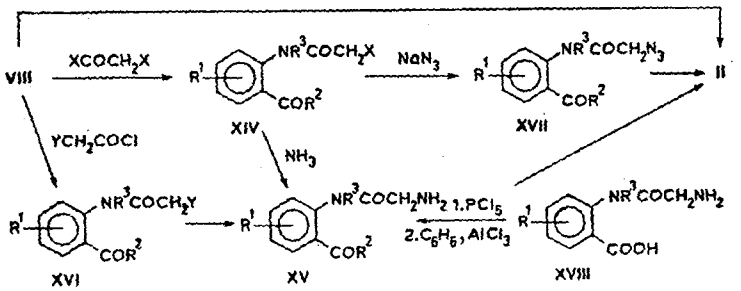


2-Quinazolinones are obtained by the action of phosgene [30], hydrocyanic acid or its salts [31, 32], carbamates [33], and cyanic acid or its salts [21] on imines of amino ketones VIII. When nitrile XIII is heated in ethanol, it is converted to 4-ethoxy-2-quinazolinone [34].



Methods for the synthesis of quinazolinones by the hydrolysis of their 2-halo [35], 2-alkoxy [36], and 2-acyloxy derivatives [37], by rearrangement of quinazoline 1-oxides [38, 39], and by oxidation of quaternary salts of quinazolines [32], tetrahydro-2-quinazolinones [33, 40], or tetrahydroquinazolines [41] have been described. The oxidative cleavage of the double bond of the pyrrole ring of 2-aminoindoles is also accompanied by the formation of 2-quinazolinones [42].

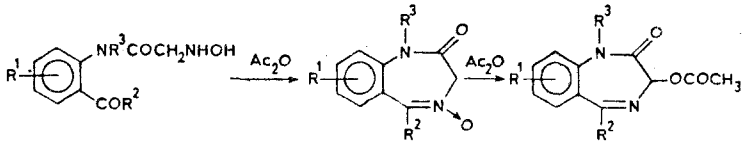
1,2-Dihydro-3H-1,4-benzodiazepin-2-ones (II). The most general method for the preparation of substances of the II type is the reaction of amino ketones VIII with derivatives of α-amino acids [43-47]. Higher yields can sometimes be obtained by treatment of amino ketones VIII with α-halo acyl halides and subsequent replacement of the halogen atom in XIV by an amino group (directly [43, 45, 48-50] or through a step involving the formation of quaternary salts with urotropin [51]) and cyclization of amino acyl derivatives XV.



XIV X = halogen; XVI Y = $HNCOOCH_2Ph$, phthalimido HNTs

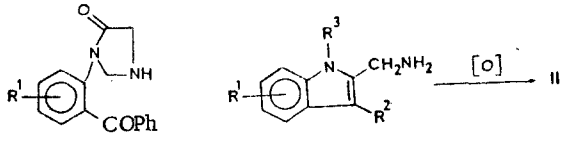
The synthesis of benzodiazepinones II from azidoacetamido ketones XVII [52] and N-aminoacetylanthranilic acids XVIII [53] also proceeds through a step involving the formation of intermediate XV.

3-Acetoxy derivatives XX are obtained by heating N-(hydroxylaminoacetyl)amino ketones in acetic anhydride [54]. The reaction evidently proceeds through the formation of 4-oxides XIX, which are converted to XX as a result of the Polonovski rearrangement.



XIX XX

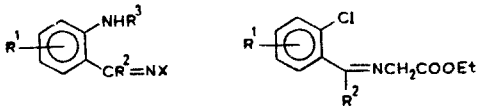
The condensation of amino ketones VIII with oxazolidine- or thiazolidine-2,5-dione in the presence of HCl leads to II [55, 56]. The preparation of benzodiazepinone II (R^1 = Cl, R^2 = Ph, and R^3 = H) by the action of an alcohol solution of HCl on imidazolidone XXI has been described [57].



