AMIDRAZONES IN THE SYNTHESIS OF HETEROCYCLES

(REVIEW)

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Data on the synthesis, on the basis of amidrazones, of mono-, di-, tri-, and tetrazoles, diazoles containing boron, oxygen, silicon, phosphorus, and sulfur atoms in the ring, mono-, di-, tri-, and tetrazines, triazepines, and benzotriazepines, as well as a number of condensed heterocyclic derivatives, are systematized.

Amidrazones, which were first obtained and described at the end of the last century, are attracting ever increasing attention [1, 2], since they find application in the manufacture of heat-resistant polymers [3] and photographic materials [4, 5] and are of interest as complexones [6-9], including those for the synthesis of biologically active complexes [8]. Individual amidrazones themselves have various sorts of biological activity (antibacterial and antifungal [10-12], tuberculostatic [11], sedative [13], antiviral [14], and anticancer activity [15]) and are known as antimetabolites [14], herbicides, rodenticides, and nematocides [16, 17]. Amidrazones are particularly valuable in the synthesis of heterocycles.

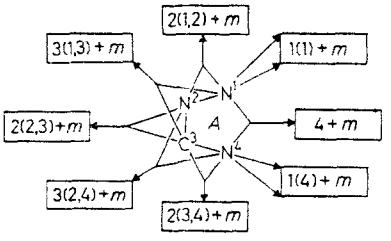
The present review seems necessary, since previous reviews [1, 2] devoted to the chemistry of amidrazones as a whole have become obsolete, and the number of publications in this area has recently increased significantly. In addition, in the case of amidrazones we wish to draw attention to the possibilities in the synthesis of heterocyclic structures of an entire class of polyfunctional derivatives of hydrazine (hydrazides, thiohydrazides, semi- and thiosemicarbazides, carbo- and thiocarbohydrazides, etc.). From our point of view, a previous review devoted to this problem [18] is far from being complete and is not systematized.

As a rule, below we have examined only amidrazones with linear structures. Information regarding related compounds in which a given part of the amidrazone fragment is included in a cyclic structure (cyclic amidrazones [19]) will be presented only when necessary. Some data on the reactions of cyclic amidrazones can be found in [20].

In setting forth the material we used the classification of the types of reactions involving the synthesis of heterocycles by means of the formula n(*a*, b) + m, where n is the number of atoms of synthone A that participate in ring formation, *a* and b are the numbers of the reaction centers of the synthone, and m is the number of reagent atoms included in the ring.

Scheme 1

Classification of the types of reactions in the synthesis of heterocycles



S. M. Kirov Academy of Military Medicine, Leningrad 194175. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 867-887, July, 1989. Original article submitted March 4, 1988.

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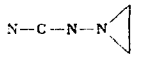
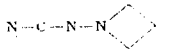
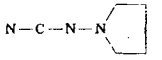
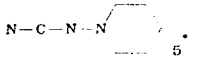
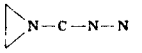
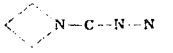
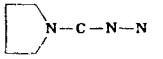
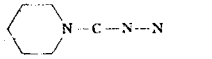
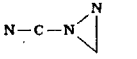
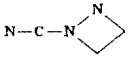
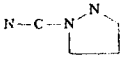
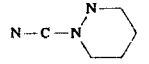
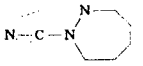
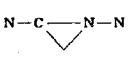
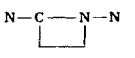
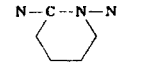
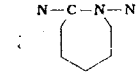
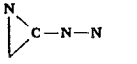
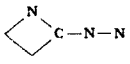
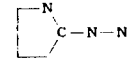
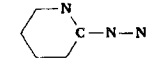
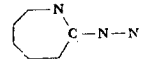
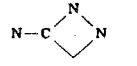
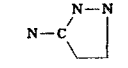
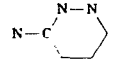
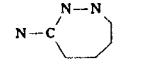
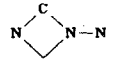
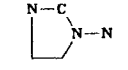
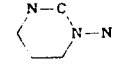
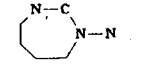
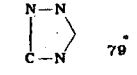
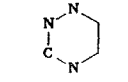
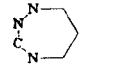
TABLE 1. Possible Cyclizations on the Basis of Amidrazones

Type		Number of reagent atoms m that enter into the ring					
n	a, b	0	1	2	3	4	5
1	1	—	—				 5
	4	—	—				
2	1,2	—			 6		
	2,3	—					
	3,4	—					
3	1,3			 26	 3		—
	2,4			 2	 5		—
4	1,4		 79	 61	 13	—	

*Types of reactions actually realized (the number of the literature citation is indicated).

Amidrazones (A) as synthones [21, 22] that have a chain made up of three nitrogen atoms separated by a carbon atom potentially may serve as a basis for the synthesis of the most diverse heterocycles with one to three nitrogen atoms (Table 1). The spectrum of theoretically possible structures becomes even broader when other heteroatoms are introduced by means of the appropriate reagents and also when amidrazones with functional groupings that contain such heteroatoms are used. The number of heterocycles can also be expanded through reactions that occur with fragmentation of the amidrazone molecule. No data on the synthesis of rings with more than seven atoms on the basis of amidrazones are available. One's attention is directed to the fact that only a small part of the synthetic schemes (nine of the 37) have thus far been realized.

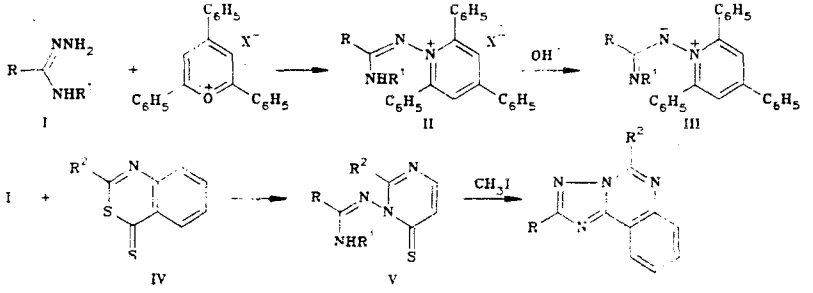
METHODS FOR THE SYNTHESIS OF HETEROCYCLES ON THE BASIS OF AMIDRAZONES

1. 1(a) + m Reactions

At the present time, of the eight possible schemes of this type (Table 1), only one, which corresponds to the formula 1(1) + 5, has been realized.

Under the influence of the triphenylpyrylium cation N(3)-substituted amidrazones I are converted to 1-amidino-2,4,6-triphenylpyridinium salts II, which are readily deprotonated to imidoyl-N-imides III [23-25]. If the starting cation contains a functional substituent in the 2 position, the resulting products II and III are capable of undergoing various intramolecular condensations that lead to two-ring systems [26].

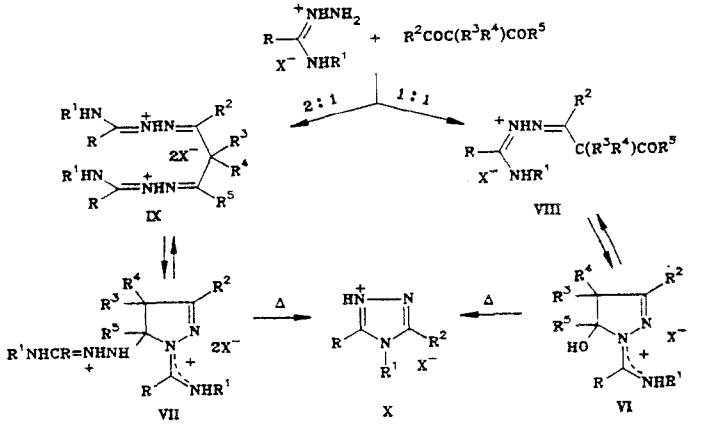
The corresponding aminoquinazolinethiones V, which are also capable of subsequent intramolecular transformations, were synthesized as a result of the reaction of amidrazones with 2-aryl-4-thioxo-1,3-benzothiazines IV [27].



