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ANNELATION OF THE 1,2,4-TRIAZOLE RING ON THE BASIS OF α-HYDRAZINO-SUBSTITUTED HETEROCYCLES AND THEIR HYDRAZONES (REVIEW)

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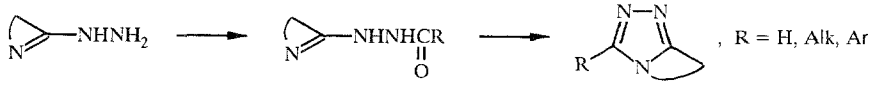
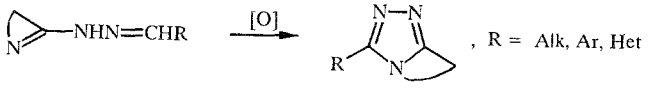
The literature data on methods for the synthesis of annelated 1,2,4-triazole systems on the basis of α-hydrazino-substituted heterocycles and their hydrazones are correlated, and their chemical properties and biological activity are examined briefly.

Annelated 1,2,4-triazole systems can be obtained on the basis of α-hydrazino-substituted heterocycles and their hydrazones by the action of various reactants.

The reaction of α-hetarylhydrazines with carboxylic acids, ortho esters, and other carboxylic acid derivatives is widely used [1-3]. This reaction was accomplished for the first time by Marckwald and Meyer in 1900 [4]. As a rule, cyclization takes place during refluxing in excess reactant to give intermediate acyl derivatives [5].



Another method is the oxidative cyclization of heterocyclic aldehyde hydrazones by the action of various oxidizing agents, among which the most widely used are inorganic oxidizing agents (lead tetraacetate [6, 7], mercury(II) acetate [8, 9], and iron(III) chloride [10]) and bromine in the presence of sodium acetate [11-13]. This reaction, which was described for the first time by Bower and Doyle in 1957 [14], was then accomplished in a large series of aza heterocycles [15-20].



There are also data on the photoelectric oxidation of hydrazones [21], an electrochemical method for the synthesis of annelated systems [22], and the oxidation of hydrazones with benzoyl peroxide [23] and other organic oxidizing agents such as nitrobenzene [10, 24]. Studies of the mechanisms [7, 25, 26] and kinetics [27, 28] of these reactions have been presented extensively in the literature, and multifaceted analyses of the biological activity of annelated 1,2,4-triazole systems have also been made [29-32].

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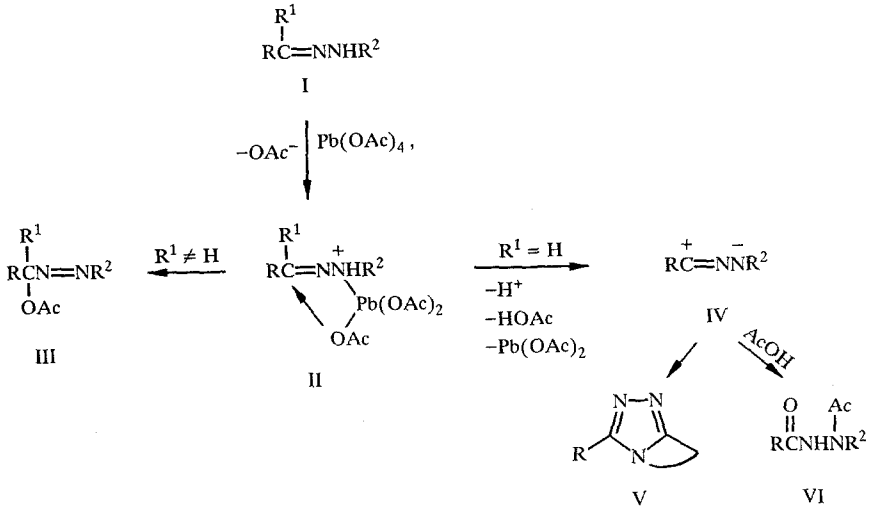
1. OXIDATIVE CYCLIZATION OF HETEROCYCLIC HYDRAZONES

1.1. Oxidation of Hetarylhydrazones with Lead Tetraacetate and Other Inorganic Oxidizing Agents

The cyclization of substituted hetarylhydrazones under the influence of lead tetraacetate is widely used for the synthesis of annelated 1,2,4-triazole compounds [6, 33, 34].

The reaction of $Pb(OAc)_4$ with substituted hydrazones I is presented in Scheme 1. Ketohydrazones form azoacetates III, while aldehydohydrazones can lead to acylhydrazines of the VI type [35, 36]. When substituent R^2 is a 2-heterocyclic group, cyclization may occur as a result of dehydrogenation of the aldehydohydrazones.

Scheme 1



A free-radical mechanism of the reaction with ketone hydrazones has been proposed [37-39]; however, attempts to prove the formation of radicals in this system were unsuccessful [40]. Systematic kinetic studies of the oxidation of heterocyclic aldehyde hydrazones [27, 28] and ketone arylhydrazones [40] with $Pb(OAc)_4$ provide evidence in favor of a polar reaction mechanism. These processes are second-order reactions – first order in both the hydrazone and $Pb(OAc)_4$. Butler [41] suggests that the reaction in most cases includes electrophilic attack of Pb(IV) at the amino nitrogen atom of the hydrazone system to give an intermediate of the II type (Scheme 1), although the site of initial attack has not been established for all cases. This is also confirmed by the favorability of the five-membered transition state of intermediate II for the migration of an acetoxy group as compared with a three-membered transition state in the case of initial attack of Pb(IV) at the methylidyne carbon atom [6].

The inductive effect of the positively charged amino nitrogen atom increases the sensitivity of the methylidyne carbon atom to nucleophilic attack, promoting the formation of an azoacetate of the III type in the intramolecular transfer of an acetoxy group, as well as intermediate nitrilimine IV in the elimination of the hydrogen atom of the methylidyne fragment.

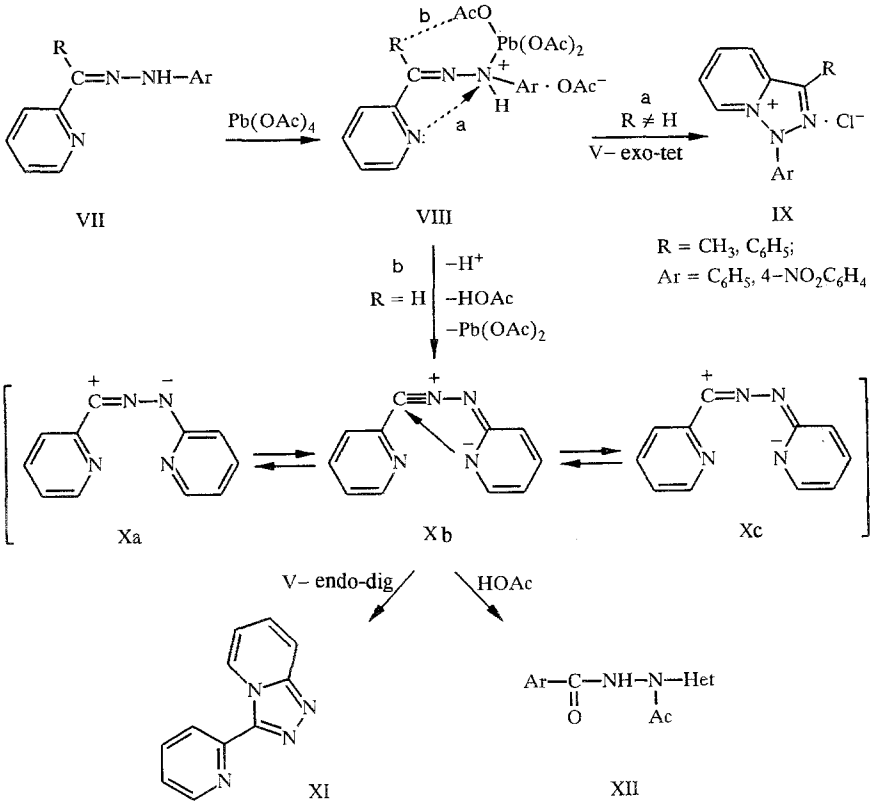
Nitrilimine intermediates of the IV type were detected for the first time in reactions with aldehydohydrazones in the form of adducts with acrylonitrile [25]; the presence of these intermediates in the reaction was later fully confirmed [26, 42, 43].

The oxidation of heterocyclic hydrazones with $Pb(OAc)_4$ may take place to give various cyclic products, depending on the structure of the substrate. In addition to the above-mentioned cyclization to give annelated 1,2,4-triazoles, oxidation may lead to annelated 1,2,3-triazolium systems when there is 2-heterocyclic substituent attached to the methylidyne carbon atom of the hydrazone [44] (Scheme 2).

It has been shown [9] that the cyclization pathway does not depend on E or Z geometry of the substrate but is fully determined by the character of methylidyne substituent R and the structure of the amino part of the hydrazone. 5-*exo*-*tet*-

Cyclization (pathway *a*) to give the corresponding 1,2,3-triazolium salts IX is characteristic for heterocyclic ketone arylhydrazones VII (R = Me, Ph) (Baldwin's empirical rule for ring closing [45] is used).

Scheme 2



The oxidation of aldehyde hetarylhydrazones VII (R = H) includes dehydrogenation to nitrilimine X and 5-*endo-dig*-cyclization of the 1,5-dipolar form of the intermediate as a consequence of nucleophilic attack by the ring nitrogen atom on the methylidyne carbon atom of the hydrazone, which leads to annelated 1,2,4-triazole systems XI [9, 46]. The formation of acetoxylation side products XII as a result of the reaction of the nitrilimine with the solvent is also possible.

There are only a few examples of the first reaction (pathway *a*) [9]; the other reaction (pathway *b*) is widely used in organic synthesis [15-20].