XXI XXII

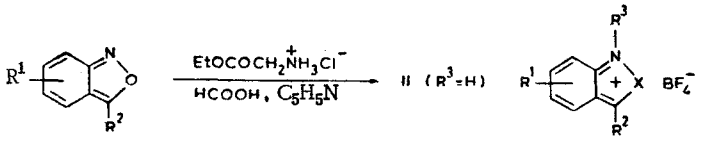
The oxidation of aminomethylindoles XXII [58-63] with potassium permanganate, chromic anhydride, ozone, and other oxidizing agents is a general method for the synthesis of diverse 1,2-dihydro-3H-1,4-benzodiazepin-2-one derivatives. This method can essentially be regarded as a modification of the methods described above for the preparation of benzodiazepinones II, which include a step involving the formation of substances of the XV type, since it is known [64] that the oxidative cleavage of the pyrrole ring of indoles leads to o-acylamino ketones.

Imines of the XXIII and XXIV type are also used as intermediates in the synthesis of II. Benzodiazepinones II and their 3-carbethoxy derivatives, respectively, are obtained by the action of bromoacetyl bromide [65] or aminomalonic ester [66] on ketimines XXIII (X = H). Esters XXIII (X = CH_2COOEt) undergo cyclization when they are heated in the presence of 2-methylimidazole [67]. Esters XXIV also give compounds of the II type when they are heated with methylamine in an autoclave [68].



XXIII XXIV

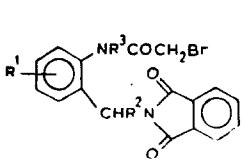
The condensation of anthranils XXV with ethyl glycinate hydrochloride in the presence of formic acid, which leads to II [69], evidently reduces to the above-described reaction of amino ketones VIII (R^3 = H) with this glycine derivative, since amino ketones of the VIII type (R^3 = H) are formed from anthranils in the presence of reducing agents [70].



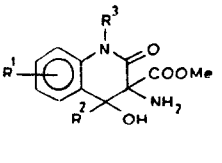
XXV XXVI

X = O, S

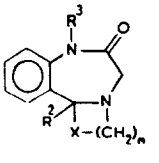
Salts of anthranils and their sulfur analogs (XXVI) also form benzodiazepinones II on reaction with the glycine ester in the presence of 2-methylimidazole [71, 72]. 1,2-Dihydro-3H-1,4-benzodiazepin-2-ones are obtained by condensation of dibenzo[b,f][1,5]diazocines with ethyl glycinate hydrochloride [73], by the action of alkali on 2-chloroacetamidobenzophenone α-oximes [74], by heating phthalimido derivatives XXVII with sodium ethoxide [75], by heating tetrahydroquinolones XXVIII in acetic acid [76], and also from 1,4-benzodiazepine derivatives, by oxidation of 1,2-dihydro-3H-1,4-benzodiazepin-2-ols [77], 1,2-dihydro-3H-1,2,3,4-tetrahydro-5H-1,4-benzodiazepines [78-80], and 2-chloromethyl-3H-1,4-benzodiazepines [81], by hydrolysis of 2-hydrazino-3H-1,4-benzodiazepines [82] and condensed three-membered systems of the XXIX type [83], and by dehydrobromination of 5-bromo-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-2-ones [84].



XXVII



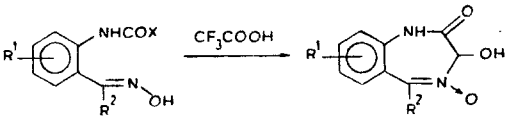
XXVIII



XXIX

X = O, S; n = 2, 3

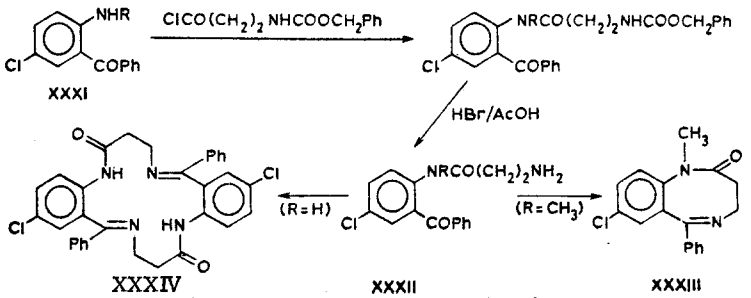
Benzodiazepinone 4-oxides XIX are formed by mild acidic hydrolysis of 4-oxides of 2-methylamino- and 2-(N-methyl-N-acetamido)-3H-1,4-benzodiazepines [85]. They are readily obtained by the action of alkali on 3-oxides of 2-chloromethylquinazolines [43, 86], by intramolecular N-alkylation of 2-chloroacetamidobenzophenone β-oximes in alkaline media or in the presence of anion-exchange resins [10, 86, 87], and also by the action of mineral acids on hydroxylaminoacetamido ketones XVIII [88]. N-Glyoxyloyl β-oximes XXXa and their hydrates (XXXb) and polymers undergo cyclization to 3-hydroxy-1,2-dihydro-3H-1,4-benzodiazepin-2-one 4-oxides [89-91].