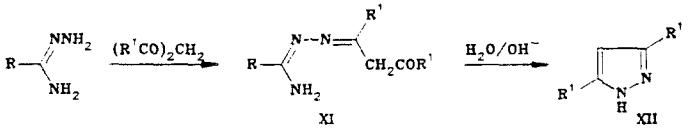
2. 2(a, b) + m Reactions

Among the 15 possible variants of this type (Table 1), only reactions of the 2(1, 2) + 3 type, which pertain primarily to reactions of amidrazones with 1,3-diketones, are currently known. Adducts with linear structures, which may subsequently undergo intramolecular cyclization both under the influence of external effects and spontaneously, are initially formed in the course of this reaction [28-31].

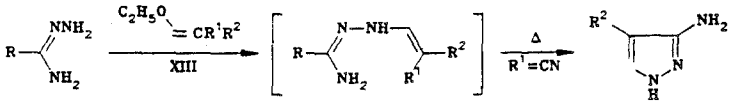
The reactions of amidrazone hydrohalides with 1,3-diketones leads to the formation of the corresponding 2-pyrazolines VI and VII, which usually exist in solution in equilibrium with open forms VIII and IX [28-30]. However, the thermolysis of pyrazolines VI and VII does not lead to pyrazoles but rather 1,2,4-triazoles X, i.e., condensation products of the 4 + 1 type (Scheme 1). Additional data in regard to this will be examined in section 4.1.



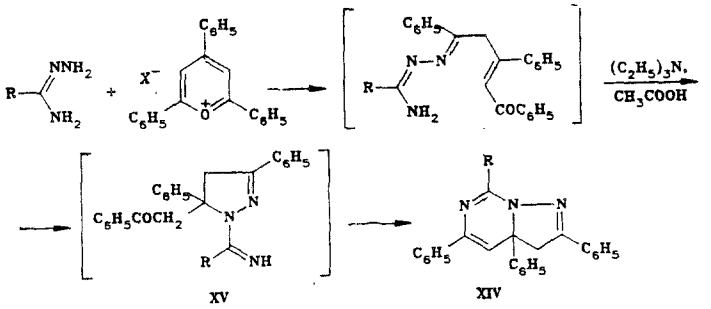
The products of the reaction of aliphatic amidrazones with 1,3-diketones are "hydrazones" XI, which give pyrazoles XII on alkaline hydrolysis [31].



The corresponding pyrazoles are also formed in the reaction of amidrazones with reagents of the XIII type [32].



Unsubstituted amidrazones react with pyrylium salts on heating to give pyridinium salts II, whereas in the presence of triethylamine and acetic acid they give pyrazolo[1,5-c]-pyrimidines XIV. In the preparation of XIV the reaction proceeds through a step involving the formation of unisolable intermediate XV, which corresponds to an adduct of the 2(1, 2) + 3 type, which then undergoes intramolecular cyclization [23].

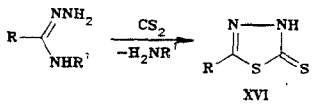


3. 3(a, b) + m Reactions

At present four variants of transformations of this type have been described.

3.1. Synthesis of Five-Membered Heterocycles by means of Reactions of the 3(1, 3) + 2 Type. These reactions occur in the reaction of amidrazones with heterocumulenes with the formula X = C = Y [isocyanates (X = O, Y = NR), isothiocyanates (X = S, Y = NR), carbodiimides (X = Y = NR), carbon disulfide (X = Y = S)] and compete with other types of reactions.

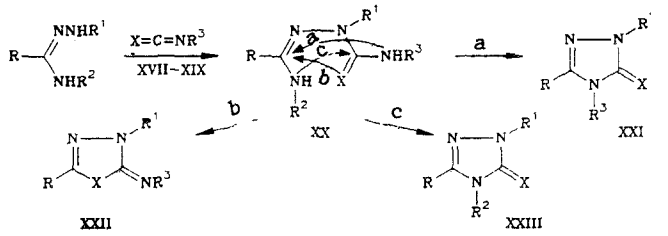
2-Thioxo-1,3,4-thiadiazolines XVI are formed unambiguously as a result of splitting out of the amino group in the reaction of amidrazones with carbon disulfide [33, 34].



Three competitive reactions, two for which (a and b) belong to the 3(1, 3) + 2 type under discussion, while the third (c) belongs to the 4(1, 4) + 1 type, usually occur with other heterocumulenes.

Scheme 2

Reaction of amidrazones with heterocumulenes



XVII X=NR⁴; XVIII X=O; XIX, XXII X=S; XXI, XXIII X=NR⁴, O, S

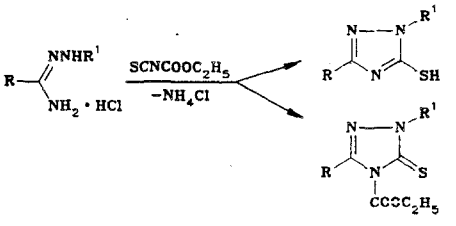
Thus 1,2,4-triazole derivatives of different types – XXI and XXIII – are formed in the reaction of amidrazones with carbodiimides XVII, which proceeds through intermediate XX. Pathway *a* predominates in the reactions of acetamidrazone, while the use of benzamidrazone most often leads to products XXIII, and the use of phenylacetamidrazone leads to mixtures of these products [35, 36].

The reaction of amidrazones with isocyanates XVIII also initially gives adducts with linear structures XX, which subsequently undergo cyclization in an alkaline medium to 1,2,4-triazoles of the XXI type (pathway *a*) [37-39] or XXIII (pathway c) [37, 40]. Pathway *a* is preferred; this is explained by the greater nucleophilicity of the imino nitrogen atom of the reagent as compared with the amide nitrogen atom in the amidrazone molecule [37].

The available data on the reactions of amidrazones with isothiocyanates are numerous and ambiguous [37-51].

Both 1,2,4-triazoles XXI and 1,3,4-thiadiazoles XXII (X = S, Scheme 2) were isolated when amidrazones were used as the bases. The condensation of $N_{(4)}$-substituted amidrazones with aliphatic and aromatic isothiocyanates without the addition of a catalyst leads to 1,2,4-triazoles XXI [38, 40-43]. At the same time, $N_{(1)}$, $N_{(4)}$-disubstituted amidrazones undergo cyclization to 1,3,4-thiadiazoles XXII; the isomeric 1,2,4-triazole-5-thiones are formed as impurities [44]. An increase in the acceptor character of substituent R increases the percentage of the 1,2,4-triazole in the reaction mixture [45].

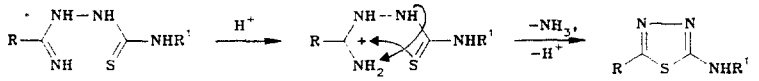
The available data on the reaction of amidrazone salts with isothiocyanates are also contradictory.