The general character of the cyclization of hydrazones by the action of $Pb(OAc)_4$ is illustrated by Table 1, in which a large number of heterocyclic systems obtained by this method are presented.

The reaction always leads to annelated triazolo heterocycles, and cyclization at, for example, the S or O atoms in reactions 17 and 18 (Tab'e 1) to give mesoionic systems was not observed. Annelated heterocycles with unsaturation at the bridgehead that might have been formed in the case of cyclization at a more remote site of the heterocyclic substituent also were not observed [6].

The character of the heterocyclic ring of the hydrazone plays a large role in the cyclization reaction. The presence of an additional sulfur or oxygen atom in a potential cyclization site (reactions 17 and 18) hinders cyclization; instead of this, one observes competitive acetoxylation of the hydrazone, and very small amounts of a substituted *s*-triazolo[3,4-*b*][1,3,4]oxadiazole [57] and a substituted *s*-triazolo[4,3-*b*]benzothiazole [18] are formed. Other methods are used to obtain these compounds.

When the second heteroatom is a nitrogen atom, the two processes compete, and the advantage of one or the other depends on the structure of the heteroring. For example, the ratio of acetoxylation to cyclization is ≈2:1 for the 1-alkyl-sub-

TABLE 1. Examples of the Synthesis of Annelated Heterocyclic Systems on the Basis of Aldehyde Hetarylhydrazones Cyclized with Lead Tetraacetate

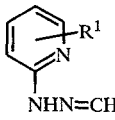
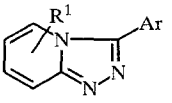
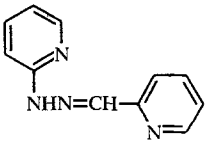
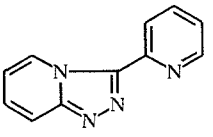
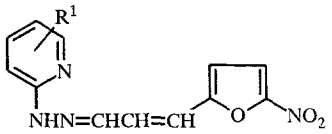
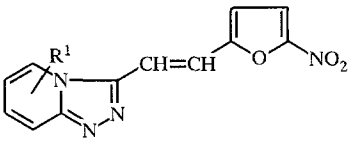
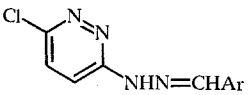
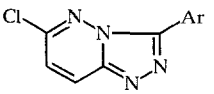
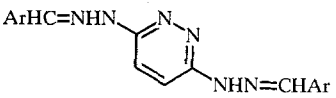
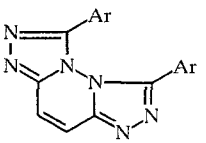
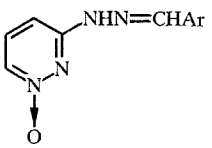
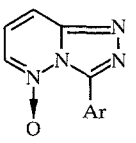
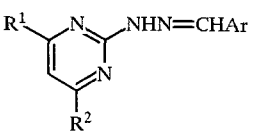
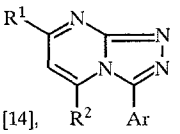
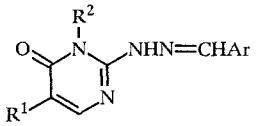
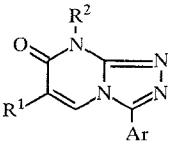
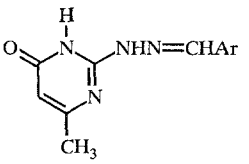
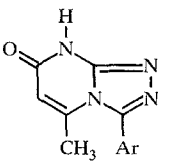
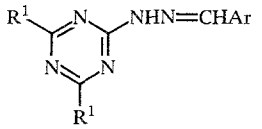
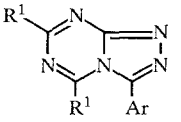
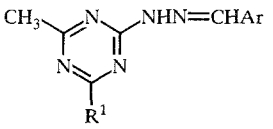
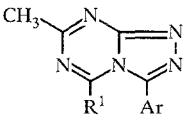
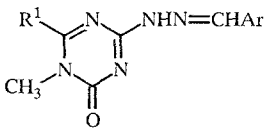
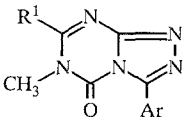
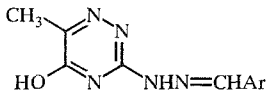
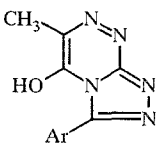
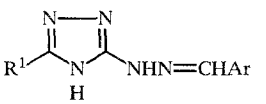
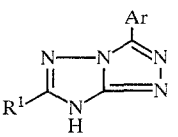
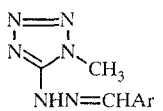
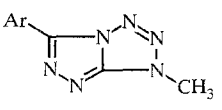
N	Hydrazone (Ar=C_6H_4X)	Cyclization product, references
1		 R^1 = H [7], R^1 = NO_2 [7, 14]
2		 [7, 9]
3		 R^1 = H, CH_3, Cl, NO_2 [47]
4		 [48]
5		 [48]
6		 [19]
7		 R^1 = R^2 = CH_3 [14], R^1 = R^2 = H [49], R^1 = CH_3, R^2 = OH [14]

TABLE 1. (Continued)

8		 $R^1 = COOC_2H_5$, $R^2 = CH_2C_6H_5$ [50, 51], $R^1 = H$, $R^2 = CH_2C_6H_5$ [49, 50], $R^1 = H$, $R^2 = C_2H_5$ [49, 50]
9		[17] 
10		 R^1 =morpholino[52], $R^1 = H$ [20]
11		 $R^1 = H, OCH_3$ [20]
12		 $R^1 = CH_3$, H [20]
13		[53] 
14		 $R^1 = C_6H_5$ [15, 27, 28, 34, 54], $R^1 = H, CH_3$ [54]
15		[16, 55] 

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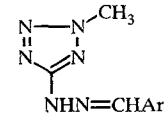
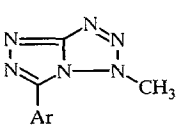
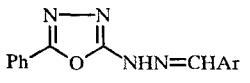
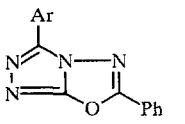
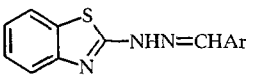
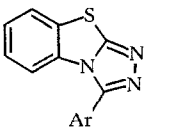
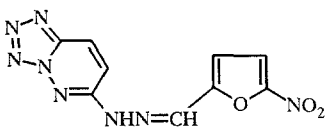
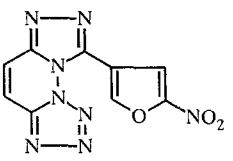
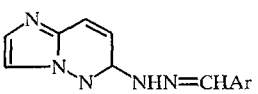
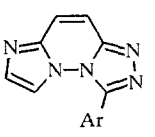
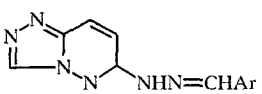
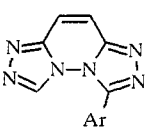
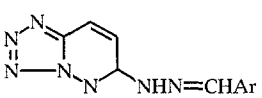
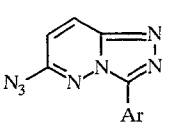
16		[56]	 *
17		[57]	 *
18		[18]	 *
19		[58]	
20		[59]	
21		[48]	
22		[60]	

*Side product; acetoxylation is the principal reaction.

stituted tetrazole ring [16], while acetoxylation dominates for 2-alkyltetrazoles [33, 56], and virtually complete cyclization is observed for the *s*-triazole ring [27, 28].

In *s*-triazolyl-5-hydrazones (reaction 14), where two cyclization pathways [at $N_{(1)}$ and $N_{(4)}$] are possible, the reaction proceeds exclusively with the participation of the nitrogen atom in the 1 position [34, 54] to give 3-aryl-6-phenyl-7H-*s*-triazolo[4,3-*b*]-*s*-triazoles; this was confirmed by alternative synthesis [27, 28].

In general, when alternative cyclization sites are present, ring closing takes place at the most nucleophilic nitrogen atom, as, for example, in reactions 7 ($R^1 = CH_3$, $R^2 = OH$), 9 and 11 ($R^1 = OCH_3$), and 13 and 14. However, an exception was noted in reaction 11 ($R^1 = H$), where cyclization takes place at the nitrogen atom that is remote from the electron-donor methyl group; this is evidently associated with the steric effect of this substituent [20].

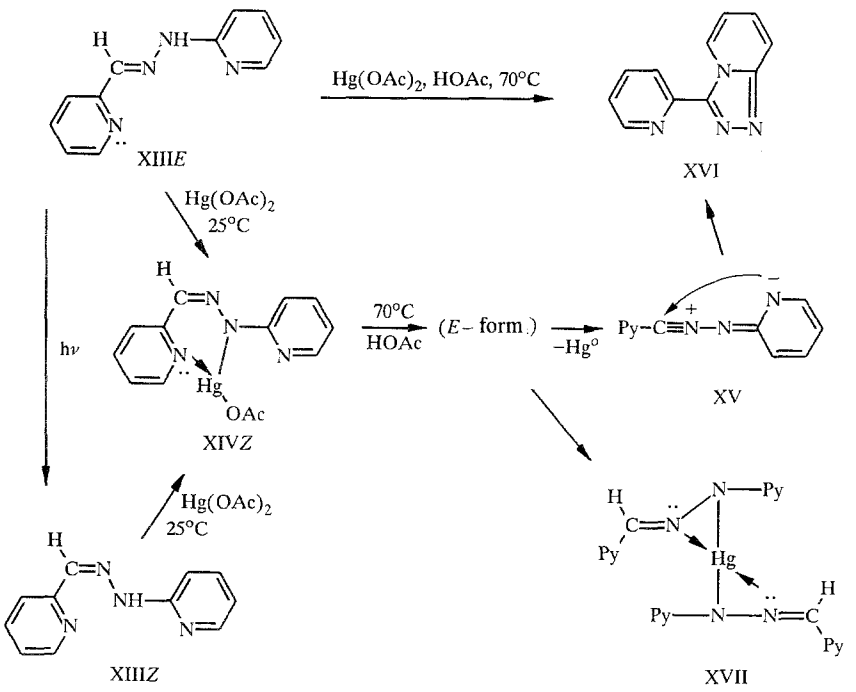
In some cases, for example, reactions 8 and 13, isomerization of the cyclization products may occur under the synthesis conditions [50, 51, 53]. Isomerizations of this sort (the Dimroth rearrangement) may arise under the influence of acids and bases or during heat treatment [50, 51, 61-64] (see section 3 for a more detailed discussion of this).