XXX a, b

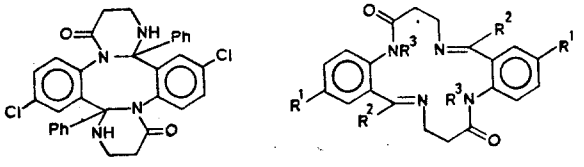
XXX a X = CHO; b X = CH(OH)$_2$

1,2,3,4-Tetrahydro-1,5-benzodiazocin-2-ones (III). The first compounds of this series were obtained by the action of N-benzyloxycarbonyl-β-alanyl chloride on aminobenzophenones XXXI with subsequent cyclization of the 2-(3-aminopropionylamino)benzophenones (XXXII) [11].



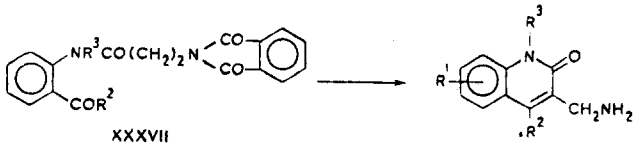
XXXIV XXXII XXXIII

However, the direction of cyclization of XXXII differs as a function of the presence or absence of a substituent attached to the amide nitrogen atom [92]. The product of cyclization of XXXII when R = CH_3 actually has the 1,5-benzodiazocin-2-one structure, while when R = H, a substance that was assigned the XXXIV structure is formed [92], although one cannot exclude the possibility of alternative structure XXXV. The authors of the present review and their co-workers have synthesized a number of compounds of the XXXVI type by both the method described above and by a simpler method — condensation of amino ketones VIII with β-alanyl chloride hydrochloride [93] — and have established that XXXVI have the dibenzo-[b,j][1,5,9,13]tetraazacyclohexadeca-9,19-diene-6,16-dione structure.



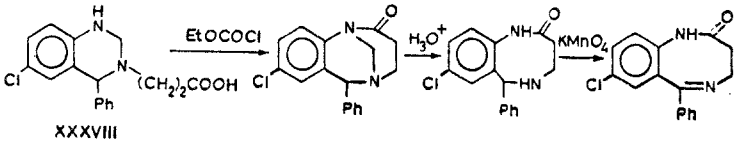
XXXV XXXVI

An attempt to obtain III from β-phthalimidopropionylamino ketones XXXVII gave the isomeric 3-aminomethylquinolones instead of the expected 1,5-benzodiazocin-2-ones [94]. 3-Aminoquinolones are also formed as side products in the preparation of 1,4-benzodiazepin-2-ones II from XV [45].



XXXVII

1-Unsubstituted III were obtained [95] from carboxyethylquinazolines XXXVIII.

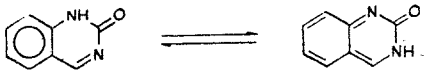


XXXVIII

1,2,3,4-Tetrahydro-5H-1,6-benzodiazonin-2-ones (IV). Compounds of the IV type are formed in the cyclization of o-acyl-N-(4-aminobutyryl)anilines in pyridine [13] or directly by condensation of amino ketones VIII with γ-aminobutyryl chloride hydrochloride without isolation of the intermediates [12].

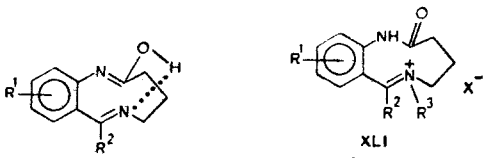
Tautomerism of 2-Quinazolinones and Their Cyclic Homologs

According to data from IR, UV, Mass, and PMR spectroscopy and polarography, I-IV with $R^3 \neq H$ have lactam structures regardless of the acidity of the medium [96-98]. Dihydroquinazolinones and their seven- and eight-membered cyclic homologs that are not substituted in the 1 position ($R^3 = H$) also have lactam structures in the crystalline state and in solutions ($CHCl_3$ and CCl_4). 2-Quinazolinone exists in chloroform in the form of two tautomeric forms XXXIXa and XXXIXb with a preponderance of the former [99].