The hydrochlorides of acetamidrazone and benzamidrazone form 1,2,4-triazoles XXI via pathway *a* in this reaction [39]. The same result was also obtained in the reaction of carbethoxymethyl isothiocyanate (XIX, X = S, $R^3 = COOC_2H_5$) with the hydrochlorides of both acetamidrazone and benzamidrazone [46] and with their $N_{(1)}$-substituted homologs [47]; however, the synthesis of 1,2,4-triazoles with different structures is possible in this case.

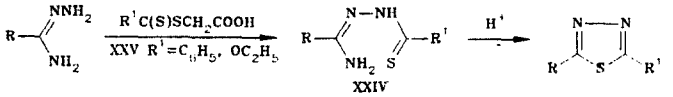
It is asserted, however, that the derivatives of unsubstituted amidrazones, which were described in [46] as 1,2,4-triazole-5-thiones XXI, are actually 2-amino-1,3,4-thiadiazoles XXII [37]. It was also found that isothioxyanates that contain a carbonyl group (XIX, R^3 =

COAlk) [48], as well as ethylcarbomethoxy isothiocyanate (XIX, $R^3 = C_2H_4COOCH_3$) [49], lead to 1,3,4-thiadiazoles XXII. In the opinion of Bany and Galewicz [50] amidrazone salts give 1,3,4-thiadiazoles XXII owing to acidic catalysis.

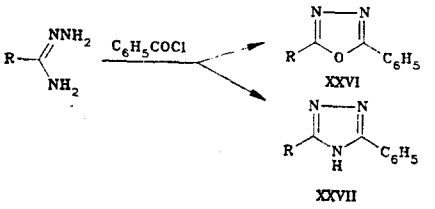


It has been established that the cyclization of linear adducts XX usually (although not always) obeys the rule – 2-amino-1,3,4-thiadiazoles XXII are formed in an acidic medium, and 1,2,4-triazole-5-thiones (XXI or XXIII) are formed in an alkaline medium [37].

1-Thioaroylamidrazones XXIV, which are formed in the reaction of the starting amidrazones with reagents of the XXV type, undergo cyclization to 2,5-disubstituted 1,3,4-thiadiazoles under the influence of acids, whereas they decompose under the influence of alkalis [52].

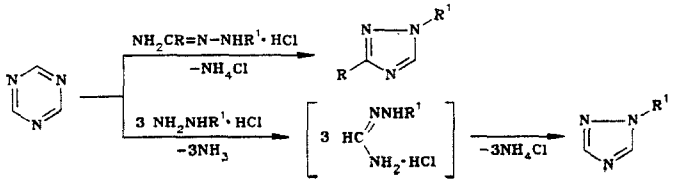


Both 1,3,4-oxadiazoles XXVI, which correspond to a reaction via the 3(1,3) + 2 scheme, and 1,2,4-triazoles XXVII, which is in agreement with the 4 + 1 scheme, can be isolated when amidrazones are heated with benzoyl chloride in strong acids [53, 54].

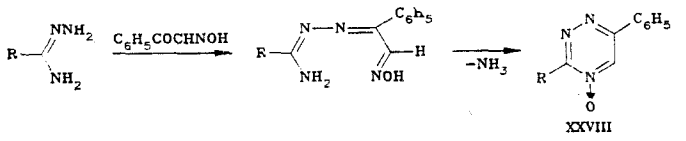


On the whole, it should be noted that the data on the reactions of amidrazones with the compounds enumerated above, despite the large volume of experimental material, are extremely contradictory and must be evaluated carefully.

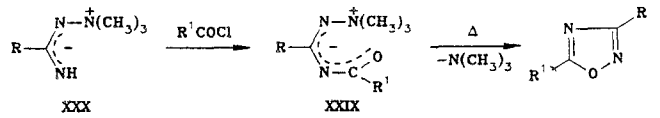
1,2,4-Triazoles were also obtained by the reaction of amidrazonium salts with 1,3,5-triazine [55], as well as by the reaction of 1,3,5-triazone with hydrazine salts [56]. In the latter case formamidrazone is an intermediate [57, 58].



3.2. Synthesis of Six-Membered Heterocycles by means of Reactions of the 3(1, 3) + 3 Type. Only the reaction of amidrazones with monooximes of 1,2-dicarbonyl compounds, which leads to 1,2,4-triazine 4-oxides XXVIII, can be assigned with confidence to this scheme [59].

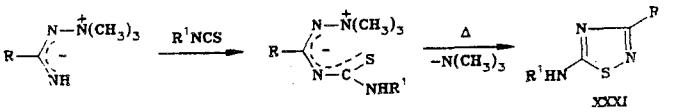


3.3. Synthesis of Five-Membered Heterocycles by means of Reactions of the 3(2, 4) + 2 Type. The thermolysis of $N_{(3)}$-acylamidrazone ylids XXIX, which are formed as a result of the acylation of ylids XXX, was used to obtain 1,2,4-oxadiazoles [60].



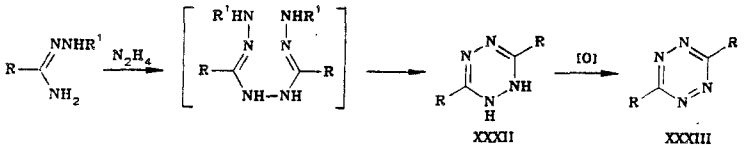
XXX XXIX

The sulfur analogs – 1,2,4-thiadiazoles XXXI – can also be obtained similarly [61].



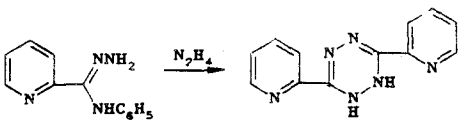
XXXI

3.4. Synthesis of Six-Membered Heterocycles by means of Reactions of the 3(2, 4) + 3 Type. The synthesis of 1,2,4,5-dihydrotetrazines and tetrazines XXXII and XXXIII by the reaction of amidrazones with excess hydrazine [62, 63], which was first accomplished by Pinner [62], can be assigned to reactions of this type

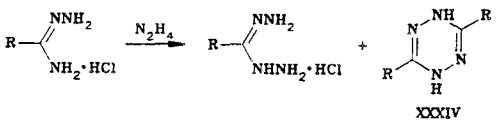


XXXII XXXIII

Later studies sometimes confirmed this type of reaction [63] and sometimes indicated a 3(1, 3) + 3 scheme [64].

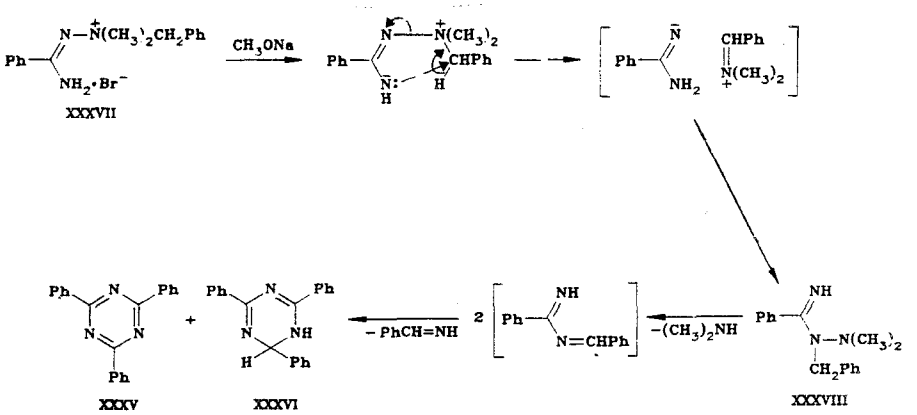


The formation of dihydrotetrazines XXXIV possibly proceeds via both schemes [65].