It should also be noted that annelation of the triazole ring with the participation of the nitrogen atom of the pyridazine ring (reaction 22, Table 1) gives rise to spontaneous valence isomerization of tetrazolo[1,5-*b*]pyridazines to the corresponding azidopyridazines [60, 65]. This sort of isomerization is evidently due to the electron-acceptor effect of the π-surplus annelated triazole ring, as a consequence of which the tetrazole ring becomes unstable and undergoes rearrangement to an electron-donor azido group [60].

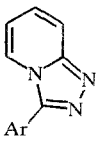
Mercury(II) acetate [8, 9] and iron(III) chloride [10, 24, 47] can also be used for the oxidative cyclization of heterocyclic hydrazones.

The oxidation of the E isomer (XIIIE) of 2-formylpyridine 2-pyridylhydrazone [8, 9] with mercury acetate (Scheme 3) leads to *s*-triazolopyridine XVI (37%) together with bis(hydrazonato)mercury compound XVII [66] and mercury metal. N-Metallo intermediate XIVZ (97%) was isolated in the same reaction (at ~20°C). The lability of this intermediate is evidently decreased as a result of the transmission of electrons in the coordination shell of mercury by the pyridine nitrogen atoms. In contrast to lead tetraacetate, the coordination shell in mercury(II) acetate is not completed and may affect the behavior of the reactant, giving rise to E−Z isomerization of the substrate [8]. Isomerization back to the E form is then observed. Thus the complete the oxidation of E substrate XIIIE includes a series of E → Z → E isomerizations prior to the start of cyclization.

Scheme 3

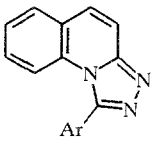


The final step evidently includes 5-*endo-dig*-cyclization of intermediate XV, the presence of which in the oxidation reaction is once again confirmed by the isolation of intermediates such as XIVZ.



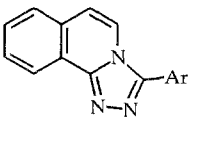
XVIII

Ar = C_6H_4R (R = H, 4-CH_3, 2-COOH, 4-OCH_3, 2-OCH_3, 4-Cl, 2-Cl, 4-NO_2, 2-NO_2), 2-furyl, 5-NO_2-2-furyl



XIX

Ar = C_6H_4R (R = H, 4-CH_3, 4-OCH_3, 2-Cl, 4-Cl, 4-NO_2)



XX

Ar = C_6H_4R (R = H, 4-CH_3, 2-COOH, 4-OCH_3, 2-OCH_3, 3-OCH_3, 4-Cl, 2-Cl, 4-NO_2, 3-NO_2, 2-NO_2)

Iron(III) chloride (alcohol, refluxing) was successfully used for the synthesis of substituted *s*-triazolo[4,3-*a*]pyridines XVIII [10, 47, 67], *s*-triazolo[4,3-*a*]quinolines [10, 47], and *s*-triazolo[3,4-*a*]isoquinolines XX [10, 24], which were obtained in 70-90% yields.

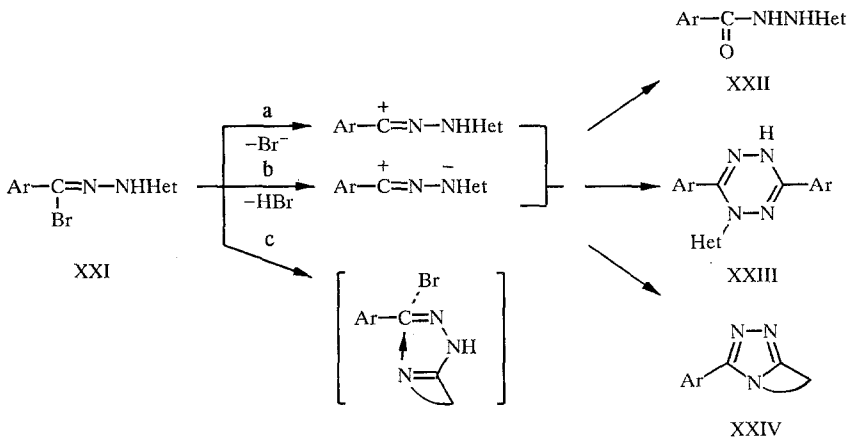
1.2. Oxidative Cyclization of Heterocyclic Hydrazones by the Action of Halogens

The oxidative cyclization of heterocyclic hydrazones can be realized by the action of halogens [48, 52, 59, 68-70]. In this case halogenation of the aromatic rings may compete with the cyclization process [11]. Stable intermediate hydrazonyl halides [6, 13], which in most cases are intermediates in the formation of cyclic structures [71-73], can sometimes be detected. However, depending on the nature of the heterocyclic ring of the hydrazone and the reaction conditions, various bromination products may be formed when bromine is used as the oxidizing agent [11, 36]. Selection of the optimum conditions and the presence of sodium acetate in the reaction mixture make it possible to obtain hydrazonyl bromides in high yields (80-90%), and they can usually be easily isolated [72, 74].

Treatment of hydrazonyl bromides with excess triethylamine in benzene or solvolysis in aqueous dioxane or acetone leads to cyclization to new 1,2,4-triazole systems in high yields (85-95%) [57, 74, 75]. In this reaction the heterocyclic ring acts as a nucleophile that attacks the labile C–Br position in the hydrazonyl bromide. Under solvolysis conditions this internal nucleophilic attack competes with external nucleophilic attack by solvent molecules on the electrophilic center. Cyclization is excluded when the more nucleophilic aniline is used as the solvent, and the only reaction products are anilino derivatives [36, 56].

In hydrazonyl bromides the bromine can be replaced by a nucleophile via various mechanisms: a) through the formation of an azacarbonium ion, b) through a 1,3-dipolar ion, which probably exists in equilibrium with a 1,5-dipolar form, or c) through anchimeric cyclization [71] (Scheme 4).

Scheme 4

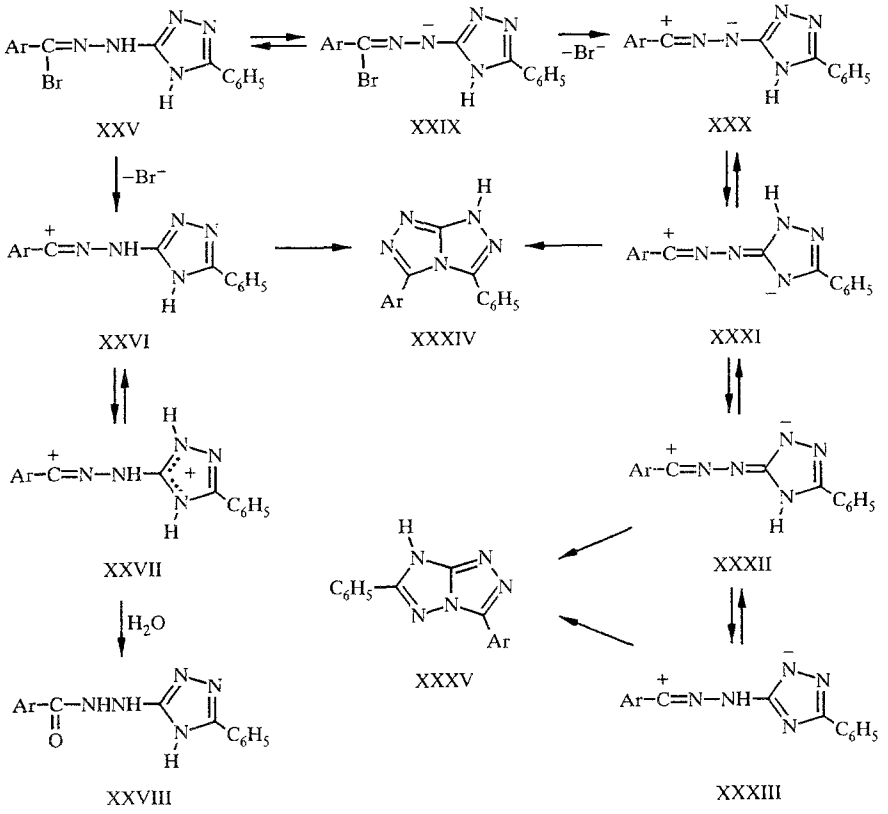


Various heterocyclic systems that can actually participate in an anchimeric reaction have been studied. In the case of tetrazolylhydrazonyl bromides kinetic data on solvolysis [71, 76] have shown that electronic effects of the heteroring had no effect whatsoever on ionization of the C–Br bond and that the tetrazole ring determines only the reaction product and does not affect the reaction rate from the point of view of anchimeric assistance.

Kinetic studies of the solvolysis of a number of hydrazonyl bromides [36, 72, 75, 76] confirm a reaction mechanism through an azacarbonium ion (pathway *a*). Another mechanism (pathway *b*) is also possible, as evidenced by the formation in some cases of tetrazine structures such as XXIII [36, 71] in addition to side hydrazides XXII (56, 57, 77] (Scheme 4). For the unequivocal selection of the reaction mechanism one must examine specific hydrazone systems and take into account the conditions of the process.