XXXIX a XXXIX b

1-Unsubstituted 1,6-benzodiazonine derivatives under normal conditions have lactam structure XL, which is evidently stabilized by an intramolecular hydrogen bond between the proton of the hydroxy group and the N_6 atom. In conformity with this assumption, salts XLI have lactam structures.

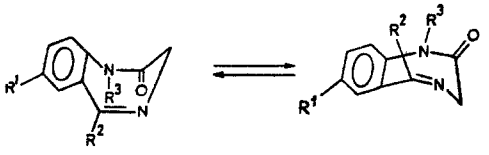


XL XLI

$R^3 = H, Alk$

Stereochemistry of 2-Quinazolinones and Their Cyclic Homologs

The pyrimidine and benzene rings in 2-quinazolinones are coplanar. The diazepine ring of 1,2-dihydro-3H-1,4-benzodiazepin-2-ones has the conformation of a distorted pseudoboat [100-106]. It has been shown by the dynamic PMR method that the conversion IIa ⇄ IIb, the rate of which depends on the character of the substituents, occurs in solutions [103, 107-110]. The III and IV systems are evidently nonplanar, but their stereochemistry has not been investigated.



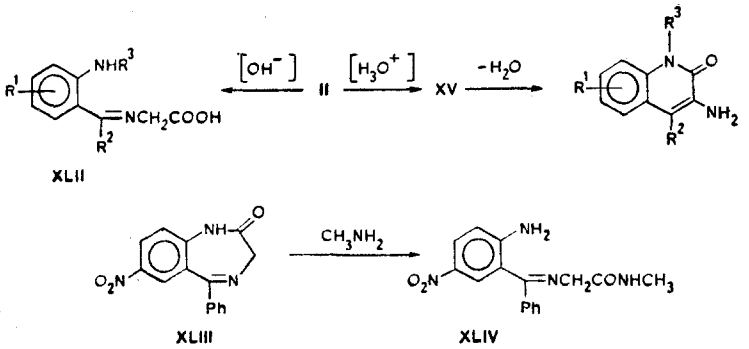
II a II b

Studies have been devoted to the synthesis, separation into optical antipodes, and the properties of chiral 1,2-dihydro-3H-1,4-benzodiazepin-2-ones [111-114].

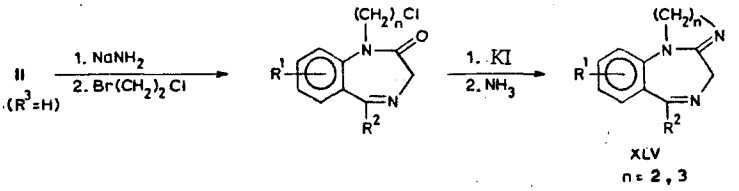
Chemical Properties of 2-Quinazolinones and Their Cyclic Homologs

Compounds of the I-IV type are weak monoacidic bases, and their basicities decrease in the order IV > II > III > I [115-117].

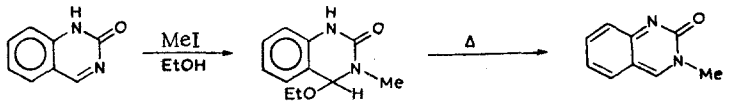
Hydrolysis and Aminolysis. The heteroring of 2-quinazolinones is extremely stable with respect to hydrolysis [6]. The acid hydrolysis of II-IV leads to amino ketones VIII and the corresponding amino acids. The isomeric 3-aminoquinolones can be obtained by mild acid hydrolysis of benzodiazepinones II [45], whereas alkaline hydrolysis gives imino acids XLII [43, 85]. Similarly, the aminolysis of nitrazepam XLIII leads to methylamide XLIV [118].



Alkylation, Alkoxylation, and Hydroxyalkylation. The sodium salts of I-IV (R^3 = H) undergo alkylation to give the corresponding 1-substituted compounds [22, 24, 43, 85, 119]. This reaction is widely used for the synthesis of diverse 1,4-benzodiazepine derivatives. Thus, for example, imidazo- and pyrimido-1,4-benzodiazepines XLV have been obtained by this method [120, 121].