XXXIV

The preparation of symmetrical 1,3,5-triazines XXXV and XXXVI by thermolysis of N(1)-benzyl-substituted ylids XXXVII has also been described [66, 67]. The proposed complex mechanism of the reaction probably proceeds with the formation of an intermediate rearrangement product XXXVIII, which, by losing a molecule of dimethylamine, undergoes a 1,4-cycloaddition with subsequent splitting out of an arylidenimine.

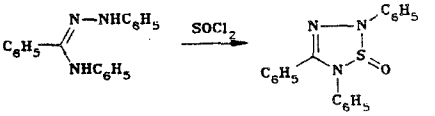


XXXVII XXXVIII XXXV XXXVI

4. 4(1, 4) + m Reactions

Approximately 75% of the literature sources that describe the use of amidrazones in the synthesis of heterocycles is devoted to condensations of this type. Of the four possible reaction schemes (Table 1), only intramolecular transformation of the amidrazone molecule has not been realized.

4.1. Synthesis of Five-Membered Heterocycles by means of Reactions of the 4(1, 4) + 1 Type. Reactions of this type have been described in part in reviews [1, 2]. The reaction of $N(_1)$, $N(_3)$-diphenylbenzamidrazone with thionyl chloride leads to 2,5-dihydro-2,4,5-triphenyl-1,2,3,5-thiatriazole-1-oxide (XXXIX) [68].

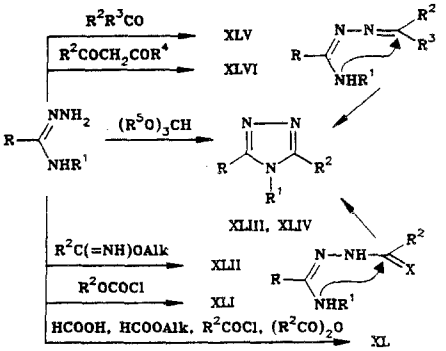


XXXIX

However, 1,2,4-triazoles with different structures are primarily obtained by means of reactions of this type [69]. Synthetic pathways that lead to 1,2,4-triazole derivatives (see Scheme 3) are realized, as a rule, through intermediates with linear structures – 1-acylamidrazones and the structurally related XL-XLII or 1-alkyldeneamidrazones XLV-XLVI. These reactions were examined for the first time by Bladin [70-73].

Scheme 3

Synthesis of 1,2,4-triazole derivatives by a reaction of the 4(1, 4) + 1 type

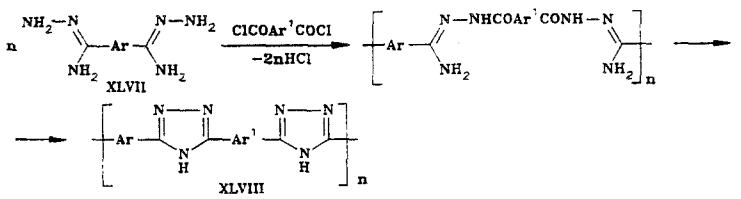


XL, XLII, XLIII, XLV, XLVI R^2=H, Alk, Ar, XLI, XLIV R^2=OAlk, OAr; XLV R^3=H, Alk, Ar, XLVI R^3=CH_2COR^4; XL, XLI X=O, XLII X=NH

The acylation of amidrazones with subsequent conversion of the intermediate XL-XLII to 1,2,4-triazoles XLIII and XLIV can be realized under the influence of acid anhydrides, acid halides, esters, imido esters, and, in individual cases, the acids themselves.

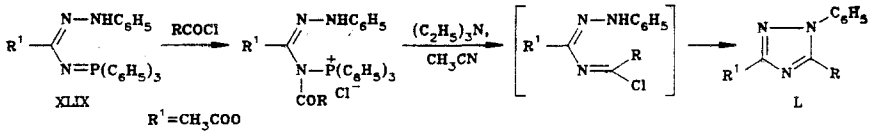
In particular, the reaction of amidrazones with various halogen compounds, which leads through intermediate acylhydrazones XL or XLI to 1,2,4-triazole derivatives XLIII and XLIV, has been studied [74, 75]. The cyclization was accomplished, as a rule, under the influence of an alkali [76].

Poly(1,2,4-triazoles) XLVIII, which are insoluble in organic solvents and are of interest as heat-resistant polymers, are obtained from bisamidrazones XLVII by this method [77].



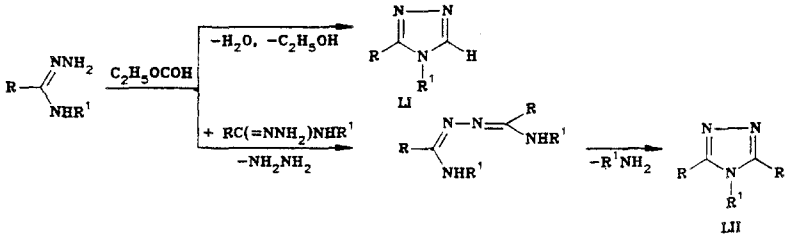
XLVII XLVIII

The reaction of phosphine imides XLIX with acyl chlorides leads to substituted 1,2,4-triazoles L [78].

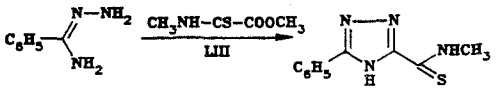


Amidrazones are also acylated by acid anhydrides [79, 80]. This method is also used in syntheses of heat-resistant polymers of the XLVIII type [81, 82].

A method for the synthesis of 3,4-diaryl-substituted 1,2,4-triazoles LI by the reaction of amidrazones with ethyl formate has been proposed [83]. In carrying out the reaction one must monitor the development of the formic acid impurity, which serves as a catalyst for the side condensation of two molecules of the amidrazone, which leads to the 3,4,5-trisubstituted 1,2,4-triazoles LII.

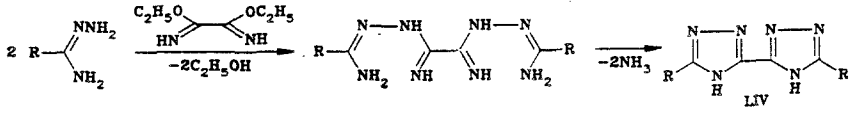


The reaction of benzamidrazone with thioxamidate LIII can also be assigned to the group of reactions under consideration [84].



The enumerated types of reactions (Scheme 3) have been used in the synthesis of 1,2,4-triazoles with a long hydrocarbon chain and with functional substituents in the 3 position [85, 86].

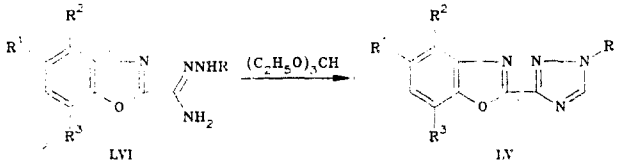
Bis(1,2,4-triazoles) LIV were obtained in the reaction of amidrazones with diethyl adipate and malonate diimides [87].



The cyclization of intermediate linear adducts of the XL-XLII type can be carried out both by refluxing in acetic acid [87] and under the influence of sodium metal [88].

In some cases the acylation of amidrazones is accomplished by means of formic acid itself with subsequent spontaneous cyclization of the corresponding 1-formylamidrazone XL (R^2 = H, Scheme 3) [89].