The mechanism of the cyclization of triazolylhydrazonyl bromides XXV, which in mixed aqueous organic solvents can form three different reaction products, depending on the acidity of the medium, was studied in greatest detail [78] (Scheme 5). Primarily N-(5-phenyl-*s*-triazol-3-yl)arenohydrazides XXVIII are formed in strongly acidic solutions, 5-aryl-3-phenyl-1H-*s*-triazolo[3,4-*c*]-*s*-triazoles XXXIV are the only products at pH 3-6, and isomeric 3-aryl-6-phenyl-7H-*s*-triazolo[4,3-*b*]-*s*-triazoles XXXV predominate in basic media.

Scheme 5

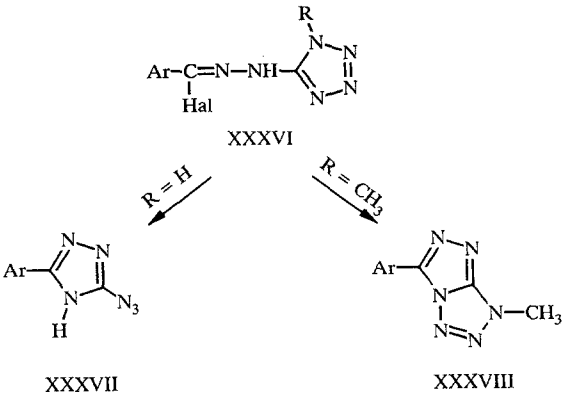


The intramolecular reaction of the *s*-triazole ring with a carbonium center is very sensitive to the intermediate structures that participate in the reaction. Virtually no intramolecular reaction is observed in the case of protonation of the triazole ring (pH < 3); at pH 3-5 the formation of azacarbonium ion XXVI is the principal reaction pathway, and the neutral triazole reacts at the $N_{(4)}$ atom to give exclusively two-ring system XXXIV; at pH > 7 one observes the base-catalyzed formation of 1,3-dipolar ions XXX-XXXIII, and the triazole anion leads primarily to reaction at the $N_{(1)}$ atom to give heterocycle XXXV. It is interesting that in the oxidation of analogous triazolylhydrazones with $Pb(OAc)_4$ cyclization takes place exclusively at the $N_{(1)}$ atom to give XXXV, since this reaction proceeds through a 1,3-dipolar ion [6, 13, 27, 28]. The relative amounts of isomeric structures XXXIV and XXXV formed in the reaction depend on the ratio of the concentrations of the substrate and base (NaOH, Na_2CO_3). For example, when [XXV, HBr]/[NaOH] is 1:4, the percentages of the isomers are 63% XXXIV and 37% XXXV, as compared with 33% and 67%, respectively, when this ratio is 1:20. The overall yields of the isomers in the reaction usually do not exceed 85% [78].

In a comparative study of the solvolysis of tetrazolylhydrazonyl bromides and chlorides it was established [72] that the higher yields of cyclic compounds and the lower yields of side hydrazides in the reactions of the chlorides as compared with the bromo-substituted compounds are due to the lower reactivities and, thus, higher selectivities of the cationic intermediates obtained from the corresponding chlorides.

Tetrazolylhydrazonyl halides XXXVI are extremely unstable — without the stabilizing effect of a methyl substituent one observes decomposition of the tetrazole ring to give more stable triazolyl azides XXXVII [13, 36, 79]. New triazolotetrazoles XXXVIII are formed when a methyl group is present [36, 56] (Scheme 6).

Scheme 6



XXXVI

XXXVII

XXXVIII

Similar fragmentation is observed for triazolooxadiazoles XXXIX, which decompose to give substituted 4-aminotriazolones XL under the influence of acids and bases [57, 74].

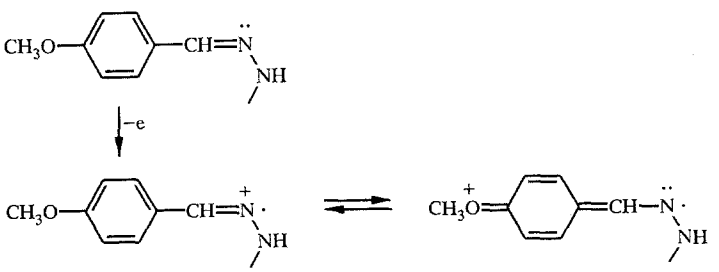
XXXIX

XL (80%)

The formation of triazolotetrazoles includes attack by the $N_{(1)}$ atom of the tetrazole ring; although attack by the $N_{(2)}$ and $N_{(3)}$ atoms is possible, it should result in the formation of a bicyclo[2.2.1] system containing bridged unsaturation and having mesoionic character. The existence of such systems, even in the form of unstable intermediates, is unlikely. Alternative attack at the $N_{(4)}$ atom gives a mesoionic annelated system, which is extremely unstable in air [56].

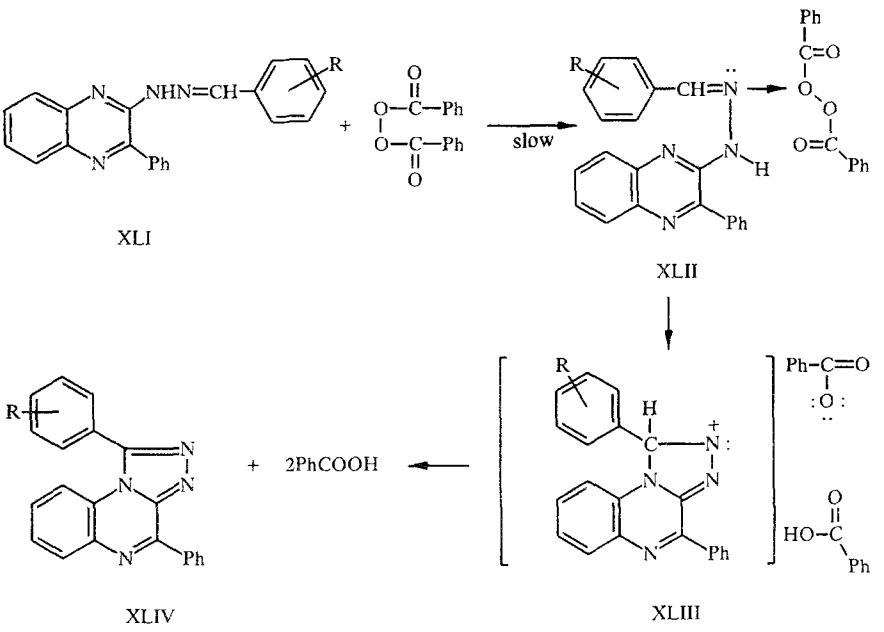
1.3. Nontraditional Methods of Oxidation of Heterocyclic Hydrazones

It has been shown that the oxidation of substituted benzaldehyde 2-phenyl-3-quinoxalinylhydrazones XLI with benzoyl peroxide (Scheme 7) proceeds via a radical mechanism rather than via an ionic mechanism [23], since inhibitors of radical processes (sulfur, nitrobenzenes) do not affect the reaction rate, and one observes virtually no formation of polymers when methyl methacrylate, vinyl acetate, and styrene are introduced into the reaction. The process is a second-order reaction — first order in the hydrazone, and first order in benzoyl peroxide. The presence of an electron-donor substituent in the aryl ring of the hydrazone increases the reaction rate (for example, for the methoxy substituent one observes a 17-fold increase in the reaction rate as compared with the nitro group). The electron pair of the nitrogen atom attacks the oxygen atom in the peroxide, and electron-donor substituents, which increase the electron density on the nitrogen atom, therefore accelerate the reaction; however, it is still not clear which nitrogen atom accomplishes this attack. Since the kinetics of the process follow the Brown–Okamoto equation rather than the Hammett correlation dependence, the existence of resonance between the reaction center and the substituent is assumed, and it is therefore most likely that the azomethine nitrogen atom (=N–) rather than the amino nitrogen atom (–NH–) participates in the reaction with the oxygen atom of benzoyl peroxide [23]:



The following reaction mechanism (Scheme 7) — the step involving the formation of intermediate XLII determines the reaction rate — is proposed on the basis of these results:

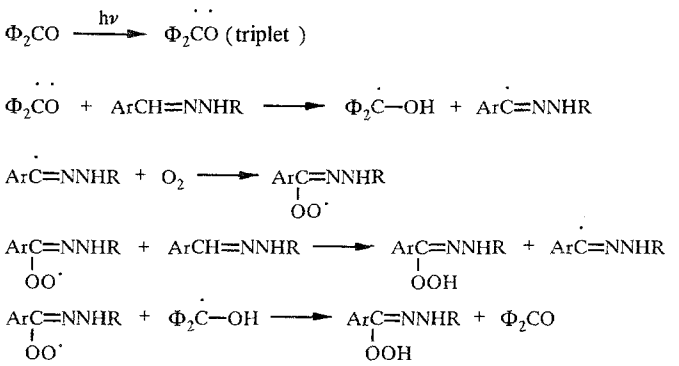
Scheme 7



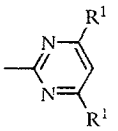
R = 3-Br, 4-Br, 4-CH_3, 4-OCH_3, 4-OC_2H_5, 3-NO_2