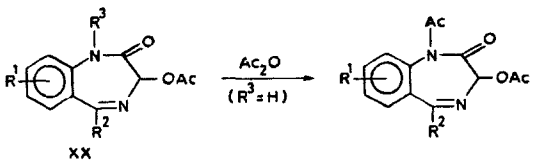
When II and IV are refluxed with methyl iodide in acetone, they undergo quaternization of the azomethine nitrogen atom [48, 98]. 2-Quinazolinone reacts with methyl iodide in ethanol to give 3-methyl-4-ethoxytetrahydro-2-quinazolinone, which upon heating is converted to 3-methyl-2,3-dihydro-2-quinazolinone [122].



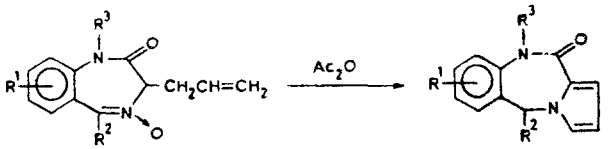
The preparation of 2-methoxy-3H-1,4-benzodiazepine 4-oxides by the action of diazomethane on N-oxides of the XIX type (R^3 = H) has been described [123]. 5-Substituted 4-hydroxy-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-2-ones were obtained by the action of Grignard reagents on 4-oxides XIX (R^2 = H) [124]. Quinazolinones I (R^2 = H) are alkylated in the 4 position by means of phenyllithium [125]. Radical trifluoromethoxylation occurs in the phenyl ring of II (R^2 = C_6H_5) when the latter are irradiated at −78°C in the presence of HF and CF_3OF [126].

3-Halo derivatives of benzodiazepinones II undergo reaction with alcohols readily to give 3-alkoxy derivatives [86, 127]. When compounds of the II type are heated with paraformaldehyde, they are converted to 3-hydroxymethyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones [128].

Acylation. 2-Quinazolinone reacts with benzoyl chloride to give 1-benzoyl-2-quinazolinone [129]. Compounds II (R^3 = H) are acylated in the 1 position by the action of acyl halides on their sodium salts [130]. The action of anhydrides and chlorides of acids on N-oxides XIX leads, as a result of a Polonovski rearrangement, to 3-acyloxy derivatives XX, which, when R^3 = H, undergo subsequent acylation in the 1 position [131-133].



In contrast to the reaction described above, the action of acetic anhydride on 4-oxides XLVI leads to pyrrolo[2,1-c][1,4]benzodiazepines XLVII [134].



XLVI XLVII

1-Carbamoyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones are obtained by the action of alkyl isocyanates on compounds of the II type (R^3 = H) [135].

Reduction. By selection of the reducing agent and the reaction conditions one can effect the selective reduction of either individual or simultaneously several fragments of the I-IV molecules. Sodium borohydride reduces the azomethine bond in quinazolinones [136]. Similar reaction products are obtained in the hydrogenation of I with hydrogen on Raney nickel and by preparative polarographic reduction [137]. Benzodiazepinones II are hydrogenated on platinum [85] and by polarographic reduction [138-141] to tetrahydro derivatives. Lithium aluminum hydride [142] and sodium borohydride (when BF_3 is present) [143] reduce them to a mixture of tetra- and dihydrobenzodiazepinones. 1,2-Dihydro-3H-1,4-benzodiazepines are formed by the action of diborane at −10°C on the same substances. Nitrazepam XLIII can be selectively reduced to the 7-amino derivative (with hydrogen on Raney nickel) or to the 7-hydroxylamino derivatives [146] (by means of $SnCl_2$). Its photochemical reduction in neutral media gives the corresponding azo and azoxy derivatives [147]. The nitrazepam is reduced polarographically in two steps to give initially 7-hydroxylaminobenzodiazepinone II (R^1 = NHOH, R^2 = Ph, and R^3 = H) and subsequently 7-amino-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-2-one [148, 149]. N-Oxides XIX are reduced to benzodiazepinones II by means of PCl_3 [85] or iron in acetic acid [150]. Zinc dust in acetic acid reduces them to tetrahydro-1,4-benzodiazepin-2-ones [151], whereas Grignard reagents and hydrogen over platinum reduce them to 4-hydroxytetrahydro-1,4-benzodiazepin-2-ones [152, 153]. The reduction of N-oxides XIX with complex hydrides leads to tetrahydro-1,4-benzodiazepin-4-ols [154]. The selective reduction of the acetyl group to a hydroxyethyl group in acetylbenzodiazepinones II (R^1 = Ac) with sodium borohydride has been described [155].