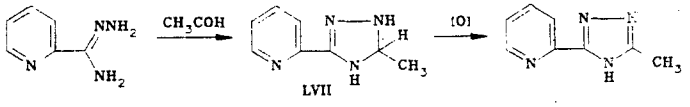
Ethyl orthoformate has also been used as the acylating agent; a large number of 3-substituted 5H-1,2,4-triazoles were synthesized in this way [90-92]. For example, 1,2,4-triazole LV was obtained from 2-benzoxazolylamidrazone LVI without isolation of the linear intermediate adduct [91].



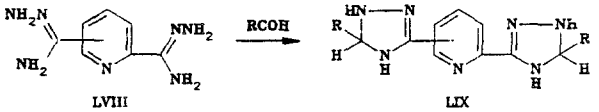
The synthesis of functionally substituted 1,2,4-triazoles through 1-acylamidrazones was also described in [93-95].

In a number of cases 1,2,4-triazoles can be synthesized through 1-acylamidrazones, thereby avoiding the step involving the amidrazone, by the reaction of imino esters with acid hydrazides [96-98] by mixing aromatic cyanides with salts of aliphatic acid hydrazides [99].

In addition to 1-acylamidrazones XL-XLII, 1-alklyidene derivatives XLV and XLVI, which are formed in the reaction of amidrazones with mono- and dicarbonyl compounds (Scheme 3), can also function as intermediates in the synthesis of 1,2,4-triazoles. This sort of reaction was studied in [100-103], particularly the reaction of 2-pyridylamidrazone with acetaldehyde, which leads to 5-methyl-3-(2-pyridyl)-1,2,4-triazol-5-ine (LVII), which is oxidized to a 1,2,4-triazole [100].



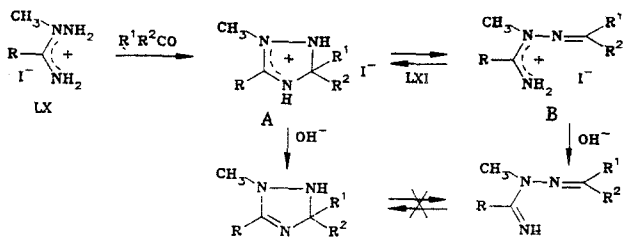
The reaction of amidrazones LVIII with a series of aldehydes, which leads to bis(1,2,4-triazolines) LIX, was studied by Case [103] and Hergenrother and Carlson [104].



The synthesis of 1,2,4-triazoles XLIII (R = $COOCH_3$, R^2 = C_6H_5, Scheme 3) was accomplished by the reaction of aldehydes with phosphine imide XLIX [105].

In the indicated studies intermediate 1-alkylidene derivatives XLV were not isolated. In the same cases in which precisely XLV are the primary reaction products 1,2,4-triazoles are synthesized from them by oxidation with potassium permanganate [106] or mercuric oxide [107, 108].

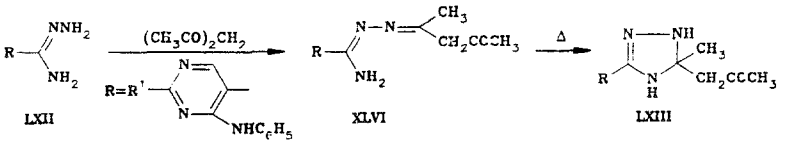
Data on the reaction of amidrazones and their hydrohalides with carbonyl compounds have been refined recently. It was estabished that amidrazones react with monocarbonyl compounds to give 1-alkylidene derivatives [109], the subsequent oxidation of which gives 1,2,4-triazoles. An isomeric or tautomeric transition to the triazoline form is not characteristic for these derivatives. Depending on the structures of the reacting compounds, the reaction of N(2)-methyl-substituted aliphatic and aromatic amidrazonium salts LX with aldehydes and ketones leads either to 1-methyl-2,3-dihydro-1,2,4-triazolium salts LXIA or to alkylidene derivatives LXIB, which in solution exist, as a rule, in the form of tautomeric A ⇄ B mixtures [110].



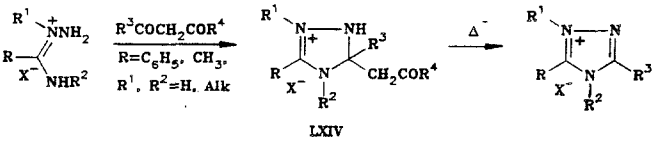
The reactions of amidrazones with 1,3-diketones examined in section 2 also sometimes lead to 1,2,4-triazoles via condensation of the 4 + 1 type. Thus, 3,4,5-trisubstituted 1,2,4-

triazoles were isolated in the reaction of $N(_3)$-substituted amidrazones with 1,3-diketones by refluxing intermediate adducts of the XLVI type in xylene [111].

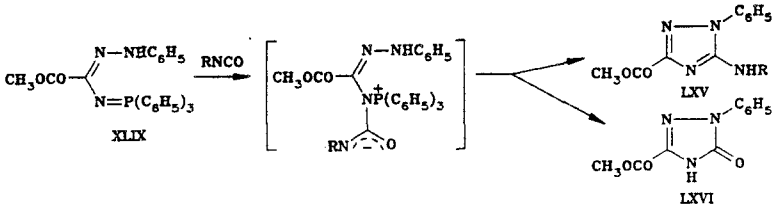
It was demonstrated [112] that the adduct of amidrazone LXII with acetylacetone (adduct XLVI) (Scheme 3) undergoes cyclization to 1,2,4-triazoline LXIII when it is heated to the melting point.



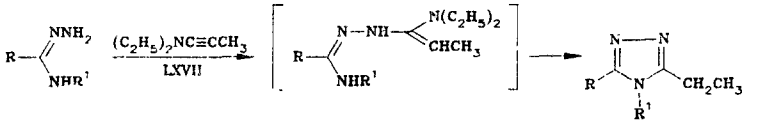
$N(_2)$-Methylbenzamidrazonium hydroiodide reacts with acetylacetone under mild conditions to give the corresponding 1,2,4-triazoline salt LXIV, which on thermolysis is readily converted to the 1,2,4-triazolium salt [28]. Other products of condensation of hydrohalide salts of amidrazones with 1,3-diketones also undergo a similar transformation on heating [29].



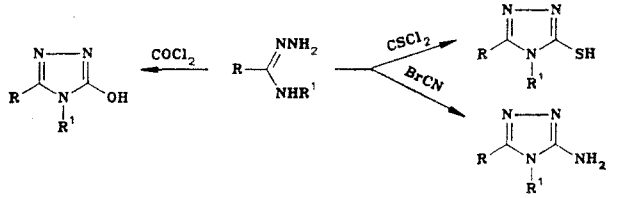
A large group of reactions that take place on reaction of amidrazones with heterocumulenes also belong to the class under consideration and to competitive reactions of the 3(1, 3) + 2 scheme already described in section 3.1. Like amidrazones themselves, triphenylphosphine imidohydrazones XLIX can react with heterocumulenes to give 5-amino-1,2,4-triazoles LXV containing small amounts of admixed 1,2,4-triazol-5-ones LXVI [113].



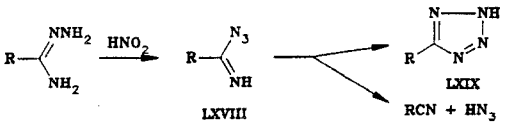
Trisubstituted 1,2,4-triazoles are formed in the reaction of $N(_3)$-substituted amidrazones with 1-diethylamino-1-propyne (LXVII) [114].



The reactions of amidrazones with phosgene and thiophosgene [115, 116] and cyanogen bromide [92, 117] have been studied.