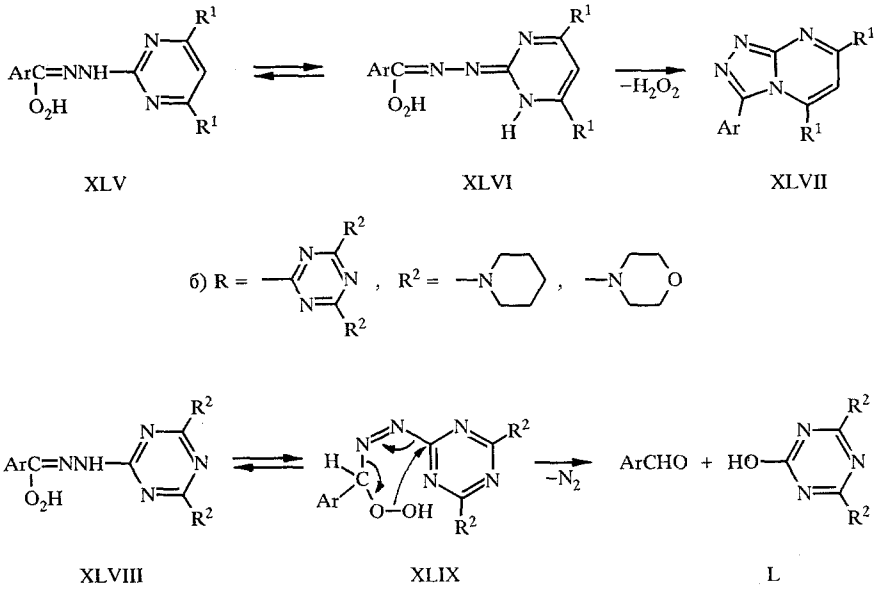
When irradiated with UV light in benzene solutions in a nitrogen atmosphere, the E isomers of 2-benzylidenehydrazinopyrimidines are readily isomerized to the corresponding Z isomers, but photosensitive auto-oxidation to give 3-aryl-1,2,4-triazolo[4,3-*a*]pyrimidines XLVII occurs in the presence of oxygen [21, 80] (Scheme 8). Thus use of acetone as a solvent and a photosensitizer was found to be most effect for the formation of cyclic compounds, the yields of which ranged from 35% to 40% [80]. The use of the Z form of the starting substrate under similar conditions did not give any results. Irradiation of the E forms of 2-benzylidenehydrazino-1,3,5-triazine derivatives also did not lead to cyclization products — the corresponding benzaldehydes and 2-hydroxy-1,3,5-triazine derivatives L were obtained in high yields [21].

Scheme 8



Φ = CH_3, C_6H_5

a) R =  , R^1 = H, CH_3



A characteristic process of this sort of photoelectric oxidation is splitting out of hydrogen by the sensitizer (in its excited triplet state) with the subsequent addition of a molecule of oxygen to the generated radical (Scheme 8). The reason for the formation of various reaction products in the case of pyrimidine and triazine derivatives can be explained by the possibility of the occurrence of processes *a* and *b* through intermediate hydroperoxy compounds. The existence of a tautomer of the XLVI type in the case of 1,3,5-triazine derivatives may prove to be impossible because of the symmetrical nature of the triazine ring and the effect of the nitrogen atoms in the 2, 4, and 6 positions [21]. Consequently, 1,2,4-triazolo[4,3-*a*][1,3,5]triazine is not formed via pathway *a*. The unsuccessful attempts to oxidize the Z isomers of pyrimidine substrates can be explained by the difficulty in eliminating a molecule of H_2O_2 because of fixation of the $-OOH$ group and the pyrimidine ring in the *anti* orientation relative to the C=N bond and intermediate structure XLVI [80].

A number of *s*-triazolo[4,3-*a*]pyridines LIV were obtained in 55-92% yields as a result of two-electron oxidative cyclization in the anode oxidation of substituted benzaldehyde 2-pyridylhydrazones in acetonitrile containing $(C_2H_5)_4NClO_4$ with added 60% $HClO_4$ on a platinum electrode using control potentials [22, 81]. Electrolysis proceeds smoothly without inhibition of the electrode and with the highest yields in an acidic medium.

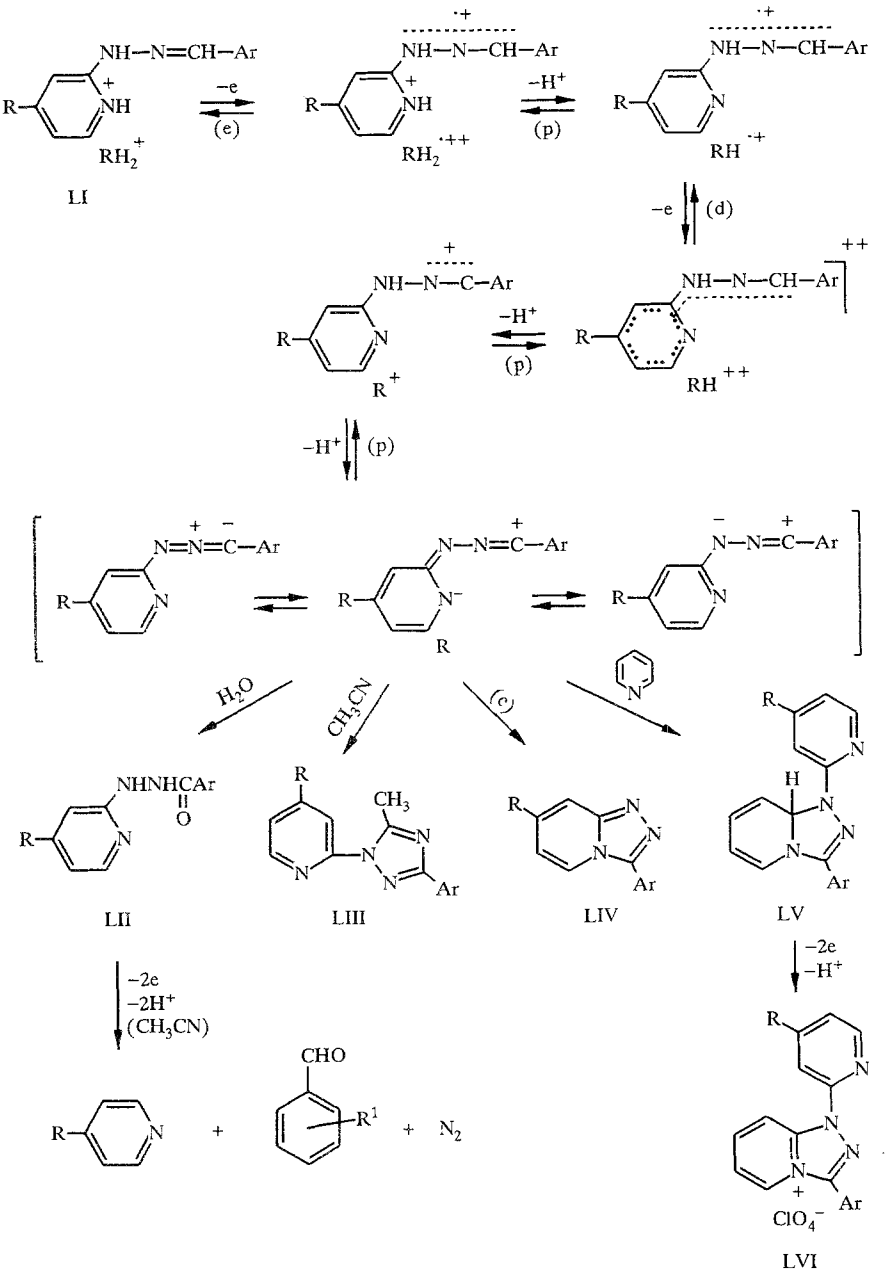
The mechanism of this process can be represented as e-D-c-p-p (e is electron transfer on the electrode, D is electron transfer in solution, c is the cyclization step, and p is deprotonation) (Scheme 9).

The step that determines the rate of the process is electron transfer in solution (step D). The conversion of the protonated form of hydrazone LI to two-ring system LIV includes the loss of two electrons and three protons and the formation of a C–N bond [22]. Oxidation of the protonated form of the hydrazone RH_2^+ gives rise to the rapid reversible formation of radical dication $RH_2^{\cdot 2+}$, which is deprotonated to give radical cation $RH^{\cdot +}$. A pair of these radical cations $RH^{\cdot +}$ dissociate in solution to give starting hydrazone RH, which is then protonated in an acidic medium, and dication RH^{2+}. The reaction process subsequently includes three steps: 1) cyclization of the dication (c), 2) deprotonation (p), and 3) deprotonation (p). The relatively high acidity of RH^{2+} evidently favors deprotonation, which leads to cation R^+. It is also possible that coulombic repulsion in the step involving the dication is unfavorable for cyclization. Cation R^+ is deprotonated to give nitrilimine R, which is an intermediate in the electrochemical reaction LI → LIV (Scheme 9).

Intermediate nitrilimine R can be cyclized in the 1,5-dipolar-ion form to 3-aryl-*s*-triazolo[4,3-*a*]pyridine LIV both in a "neutral" medium and in the presence of $HClO_4$ (in 62% and 72% yields, respectively). However, intermolecular 1,3-cycloaddition, which leads to side compound LIII (45%) and cyclic compound LIV (in only 26% yield), takes place more rapid-

ly in a basic medium in the presence of pyridine. One can also conceive of the formation of 1-(2-pyridyl)-3-aryl-*s*-triazolo[4,3-*a*]pyridinium perchlorate LVI through intermediate two-ring system LV, which is then oxidized by the applied potential as a result of the loss of two electrons and one proton. This type of reaction has already been used for the annelation of pyridine rings by means of the anode oxidation of some aldehyde hydrazones in the presence of pyridine [82].