Tetrahydrobenzodiazocine derivatives III are reduced by hydrogen on Raney nickel to 1,2,3,4,5,6-hexahydro-1,5-benzodiazocin-2-ones, whereas they are reduced by lithium aluminum hydride to hexahydro-1,5-benzodiazocines [156].

Oxidation. 2-Quinazolinones are extremely stable with respect to oxidizing agents [6]. Compounds II are oxidized to 4-oxides XIX by hydrogen peroxide or peracids [157, 158]. 3-Hydroxy-1,2-dihydro-3H-1,4-benzodiazepin-2-ones are oxidized by ruthenium tetroxide to unstable 1,2-dihydro-3H-1,4-benzodiazepin-2,3-diones [80]. The corresponding 7-acyl derivatives are obtained by the action of ammonium hexanitroferrate on 7-alkyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones [159]. Oxidation of compounds of the XLVIII type with Fremi's salt (potassium nitrosyldisulfonate) leads to benzoquinonodiazepinones XLIX [146].

XLVIII XLIX

The biological oxidation of benzodiazepinones II in the human organism and in animals [5], as well as in in vitro experiments in the presence of enzymes of the microsomal fractions of the liver [160], leads to 1,2-dihydro-3H-1,4-benzodiazepin-2-ones that contain a hydroxy group in the 3 or 9 position or in the phenyl ring of the 5-aryl substituent. The 3-hydroxy derivatives are obtained in rather high yields by microbiological oxidation of benzodiazepinones II [161].

Nitration [162, 163]. 1,2-Dihydro-3H-1,4-benzodiazepin-2-ones that are unsubstituted in the 7 position are nitrated to give the 7-nitro derivatives, whereas in the case of 7-substituted II ($R^1 \neq H$, R^2 = Ph) the nitro group enters the meta position of the phenyl ring, and in the case of further nitration it enters the 9 position.

Halogenation. 2-Haloquinazolinones are formed by the action of phosphorus halides on quinazolines I (R^3 = H) [15, 18]. 3-Methoxy-1,2-dihydro-3H-1,4-benzodiazepin-2-ones react similarly [164]. Benzodiazepines II with an extremely labile chlorine atom in the 1 posi-

tion are obtained in the reaction of lactams II (R^3 = H) with organic or mineral hypochlorites [165, 166]. The chlorine atom migrates readily intramolecularly from the N_1 atom to the α-carbon atom of substituent R^2 if there is at least one hydrogen atom attached to this atom.

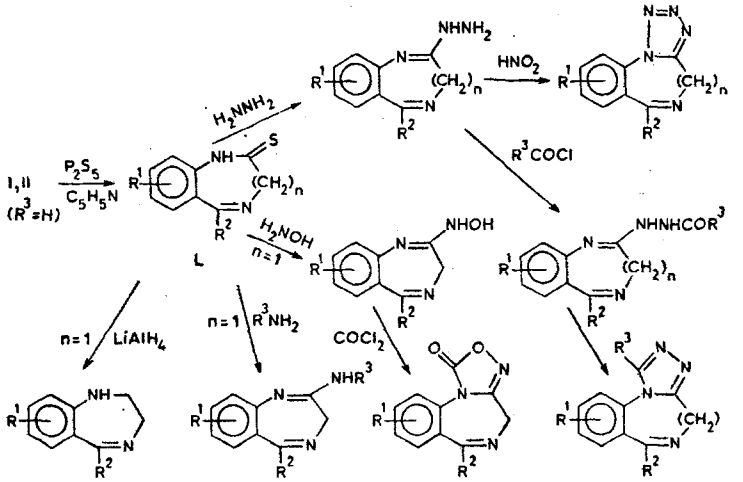
7-Chloro-1,2-dihydro-3H-1,4-benzodiazepin-2-ones are obtained by the action of chlorine on II (R^1 = H) in the presence of ferric chloride [167] or N-chlorosuccinimide [168]. In addition, 7-halo-1,2-dihydro-3H-1,4-benzodiazepin-2-ones are obtained from the corresponding amino derivatives through the diazonium salts [169].