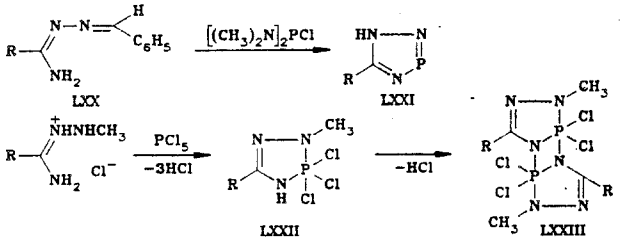


Tetrazoles are obtained by the diazotization of amidrazones with nitrous acid or its salts [74, 118]. The thoroughly investigated mechanism of the reaction [119] suggests the formation of intermediate axide LXVIII, which may both undergo cyclization to tetrazole LXIX and decompose [120].

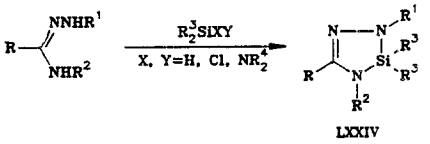


This reaction has often been used for the synthesis of tetrazoles that have different biological activities [10, 92, 121, 122]. Some data on the syntheses of tetrazoles were also presented in [1, 123-125].

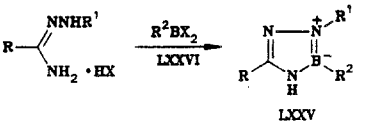
The reaction of Schiff bases LXX with bis(dimethylamino)chlorophosphine in the presence of triethylamine in benzene led to 1H-1,2,4,3-λ^3-triazaphospholes LXXI [126], while $N(_1)$- or $N(_2)$-monosubstituted hydrochlorides of amidrazones undergo condensation with PCl_5 to form 3,3,3-trichloro-1,2,4,3-λ^5-triazaphospholines LXXII, which at room temperature undergo dimerization to LXXIII [127].



The reaction of benzamidrazones with bifunctional silanes gives 1,2,4,3-triazasilolenes LXXIV [128].



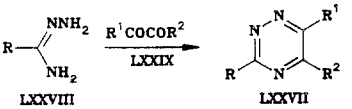
Boratriazaroles LXXV, which were previously synthesized in low yields from 2,5-diphenyltetrazole [129], can be obtained from the corresponding amidrazonium salts and boric acids LXXVI (X = Cl, OH, OAlk, $NAlk_2$) [130].



Bis(boratriazaroles) were obtained by condensation of bis(amidrazones) with boric acids [131]. The peculiarities of the structures and properties of heterocycles LXXV were examined in [132-134].

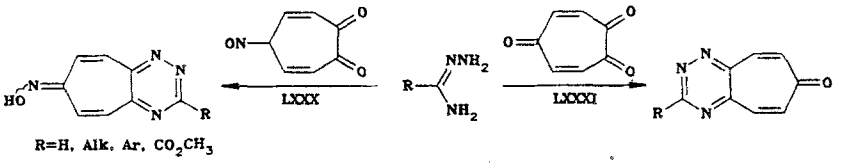
4.2. Synthesis of Six-Membered Heterocycles by means of 4(1, 4) + 2 Reactions. Reactions of this type are used chiefly to obtain 1,2,4-triazine derivatives, data on the synthesis of which were presented in previous reviews [14, 135]. The principal reagents here are 1,2-diketones, α-keto esters, and α-keto acids.

The most well-known method for the synthesis of 1,2,4-triazines LXXVII is the reaction of amidrazones LXXVIII with 1,2-diketones LXXIX [13, 59, 79, 92, 100-103, 136-161]. Data on research in this area accomplished prior to 1973 are presented in a monograph [148].

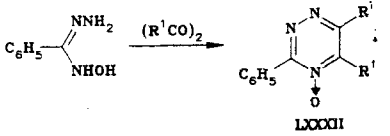


The most diverse amidrazones and diketones have been used in this type of reaction. In particular, in addition to aliphatic and aromatic 1,2-diketones with linear structures, cyclic diketones – cyclohexane-1,2-dione [100], 4,7-phenanthroline-5,6-dione [102, 137, 138], and phenanthrenequinone [150, 159] – were also used.

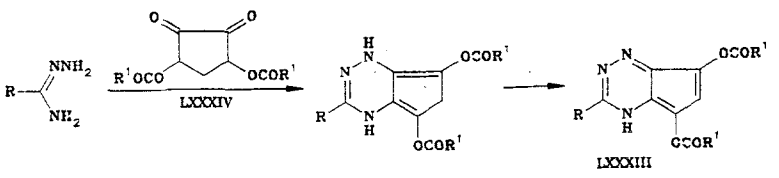
New examples of this reaction were recently obtained with linear LXXIX ($R^1 = R^2 = CH_3$; $R^1 = R^2 = C_6H_5$; $R^1 = H$, $R^2 = C_6H_5$; $R^1 = CH_3$, $R^2 = C_6H_5$; $R^1 = H$, $R^2 = CH_3$; $R^1 = R^2 = COOCH_3$) [59, 146] and cyclic diketones, viz., 5-nitrosotropolone (LXXX) and p-tropolinone (LXXXI) [147].



1,2,4-Triazine 4-oxides LXXXII were obtained by the reaction of N(3)-hydroxyamidrazones with 1,2-diketones [59].

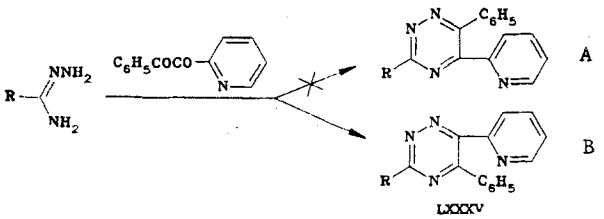


Derivatives of the previously unknown cyclopenta-1,2,4-triazine systems LXXXIII were synthesized from diketones LXXXIV and amidrazones.

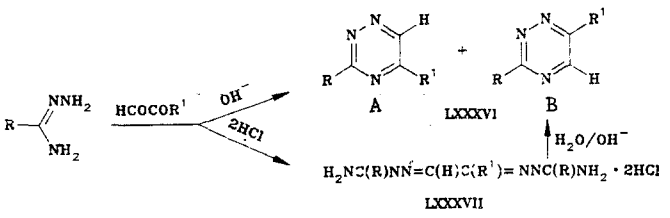


The regiospecificity in the reaction of amidrazones with unsymmetrical 1,2-diketones, which was specially examined in only two studies [139, 144], despite the fact that examples of this reaction have been described repeatedly [101, 139, 142, 144, 152, 153], requires particular attention.

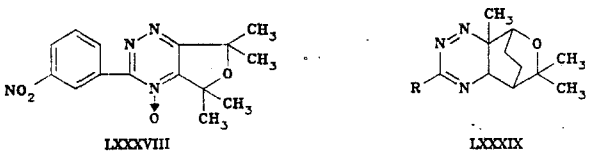
The choice between structures LXXXVA and LXXXVB was made on the basis of a study of chelates based on them. In the opinion of Case [139], the bidentate character constituted evidence in favor of structure LXXXVB.