Scheme 9



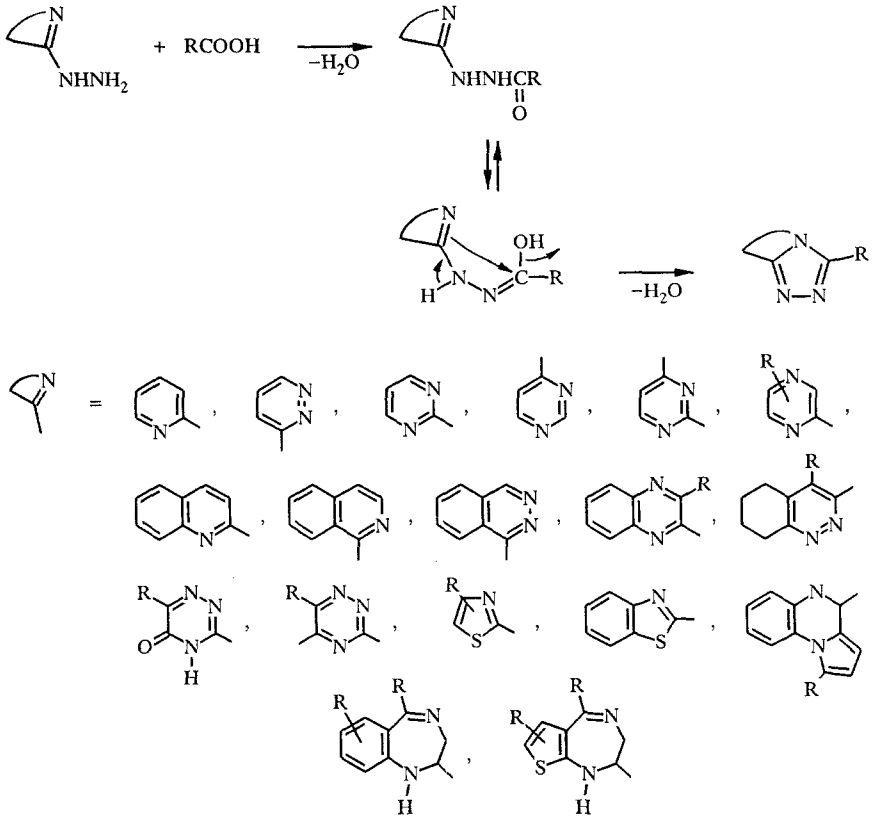
R = H, NO_2; R^1 = H, 2–CH_3, 4–CH_3, 4–OCH_3, 4–NO_2, 4–$N(C_2H_5)_2$

2. SYNTHESIS OF ANNELATED 1,2,4-TRIAZOLE SYSTEMS ON THE BASIS OF α-HYDRAZINO-SUBSTITUTED HETEROCYCLES

The synthesis of annelated 1,2,4-triazole systems in the reaction of hydrazino derivatives of heterocycles with carboxylic acids, acid derivatives, and other carbonyl compounds is widely used in practice [83-93]. This method was realized for the first time in 1900, when *s*-triazolo[4,3-*a*]quinoline was obtained by the action of formic acid on α-hydrazinoquinoline [4]; related studies of the cyclization of hydrazino derivatives of pyridine [94, 95], phthalazine [96], and other heterocycles [97-100] were later published, and the number of condensing reagents was also increased [101-104]. This method makes it possible to obtain annelated *s*-triazole systems with the most diverse substituents in the 3 position [32, 105-108] and is thus not limited to aryl derivatives, as in the case of the oxidation of hydrazones with $Pb(OAc)_4$ and bromine.

The reaction of hetarylhydrazines with aliphatic carboxylic acids is most widely used [24, 109-115]. Cyclization usually takes place when hetarylhydrazines are refluxed with a large excess of the carboxylic acid, which also acts as the solvent, and proceeds through intermediate acyl derivatives [89, 96, 116-119] (Scheme 10). The yields of the cyclization products range from 35% to 90% [107, 114, 120-122].

Scheme 10



In some cases acyl derivatives of hetarylhydrazines are the principal products, and cyclization is not observed [59, 100, 123-125], particularly if acids with long R radicals are used in the reaction [1, 3], and this method is therefore useful only in the case of lower carboxylic acids. However, the acyl derivatives can be converted to annelated triazole systems by heating with phosphorus oxychloride [3, 114, 123, 126] or phosphorus pentoxide [124, 126] and by refluxing in phenol [1, 88, 127]. 3-Alkyl-5-phenylthiazolo[2, 3-*c*]-*s*-triazoles [114], 3-alkyl-5,7-bis(dimethylamino)-*s*-triazolo[4,3-*a*]-*s*-triazines [124], and 9-alkylbis-*s*-triazolo[1,5-*a*:4′,3′-*c*]pyrimidines [126] were obtained in this way. The cyclization of intermediate hydrazides may also occur under the influence of polyphosphoric acid [103]. Thus *s*-triazolo[4,3-*b*]isoquinoline and its 3-methylated derivative were obtained by heating with polyphosphoric acid [125]. These compounds are stable only in the form of perchlorates, which can be obtained directly from the reaction mixtures.

Cyclization under the influence of carboxylic acids may sometimes be accompanied by the Dimroth rearrangement [53, 119, 124, 128]. Isomerization to [1,5-*a*] isomers particularly frequently complicates the production of *s*-triazolo[4,3-*a*]pyrimidines [63, 117, 127, 129]. It was found that hydroxy groups in the pyrimidine ring promote cyclization and hinder isomerization [116, 130-132]. The [4,3-*a*] isomer can be obtained by cyclization of 2-hydrazino-4-hydroxypyrimidine with formic acid under mild conditions [132]; however, one usually obtains a mixture of isomers [63, 127] or the [1,5-*a*] isomer [117, 133, 134]. The introduction of a phenyl group or alkyl substituents into the pyrimidine ring also hinders isomerization of the cyclic compound [135, 136]. Unsymmetrically substituted 2-hydrazinopyrimidines cyclize to give two isomeric (with respect to the location of the substituent) rearrangement products [129].

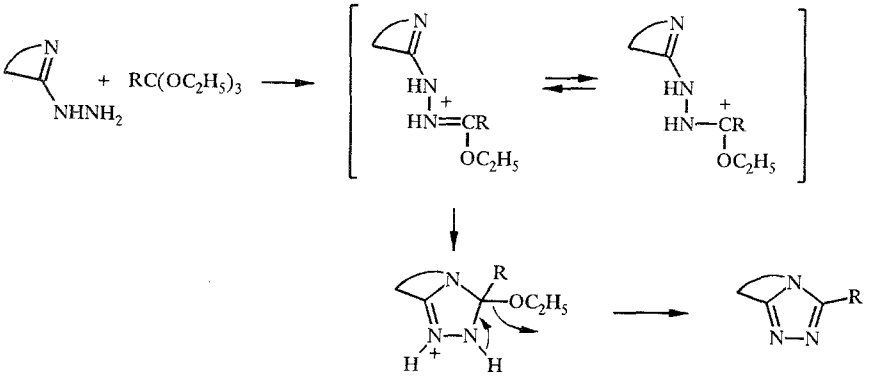
The Dimroth rearrangement is also observed in the cyclization of 5-hydrazino-1,2,4-triazine derivatives; the reaction pathway is determined by the temperature conditions [119]. The presence of a mercapto group in the molecule hinders isomerization, and prolonged refluxing in formic acid is necessary [119]. In the case of 3-hydrazino-1,2,4-triazine derivatives cyclization under the influence of carboxylic acids may take place at both the $N_{(2)}$ and $N_{(4)}$ atoms. It has been shown [53, 98, 137] that the nitrogen atom in the 2 position participates in the cyclization in the reaction with formic acid and that subsequent isomerization of the reaction product is possible [53].

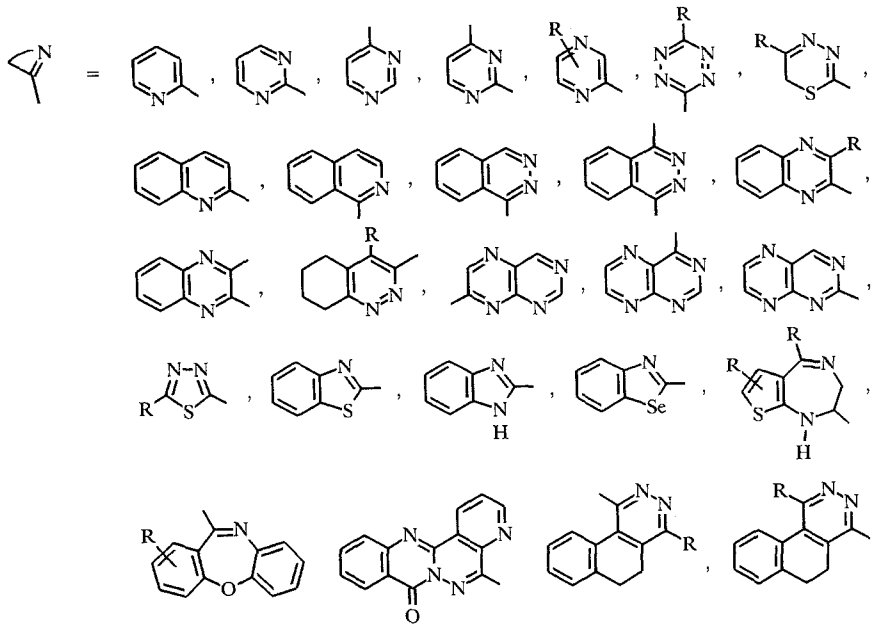
The reaction of α-hetarylhydrazines with ortho esters is one of the most convenient methods for obtaining annelated 1,2,4-triazole systems [1, 83, 104, 120-122, 138-141]. This method is widely used in the synthesis of heterocycles [3, 24, 32, 62, 85, 88, 90, 101, 103, 117, 142-147] (Scheme 11) — the yields of cyclic compounds are usually higher than in the case of synthesis with carboxylic acids and range from 45% to 98% [83, 104, 120-122, 136, 139-141]. Cyclization proceeds through ethoxymethylenehydrazino derivatives, which can be isolated in some cases [2, 59, 100, 147].