3-Halo-1,2-dihydro-3H-1,4-benzodiazepin-2-ones are synthesized by the action of N-halosuccinimide on the 3-substituted analogs [170] or by replacement of the hydroxy group in this position by means of thionyl chloride [171]. The 3-fluoro derivatives are obtained by the action of ClO_3F in the presence of butyllithium on benzodiazepines II or by the action of HF and $SbCl_5$ on XVI [172]. The reaction of 7-acetyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones in MoF_6 leads to 7-(1,1-difluoroethyl)-substituted derivatives [173].

Amination and Nitrosation. The sodium salts of lactams II (R^3 = H) react with chloroamine to give the 1-amino derivatives, which are readily deaminated by nitrous acid [174]. The reduction of the corresponding nitro compounds or replacement of the halogen atoms or carbalkoxy groups in the 3 position by amine residues also lead to the amino derivatives of 1,2-dihydro-3H-1,4-benzodiazepin-2-ones [175-177]. The 7-cyano, 7-azido, and 7-tetrazyl derivatives are obtained from 7-amino-1,2-dihydro-3H-1,4-benzodiazepin-2-ones through the diazonium salts [178, 179].

The nitrosation of compounds of the II type (R^3 = H) with sodium nitrite in glacial acetic acid has been described [180].

Replacement of the Carbonyl Oxygen Atom by a Sulfur Atom. This reaction takes place readily when I and II are treated with phosphorus pentasulfide, usually in pyridine [6, 181-183]. It is of great preparative value, since it makes it possible to realize the conversion to quinazoline [18] and 3H-1,4-benzodiazepine derivatives [181], as well as to condensed systems with fused triazole [184], tetrazole [18], and other rings.

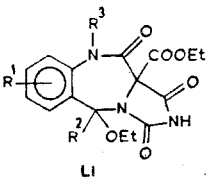


It has been shown [185] that it is possible to convert quinazoline-2-thiones to quinazolinones by oxidation with potassium permanganate.

Reaction with Hydroxylamine Hydrochloride. Lactams II undergo this reaction to give the corresponding oximes [186].

Addition to the Azomethine Bond. When Lewis acids are present, II add α-oxides to give oxazolidino[3,2-d][1,4]benzodiazepines [187], oximes to give dihydro-1,2,4-oxadiazolo[4,5]-[1,4]benzodiazepin-2-ones [188], and acetyl chloride and diketene to give dihydro-1,3-oxazino[1,4]benzodiazepin-2-ones [189].

The reaction of 3-carbamoyl-3-ethoxycarbonyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones with phosgene in ethanol leads to imidazolidino[5,1-c][1,4]benzodiazepin-2-ones (LI) [190].



LI

Condensation with Electrophilic Reagents at the Methylene Group. 1,2-Dihydro-3H-1,4-benzodiazepin-2-ones and -2-thiones react with quaternary salts of heterocycles [191], carbonyl compounds [192], and their derivatives [193] to give 3-alkylidene-, 3-arylidene-, and 3-hetarylidene-1,2-dihydro-3H-1,4-benzodiazepin-2-ones.

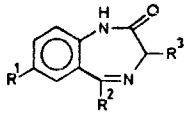
Complexing. 1,2-Dihydro-3H-1,4-benzodiazepin-2-ones and their homologs III and IV give coordination compounds with Lewis acids (BF_3, $ZnCl_2$, SiF_4, $CoCl_2$, BiI_4^-, etc.) and thiocyanates [97, 194-196]; in this case the nitrogen atom in the 4 position acts as the donor of the electron pair. Some of the complexes are deeply colored, and this makes it possible to use them in the analysis of benzodiazepinones II.

Rearrangements and Isomerizations. Diverse rearrangements and isomerizations in the II series have been described (see an earlier review [197]). Let us note only that these processes lead not only to new derivatives of 1,4-benzodiazepine but also to compounds of other classes: indoles, isoindoles, indolquinolines, quinolines, oxazoloquinolines, quinoxalines, quinazolines, etc.