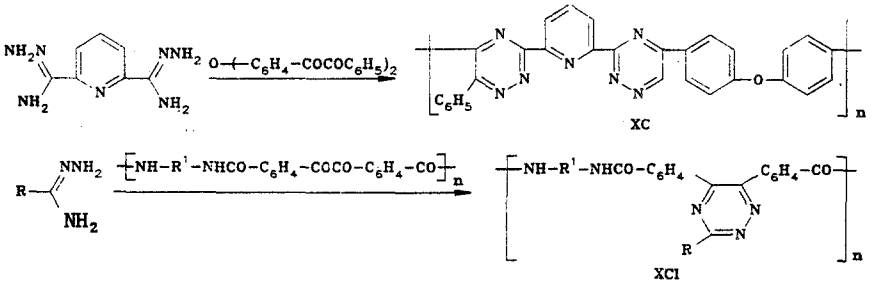
It was found that 1,2,4-triazines LXXXVIA and LXXXVIB are formed in the reaction of amidrazones with unsymmetrical 1,2-diketones in an alkaline medium, whereas osazones LXXXVII are formed in an acidic medium [144]. It was established that the direct conversion of the amidrazone to a 1,2,4-triazine under basic conditions leads primarily to isomer A, whereas the 6 isomer (B) is formed almost exclusively in the hydrolysis of the osazone.



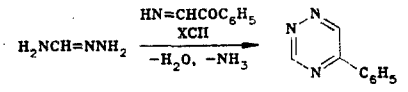
Interest in the reaction of amidrazones with 1,2-diketones is increasing constantly, for its products are used as ligands [156] and corrosion inhibitors [157] and are also of pharmacological interest [13, 159, 160]. Thus 5,7-dihydro-5,5,7,7-tetramethyl-3-(3-nitrophenyl)furo[3,4-e]-1,2,4-triazine-4-oxide (LXXXVIII) has sedative–hypnotic properties [13], while LXXXIX is of interest as a tranquilizer [160].



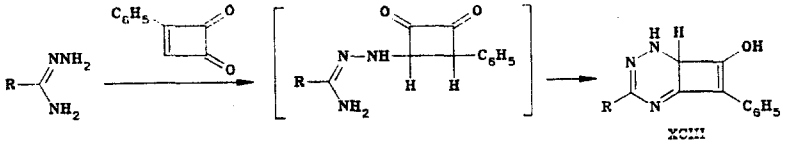
Heat-resistant water-soluble polymers XC [161] and XCI [158] can be synthesized via the same type of reaction.



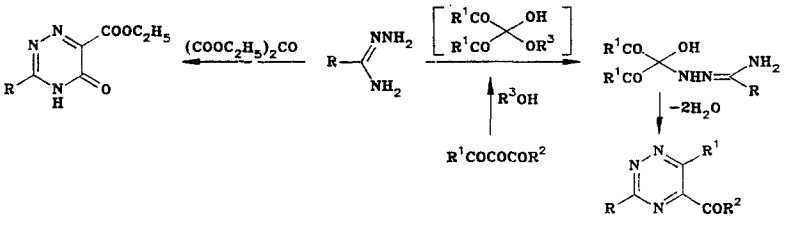
One can use the nitrogen analogs in place of 1,2-diketones. Thus formamidrazone reacts with phenylglyoxalimine (XCII) to give 5-phenyl-1,2,4-triazine [162].



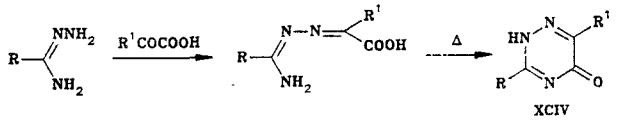
If the 1,2-diketones also contain other reaction centers, the reaction may proceed differently. Thus the reaction of amidrazones with phenylcyclobutenedione leads to bicyclic derivatives XCIII [163].



Functionally substituted 1,2,4-triazines can be obtained by the reaction of amidrazones with 1,2,3-tricarbonyl compounds [164-166].

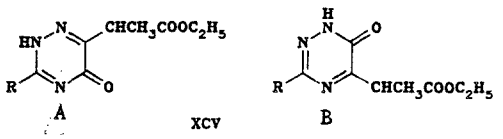


Alkyl- and aryl-1,2,4-triazin-5-ones XCIV are synthesized by the action of α-keto acids and their esters both directly on amidrazones [167] and on amidrazones obtained in the course of the synthesis without prior isolation [168, 169].



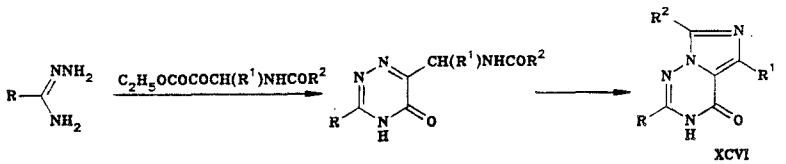
XCIV

Just as in the reaction of amidrazones with unsymmetrical 1,2-diketones, the formation of isomeric products, for example, XCVA and XCVB in the reaction with 2-methyl-3-oxosuccinate [170, 171], is possible in these cases. However the conditions for the formation of isomers A and B were not studied.



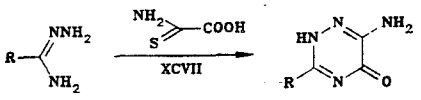
XCV

A method for the synthesis of imidazo[5,1-f]-1,2,4-triazines XCVI is based on the reaction of amidrazones with acylamino-α-keto esters [172].



XCVI

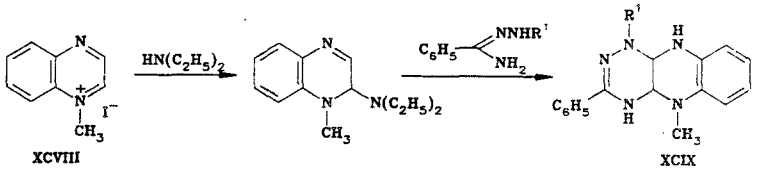
Instead of α-keto carboxylic acids and their esters one can use their sulfur analogs – thioxamidates XCVII [84, 173].



XCVII

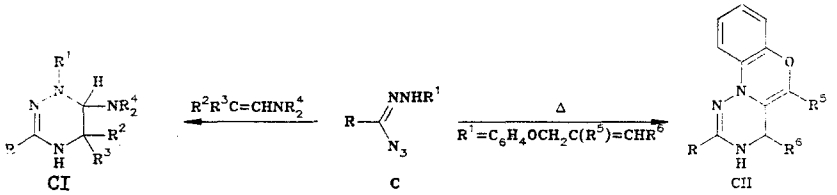
Individual representatives of 1,2,4-triazones can also be obtained as a result of specific reactions.

Thus in a series of studies of the annelation of the triazine ring by means of quinoxalinium salts XCVIII amidrazones [174] or 1-acylamidrazones [174, 175] were used as synthones. Partially hydrogenated derivatives of new heterocycles – 1,2,4-triazino[5,6-b]quinoxalines XCIX – were obtained by cyclization of salts XCVIII with amidrazones. The relative orientation of the rings in triazine XCIX was demonstrated by means of PMR spectroscopy [175].



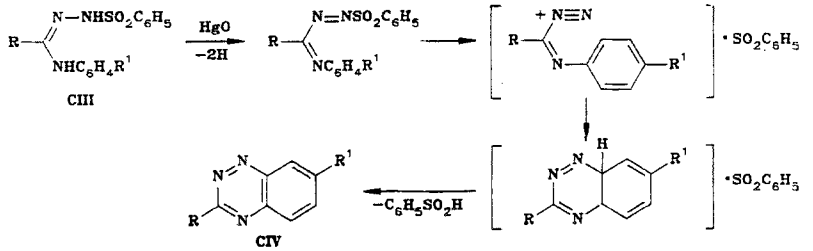
XCVIII XCIX

Azidohydrazones C, which are related to amidrazones, react with enamines to give 1,4,5,6-tetrahydro-1,2,4-triazines CI [176], whereas when the appropriate functional substituent is present, they are converted to 3,4,4a,5-tetrahydro-1,2,4-triazino[6,1-c]-1,4-benzoxazines CII [177].