The use of ortho esters for the cyclization of 2-hydrazinopyridines was found to be less effective than in the case of carboxylic acids, and the yields of the two-ring systems decreased to 13-20% [2, 3], in contrast to the synthesis of *s*-triazolo[3,4-*a*]pyrazines, in which ortho esters are the most effective cyclization agents, and the use of acids and other derivatives gives only 10% of the cyclic compound [139, 140]. Such differences in behavior may be associated with the basicities of these heterocycles [3]. It is interesting to note that the quinoxalinyl-substituted hydrazine that is related to the pyrazine readily cyclizes with acids, ortho esters, and other acid derivatives in good yields [104, 140].

If alternative cyclization pathways are possible, both are usually realized. For example, two isomers were obtained for unsymmetrically substituted 2-hydrazinopyrimidines [17, 61, 63, 127, 129, 131, 148], although cases in which only one isomer was isolated have been described [85]. The Dimroth rearrangement, which usually leads to mixtures of isomers, can be observed in the cyclization of hydrazino derivatives of pyrimidine and pteridine with ortho esters [128, 134, 143, 149]. Methylated derivatives of bis-*s*-triazolo[4,3-*a*:4′,3′-*c*]pyrimidine undergo only partial isomerization; only one triazole ring undergoes rearrangement [122].

Scheme 11





In some cases diethoxymethyl acetate has been used successfully in place of ortho esters [20, 59, 64, 70, 150]. The following new polyaza heterocyclic compounds were obtained by means of it: 9,10-dihydrobenzo[*f*]imidazo[1,2-*c*]-*s*-triazolo[3,4-*a*]phthalazines and 9,10-dihydrobenzo[*f*]bis-*s*-triazolo[3,4-*a*:4′,3′-*c*]phthalazines [142], as well as pyrido[2,3-*d*](or [3,2-*d*])-*s*-triazolo[4,3-*b*]pyridazines [151], imidazo[1,2-*b*]pyrido[2,3-*d*](or 3,2-*d*])-*s*-triazolo[3,4-*f*]pyridazines [70], and imidazo[1,2-*b*]-*s*-triazolo[3,4-*f*]pyridazines [59, 100]. The use of formic acid and various ortho esters for the synthesis of the latter compounds gave only acylation products [59]. The reaction of 6-hydrazinopurine with diethoxymethyl acetate leads to *s*-triazolo[3,4-*i*]purine, while the use of formic acid gives rise to decomposition of the pyrimidine ring and the formation of N-[4(5)-*s*-triazol-3-ylimidazol-5(4)-yl]formamide [64].

A number of annelated 1,2,4-triazole systems can be obtained in reactions of carboxylic acid anhydrides [90, 101, 103-105, 116, 123, 137, 152] and chlorides [101, 106, 137]. The reaction with ketones leads to the corresponding hydrazone systems, which undergo dealkylation under pyrolysis conditions [120, 153]; the departure of the sterically more hindered molecule as a hydrocarbon is preferable in the case of unsymmetrical ketones [120]. However, the pyrolytic decomposition of ketone α-hetarylhydrazones led to the synthesis of *s*-triazolo derivatives in only 10% yield [140, 153].

The reaction of hydrazino derivatives of quinoxaline with α-keto acids also leads to hydrazines, which, as a result of pyrolysis or prolonged refluxing with organic solvents, undergo cyclization to *s*-triazoloquinoxalines; the formation of the corresponding pyrazolone derivatives in addition to cyclic compounds is possible in the reaction with β-keto esters, while the reaction with diketone gives *s*-triazoloquinoxalines, pyrazoles, or pyridazine derivatives [120].

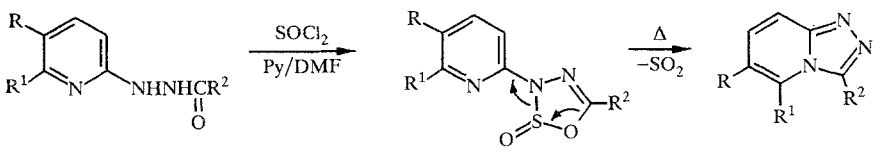
Ethyl imidate hydrochloride, cyclization with which takes place under mild neutral conditions and gives the products in good yield, was used to obtain 3-substituted *s*-triazolo[4,3-*a*]pyrimidines [50]; however, isomerization of the cyclization product to give the [1,5-*a*] isomer is possible. *s*-Triazolo[3,4-*b*]-*s*-thiadiazoles [147] and 4H-*s*-triazolo[3,4-*c*]thieno[2,3-*e*][1,4]diazepines [32] were similarly obtained.

Triazole systems can also be obtained by the direct reaction of the corresponding hydrazides with a heteroring containing a chloro or mercapto group in the α position [2, 120, 154, 155]. Compounds with multiple bonds — diphenylketene, diphenylthioketene, N-tolyldiphenylketeneimine, and ethoxyacetylene — can be used for the cyclization of 1-hydrazinoisoquinoline; cyclization products were obtained in 5% to 60% yields in all cases [2, 156].

The reaction of hetarylhydrazines with chlorides of aromatic and heterocyclic acids (usually in the presence of pyridine or triethylamine) is a general method for obtained annelated 1,2,4-triazole systems with an aryl or hetaryl substituent in the 3 position [2, 84, 96, 99, 101, 102, 120]. Subsequent refluxing of the intermediate hydrazines in phenol [1], with phosphorus oxychloride [3, 14, 114, 137, 139, 140, 157], or with polyphosphoric acid [158, 159] is sometimes necessary; the yields of cyclic compounds range from 20% to 92%. Benzoic acid was successfully used to obtain *s*-phenyl-*s*-triazolo[4,3-*a*]pyridine derivatives (in 20% to 65% yields) [3, 107]; however, attempts to cyclize 2-hydrazinothiazoles [114] and 2-hydrazinopyrazines

[140] with it were unsuccessful. In addition to aromatic and heterocyclic acids, one can use their esters [1, 3], imino esters [2, 50], and anhydrides [1]; the direct reaction of arylhydrazides with heterocycles containing a functional group in the α position is also used [1, 88, 155, 160].

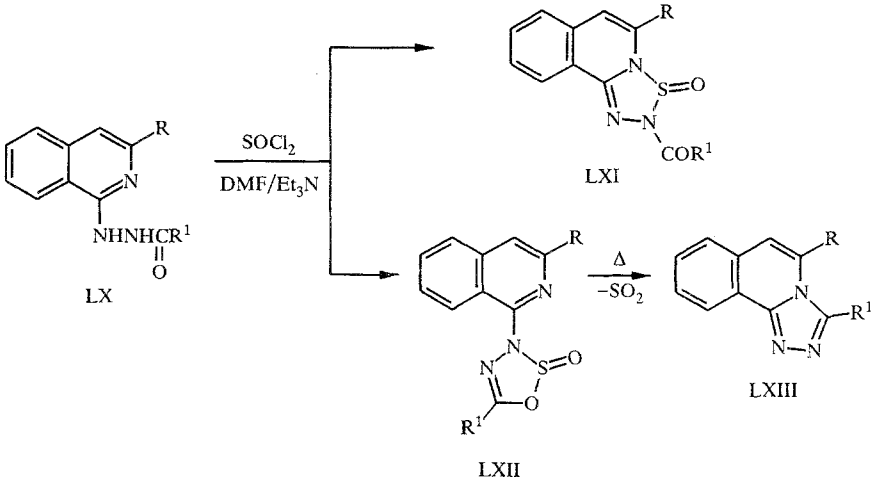
Scheme 12



LVII LVIII LIX

R, R^1 = H, Cl; R^2 = C_6H_5, 4–$NO_2C_6H_4$, 2–Py, 4–Py

Thionyl chloride can be used as a cyclizing agent for acylated hetarylhydrazines [2, 161] (Scheme 12). 2-(2-Aroylhydra-zino)pyridines LVII react with thionyl chloride to give 3-(2-pyridyl)-3H-1,2,3,4-oxathiadiazole S-oxides LVIII (in 39-68% yields), which undergo thermolysis to give the corresponding *s*-triazolo[4,3-*a*]pyridines LIX in virtually quantitative yields [161].



LX LXI LXII LXIII

R = H, Cl; R^1 = C_6H_5, 2–$NO_2C_6H_4$

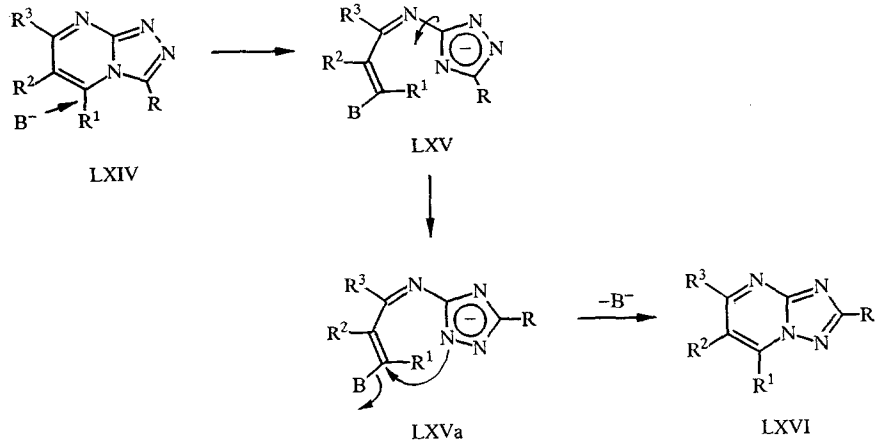
1-(2-Aroylhydrazino)isoquinolines LX react with thionyl chloride to give 2H-1,2,3,5-thiatriazolo[4,5-*a*]isoquinoline S-oxides LXI (in 38-61% yields) or 3-(1-isoquinolyl)-3H-1,2,3,4-oxathiadiazole S-oxides LXII (in 42% yields); only the latter undergo thermolysis with the loss of a molecule of SO_2 and subsequent 1,5-dipolar cyclization to give *s*-triazolo[3,4-*a*]isoquinolines LXIII (in 10% yields) [161]. The presence of a methyl group in the 6 position of the pyridine ring slows down cyclization to 3,5-disubstituted *s*-triazolo[4,3-*a*]pyridines; UV and NMR spectroscopic data showed steric interaction between the substituents [3]. In the case of the reaction of 2-hydrazino-8-methylquinoline with acetic acid interaction of the methyl groups proved to be so strong that cyclization was completely precluded [162].