Pharmacological Properties and the Application of 2-Quinazolinones and Their Cyclic Homologs

2-Quinazolinones have sedative, anticonvulsive, depressant, antiphlogistic, antipyretic, analgesic, and hypotensive activity [17, 22, 25, 32]. It has been recommended [198] that they be used as stabilizers for photoemulsions and photocontact printing. Preparations of the II series have powerful tranquilizing, antispasmodic, and myorelaxant activity vis-à-vis low toxicity.

Some of them have a soporific effect. Diazepam (Valium or Seduxen, LII, R^1 = Cl, R^2 = Ph, R^3 = CH_3), nitrazepam (Mogadon or Eunoctin, LII, R^1 = NO_2, R^2 = Ph, R^3 = H), clonazepam (LII, R^1 = NO_2, R^2 = o-ClC_6H_4, R^3 = H), oxazepam (Tazepam, LII, R^1 = Cl, R^2 = Ph, R^3 = OH),



and lorazepam (LII, R^1 = Cl, R^2 = o-ClC_6H_4, R^3 = OH) have found extensive application in medicine. The Soviet preparation fenazepam (LII, R^1 = Br, R^2 = o-ClC_6H_4, R^3 = H) has been accepted for use in medical practice [199, 200]. The first attempts to ascertain the mechanism of the action of 1,4-benzodiazepines led to the elucidation of some aspects of their effect on the CNS. It was shown that tranquilizers of the II series increase the activity of the γ-aminobutyric acid receptors [201]. Receptors with which these preparations interact were detected in the brain [20].

The relationship between the structure and pharmacological properties of II has been investigated in a number of papers [5, 114, 119, 203-207]. The nature of the effect of the halogen atoms in 5-halophenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones on their tranquilizing activity, which was evaluated from tests of antagonism with Corazole, is extremely interesting. Transferral of the halogen atom from the ortho to the meta position leads to a pronounced decrease in activity. Thus, e.g., in the 7-chloro-5-fluorophenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one series a decrease in the activity by a factor of more than four orders of magnitude is observed on passing from the ortho to the para isomer [5]. The decrease in the activity when the halogen is moved from the ortho to the para position is expressed more markedly, the higher the electronegativity of the halogen atom [206]. At the same time, the activity of o-halophenyl derivatives is virtually independent of the nature of the halogen.

Compounds III and IV also have an effect on the CNS, but their tranquilizing, myorelaxant, and antispasmodic properties are manifested at considerably higher dose levels as compared with the corresponding I and II. Whereas the tranquilizing effect is the major

effect in the pharmacological spectrum of 2-quinazolinones and 1,2-dihydro-3H-1,4-benzodiazepin-2-ones, hypno-sedative effects dominate in the case of 1,2,3,4-tetrahydro-1,5-benzodiazocin-2-ones and 1,2,3,4-tetrahydro-5H-1,6-benzodiazonin-2-ones [208].

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INTRAMOLECULAR CYCLIZATION OF 2-ARYL-3-AMINOACETYL-1,4-NAPHTHOQUINONES TO 3-BENZOCOUMARANONE DERIVATIVES*

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The isomerization of 2-aryl-3-(N-alkyl-N-arylamino)acetyl-1,4-naphthoquinones to 2-(N-alkyl-N-arylamino)-4-aryl-5-hydroxy-6,7-benzocoumaran-3-ones was studied. The structures of the compounds obtained were confirmed by the data from the UV, IR, mass and PMR spectra.

2-Aryl-3-(N-alkyl-N-arylamino)acetyl-1,4-naphthoquinones (I) are intramolecular donor-acceptor complexes (self-complexes) [2, 3]. Isomerization products in the form of yellow crystals that dissolve in aqueous alkalis to give red solutions and are isolated unchanged from them when the solutions are acidified were unexpectedly obtained during a study of their solubility in acetic acid. Benzocoumaranone structure II was established for the products of isomerization of aminoacetylnaphthoquinones I from the data from the UV, IR, mass, and PMR spectra (see Table 1 and the experimental section). The carbonyl bands of the five-membered ring are observed in the IR spectra of these compounds at 1705-1730 cm^{-1}; their assignment is in agreement with the data on the absorption of coumaranones [4, 5].

Benzocoumaranones II were characterized in the form of acetyl and benzoyl derivatives III and IV. Since the cyclization proceeds in the same way in all cases, it was subsequently more convenient to study it in the case of 2-(N-methylanilino)-4-phenyl-5-hydroxy-6,7-benzocoumaran-3-one (IIa).

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