CI C CII

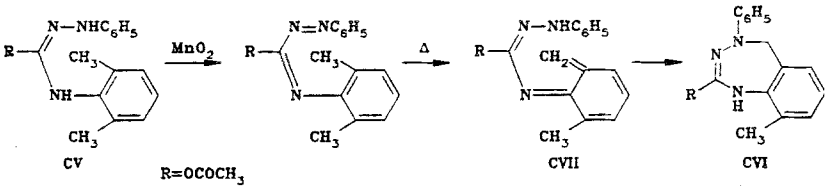
$N(_1)$-Phenylsulfonyl-$N(_3)$-arylbenzamidrazones CIII are oxidized by mercuric oxide to give 3-aryl-1,2,4-benzotriazines CIV [178].



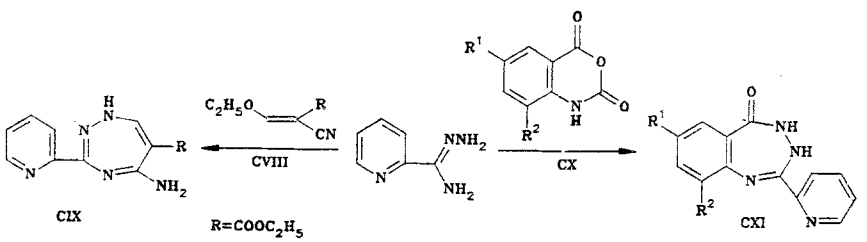
Some reactions of cyclic amidrazones (1,2-diaminoimidazole [179, 180], 1,2-diaminobenzimidazole [181], 2-hydrazinonaphth[1,2-d]imidazole [182], 2-hydrazinobenzimidazole [180, 183, 184], 1-amidino-1,2,4-triazole [185], and other nitrogen heterocycles [186]), which leads to the formation of polynuclear systems that contain a 1,2,4-triazine ring, have also been described.

4.3. Synthesis of Seven-Membered Heterocycles by means of Reactions of the 4(1, 4) + 3 Type. Only isolated reports of the synthesis of 1,2,4-triazepine derivatives on the basis of amidrazones are known.

In particular, the product of oxidation of amidrazone CV by refluxing in cylene gives 1,3,4-benzotriazepine CVI [187]. The proposed mechanism of the reaction assumes the existence of intermediate CVII.



5-Amino-6-carbethoxy-3-(2-pyridyl)-1H-1,2,4-triazepine (CIX) is formed in the reaction of 2-pyridylamidrazone with ester CVIII [32]. The reaction of the same amidrazone with anhydride CX leads to 1,3,4-benzotriazepin-5-one derivatives CXI [188].



The data on the synthesis of condensed heterocycles that include a 1,2,4-triazepine fragment from cyclic amidrazones — phenyl-1,2-diaminoimidazole [189-193], 2,3-diaminobenzimidazoles [180, 194], 3,4-diamino-1,2,4-triazoles [195], 3,4-diamino-5-oxo-4,5-dihydro-1,2,4-triazine [196], and 2-hydrazinobenz(naphth)imidazoles [197] — are more voluminous.

Thus the use of amidrazones makes it possible to realize the purposeful synthesis of the most diverse heterocycles, for some of them the methods based on the use of amidrazones are presently the only methods (1,2,4,3-triazaphospholes LXXI, 1,2,4-triazino[5,6-b]quinozalines XCIX). In other cases, however, the use of amidrazones as synthones serves as the simplest, cheapest, and most accessible method of synthesis (1,2,4-triazoles and 1,2,4-triazines with various structures) or makes it possible to achieve the highest yields as compared with other variants (boratriazaroles LXXV).

Using amidrazones one can obtain many heterocyclic derivatives with valuable properties. Since the amidrazone fragment is present in antibiotics (toxoflavin [198] and fervenulin [199]

and its homologs [200]), it might be assumed that the perfection of syntheses based on amidrazones will lead to the discovery of more convenient methods for the synthesis of these and other biomolecules.

It is apparent from the material presented in this review that the true possibilities of amidrazones in the synthesis of heterocycles are still far from having been exhausted.

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REACTIONS OF 4-METHYL-7-DIETHYLAMINOCOUMARIN THAT PROCEED WITH ELECTRON TRANSFER

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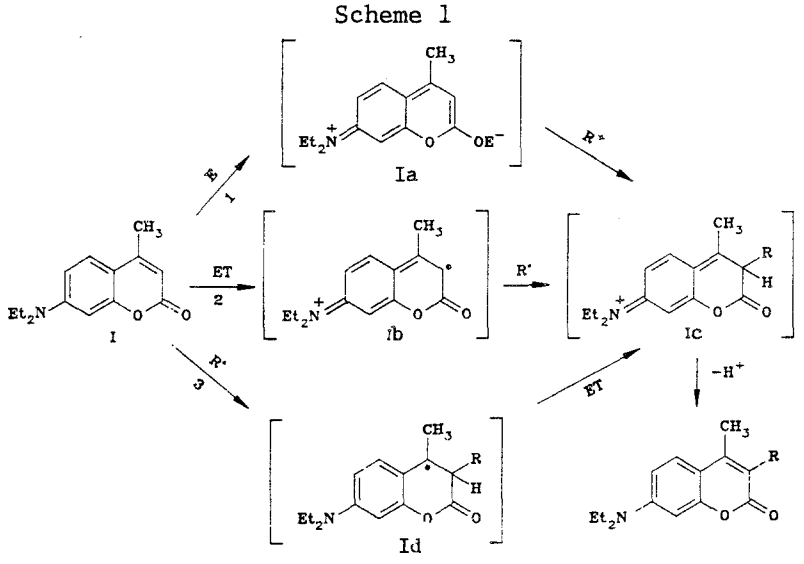
The reactions of 4-methyl-7-diethylaminocoumarin with various oxidizing agents, viz., nitrous acid, nitromethane in the presence of Lewis acids, tetranitromethane, lead tetraacetate, phenyliodosodiacetate, and p-benzoquinone, as well as with typical one-electron oxidizing agents [$(p\text{-}BrC_6H_4)_3N^+SbCl_6^-$, $NOBF_4$, $NOSbCl_6$, $[Fe(biPy)_3](ClO_4)_3$], were studied. It was shown that most of the reactions can be interpreted as proceeding with the intermediate formation of the cation radical of the starting coumarin and lead to new substituted 7-aminocoumarins when suitable substrates (unsaturated compounds, radicals, etc.) are present.

We have previously reported [1] electrophilic substitution reactions in 4-methyl-7-diethylaminocoumarin (I). It was shown that relatively mild Lewis acids ($ZnCl_2$, $HgCl_2$) are capable of coordinating with the exocyclic oxygen atom with the formation of polarized complexes Ia, which are subject to regioselective electrophilic attack at the $C(_3)$ atom (Scheme 1, pathway 1).

Considering the high tendency of 7-aminocoumarins to undergo one-electron oxidation* [2], it seemed of interest to evaluate the behavior of coumarin I under oxidative conditions; one might have assumed the formation of cation radical Ib, in which the cationic and radical centers are markedly dispersed (Scheme 1).

Scheme 1



E=$ZnCl_2$, $HgCl_2$ etc.

*According to electrochemical data [2], coumarin I is comparable to triethylamine in this respect.

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