3. CHEMICAL PROPERTIES AND BIOLOGICAL ACTIVITY OF ANNELATED 1,2,4-TRIAZOLE SYSTEMS

In examining the chemical behavior of *s*-triazolo heterocyclic systems it is impossible to disregard the above-mentioned Dimroth rearrangement [132, 163]. This sort of rearrangement can occur both in the synthesis of cyclic systems [50, 53, 61-63, 128, 143, 149] and by prolonged refluxing of the starting [4,3-*a*] isomers in the presence of an acid or alkali or simply by heating the substrate [50, 63, 64, 122, 124, 128, 132, 140, 149, 164].

The rearrangement of the Dimroth type that occurs as a result of attack on the 5 position of the annelated *s*-triazolo[4,3-*a*] system by the nucleophile to give intermediates LXV as a result of cleavage of the $N_{(4)}-C_{(5)}$ bond, subsequent rotation of the triazole ring, and ring closure to give an annelated system can be widely used as a preparative pathway to the [1,5-*a*] series [64, 124, 136, 140] (Scheme 13).

Scheme 13



Whereas the classical Dimroth rearrangement usually takes place only with neutral molecules under alkaline conditions, *s*-triazolo[4,3-*a*]pyrimidines undergo rearrangement both in alkaline and acidic media but not in neutral media [136]. The rates of rearrangement of starting heterocycle LXIV increase significantly over the pH range 10-12.5, whereas over the pH range 0-3.0 the rates are maximal at pH 1.7 and decrease on both sides of this value. In each case the maximum rates in an acidic medium are observed at pH values that approach the pK_a value of the corresponding substrate; this may be the result of two opposing effects: 1) hydrogen-ion catalysis of cleavage of the pyrimidine ring of LXIV to give intermediates LXV; 2) stabilization of starting substrates LXIV in the form of their cations [136].

The introduction of alkyl substituents into the starting LXIV heterocycles has a significant effect on the rate of rearrangement in the same direction, regardless of the acidity of the medium. In an alkaline medium the introduction of a methyl or ethyl substituent in the 3 position of the LXIV heterocycle leads to a 0.5 unit increase in the pK_a value of the substrate and to an appreciable decrease in the rate of rearrangement. On the other hand, the electron-acceptor 3-phenyl group decreases the pK_a value and somewhat increases the rate of rearrangement. 6-Methylated LXIV ($R^2 = CH_3$) undergoes rearrangement at a rate that is slower by a factor of six than the rate of rearrangement of the starting heterocycle, and 7-methylated isomer LXIV ($R^3 = CH_3$) behaves similarly; however, the presence of a 5-methyl group in LXIV ($R^1 = CH_3$) decreases the rate of rearrangement by a factor of 65, which is probably due to the steric hindrance created by the methyl group with respect to attack by the nucleophile on the $N_{(4)}-C_{(5)}$ bond prior to its cleavage. For this reason the 3,5- and 5,7-dialkyl derivatives undergo rearrangement extremely slowly, and the 3,5,7-trialkyl derivatives undergo rearrangement most slowly [136].

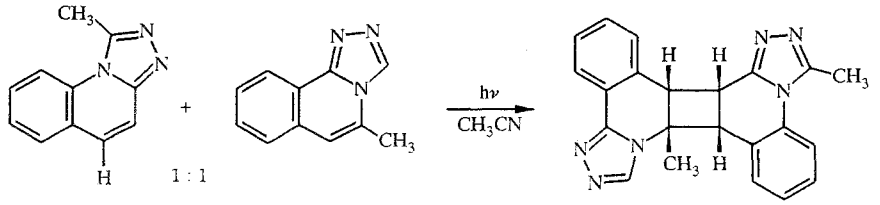
It should be noted that, whereas *s*-triazolo[4,3-*a*]pyrimidines LXIV undergo complete rearrangement in aqueous buffer solutions, *s*-triazolo[4,3-*c*]pyrimidines, although they do undergo hydrolytic cleavage much faster than LXIV, undergo complete rearrangement only in glacial acetic acid; this is explained by the nature of the products of ring cleavage: for [4,3-*a*] compounds the intermediate is reactive hydroxymethylene derivative LXV, whereas in the case of the [4,3-*c*] isomers the cleavage product is a relatively inert amide [149].

The isomeric systems are easily distinguished by means of UV and NMR spectra [61, 132, 136].

Photodimerization is another interesting property of annelated *s*-triazole systems [165, 166]. Ultraviolet irradiation of a number of methyl-substituted *s*-triazolo[4,3-*a*]pyridines gave thermally unstable cyclobutane photodimers by reaction of the $C_{(5)}-C_{(6)}$ double bond of one molecule with the $C_{(7)}-C_{(8)}$ double bond in another [165]. Substituents do not have a pronounced effect on photodimerization, but the choice of solvent is important — tetrahydrofuran, dimethoxyethane, and diethyl ether proved to be the most suitable solvents.

Irradiation of *s*-triazolo[4,3-*a*]quinoline and its methyl derivatives at 300 nm also led to cyclobutane dimers with a "head-to-tail" configuration (in 30-57% yields); however, *s*-triazolo[3,4-*a*]isoquinolines gave isomeric compounds with a "head-to-head" configuration (in 54-76% yields), with the exception of the 5-methyl derivative [166]. A similar reaction of 3-methyl-*s*-triazolo[4,3-*a*]quinoline (LXVII) and 5-methyl-*s*-triazolo[3,4-*a*]isoquinoline (LXVIII) led to cyclobutane adduct LXIX with a "head-to-tail" configuration as the only product (in 65% yield) [166] (Scheme 14).

Scheme 14



LXVII LXVIII "head to tail" LXIX

Irradiation of *s*-triazole derivatives of quinoxaline, quinazoline, and phthalazine under similar conditions did not give any phototransformation products.

Many reactions involving electrophilic substitution of the hydrogen atom in the 3 position of the annelated system were unsuccessful [167, 168]. Only bromination could be accomplished in the *s*-triazolo[4,3-*a*]pyridine series, 3-H can be replaced only by deuterium under neutral conditions, and the ring is also resistant to nucleophilic substitution [167]. Bromination by means of N-bromosuccinimide (50% yield) could be accomplished for *s*-triazolo[3,4-*b*]benzothiazole; this compound can also undergo the Mannich reaction with hydrochlorides of secondary amines (dimethylamine and piperidine), but the process does not go to completion. The Vilsmeier reaction gave *s*-triazolo[3,4-*b*]benzothiazole-3-carbaldehyde, which can then undergo various reactions [168]. However, unsaturated substituents or functional groups are more easily introduced into the 3 position of the annelated *s*-triazole system during cyclization using functionalized reagents [1-3, 29, 31, 103, 106, 141].

Commencing with the nineteen sixties, one notes increasing interest in the pharmacological activity of derivatives of annelated 1,2,4-triazole systems. The anti-inflammatory activity of a number of *s*-triazolo heterocycles [30, 31, 51, 108, 169-171], the antituberculosis activity of derivatives of *s*-triazolobenzothiazole [172] and *s*-triazolophthalazine [173], the antimicrobial and antiviral activity of substituted *s*-triazolopyridazines [174-177], *s*-triazolo-*as*-triazines [111], and *s*-triazolopyridines [47], the analgesic action of pyrimidine derivatives [51, 171], and the anticonvulsive action of a number of substituted *s*-triazolodiazepines [32, 110, 178] and *s*-triazolopyridines [107] are reported in numerous patents and papers. Derivatives of *s*-triazolobenzodiazepine, *s*-triazolothienodiazepine, *s*-triazoloisoquinoline, and other annelated systems can be used as antidepressants [31, 32, 155, 160] and tranquilizing agents [106, 107, 110, 171, 178-181]. The hypotensive [170, 181] and antimetabolic [87, 111] action of a number of triazole systems and the use of pyrimidine and other derivatives as bronchodilating agents and respiratory stimulators [160, 171, 182] are also reported in the literature.

Derivatives of individual *s*-triazolopyridines, *s*-triazolopyrimidines, and *s*-triazolobenzothiazoles intensify the action of the antibiotics and anti-inflammatory substances phleomycin and bleomycin. Intensifiers of this sort may increase the antibacterial effect of phleomycin on *Escherichia coli* in vitro by a factor of greater than 50 [29, 141, 183].

Derivatives of annelated 1,2,4-triazole systems also proved to be useful in cancer chemotherapy [3]. It was shown that individual *s*-triazolopyrimidines slow down the growth of *Lactobacillus casei* and *Streptococcus faecalis* and are also active against experimental tumors [133, 184-187].

The fungicidal and bactericidal activity of a number of *s*-triazolobenzothiazoles and *s*-tirazoloquinolines, which proved to be most effective against *Pyricularia oryzae* [105, 144], and the pesticidal activity of derivatives of thiazolo-*s*-triazoles [188, 189] are reported in the literature.

Individual representatives of *s*-triazolo heterocycles are used in photography as stabilizers for photoemulsions [88, 146, 190, 191].

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