METHODS FOR THE SYNTHESIS OF CONDENSED 1,2,4-TRIAZOLES (REVIEW)

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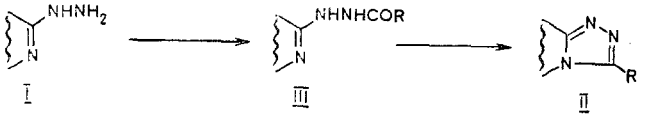
The literature data on methods for the synthesis of condensed 1,2,4-triazoles are examined.

Despite the fact that more than 400 papers and patents devoted to the preparation, properties, and applications of condensed 1,2,4-triazoles are presently known, there has not yet been a special review devoted to this topic. A short chapter on this problem is contained in a review of the chemistry of 1,2,4-triazole [1]. All of the important studies in which problems involved in the preparation of condensed 1,2,4-triazoles are examined were selected in the present review.

Annelation of the 1,2,4-Triazole Ring on the Basis of α-Hydrazino-Substituted Heterocycles

The annelation of the 1,2,4-triazole ring to various heterocycles through α-hydrazino derivatives is one of the most widely used transformations.

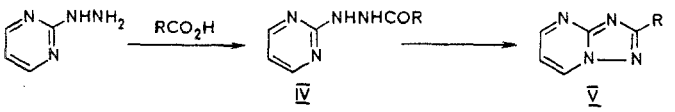


I III II

Condensed Triazoles of the II (R = H, alkyl) Type. The reaction of α-hetarylhydrazines I with aliphatic carboxylic acids is the most widely used method in a preparative respect. As a rule cyclization takes place during refluxing of the hetarylhydrazine with a large excess of the carboxylic acid and proceeds through intermediate N-hetaryl-N'-acylhydrazine III, which, in some cases, particularly if the number of carbon atoms in group R is higher than two, is the chief reaction product. This complication is observed in the cyclization of 2-pyridyl- [2-4] and 2-thiazolylhydrazines [5, 6]. The cyclization of 2-oxo(thioxo)-4-pyrimidyl- [7-9], 3-pyridazinyl- (80-91% yields) [10-13], and 2-quinoxalinylhydrazines (65-85%) [14], 3-hydrazino-6-phenyl-symtetrazine [15], 5-aryl-7-halo-2-hydrazino-1,4-benzodiazepine [16], and 5-hydrazino-1,2,4-triazine [17, 18] may serve as examples of the successful application of aliphatic carboxylic acids.

Hetarylhydrazines of the III type can nevertheless be converted to triazoles II by heating in phosphorus oxychloride or phenol. Thus a number of N-(2-pyridyl)-N'-acylhydrazines have been converted to compounds of the II type in 40-50% yields by refluxing in phenol [2, 3, 19]. The cyclization of hydrazines III with the benzothiazole ring has been reported [5]. Phosphorus oxychloride has been used for the cyclization of N-acyl-N'-(2-thiazolyl)hydrazine [6]. As in a number of similar hydrazones of the quinoxaline series [14], the pyrolysis of 2-pyridylhydrazones of aliphatic methyl ketones gives triazoles II ($R=CH_3$) in up to 10% yields [20].

In some cases the reaction may be accompanied by rearrangement. Thus, despite the available data [21, 22], the cyclization of 2-pyrimidylhydrazines by means of carboxylic acids is accompanied by the Dimroth rearrangement [23, 24].

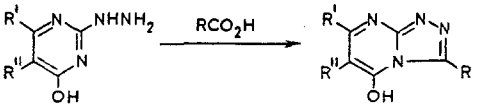


IV V

T. G. Shevchenko Kiev State University, Kiev 252017. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 147-164, February, 1977. Original article submitted June 15, 1976.

The initial product is acylhydrazine IV, which gives pyrimidotriazole V on prolonged refluxing in excess carboxylic acid [23, 25-29].

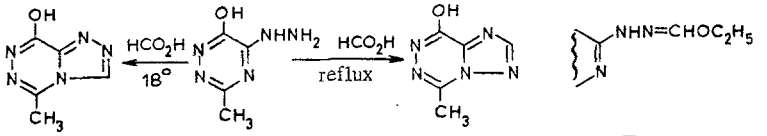
Hydroxyl groups in the pyrimidine ring facilitate cyclization [23, 25, 26, 29, 30] and hinder isomerization [25, 29]. Thus an isomer of the (4,3-a) series can be isolated for 4-hydroxy-2-pyrimidylhydrazines in some cases under mild conditions (55°, 1 h) when R = H [23, 25], whereas when R = CH_3, even prolonged refluxing in glacial acetic acid does not lead to isomerization [25, 29].



VI VII

The introduction of a phenyl group in 4-hydroxy-2-pyrimidylhydrazine VI decreases the effect of the hydroxyl group; this affects the ease of cyclization [26] and rearrangement [31]. Cyclization with the participation of carboxylic acids always takes place primarily at the 3-N atom if there is a hydroxyl group in the 4 position of the pyrimidine. Other types of substituents do not have a substantial effect on the direction of cyclization [25, 26, 29, 32, 33]. Unsymmetrically substituted 2-pyrimidylhydrazines undergo cyclization to give two isomeric (with respect to the position of the substituent) V [27]. It is clear that 3-substituted 4-hydroxy-2-pyrimidylhydrazines form only one isomer on reaction with carboxylic acids [23, 24], but the possibility of the (4,3-a) → (1,5-a) rearrangement is not excluded [34].

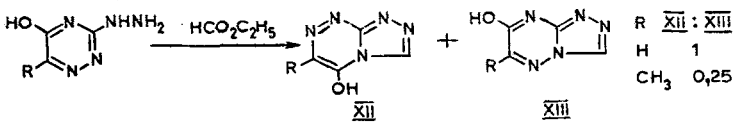
The Dimroth rearrangement has also been noted for 5-hydrazino-1,2,4-triazine VIII, from which, depending on the temperature, IX and X, with different ring fusions, can be obtained [35].



X VIII IX XI

In the case of 6-mercapto derivatives of VIII the reaction proceeds with somewhat greater difficulty; thus refluxing in formic acid for 48 h is required for the (4,3-d) → (1,5-d) rearrangement [35]. The cyclization of 3-hydrazino-1,2,4-triazines by means of carboxylic acids to condensed 1,2,4-triazoles is possible both at the 2-N atom and the 4-N atom. It has been shown by different methods [36-38] that the 2-N atom participates in cyclization by means of HCO_2H to give the corresponding II. The effect of the pH of the medium on the character of the cyclization of 3-hydrazino-1,2,4-triazines is discussed in [39].

The reaction of α-hetarylhydrazines I with ortho esters always proceeds without Dimroth rearrangement. This is one of the most convenient methods for the preparation of condensed 1,2,4-triazoles II. Ethoxymethylidene derivatives XI, which can be isolated in the individual state in the case of 2-hydrazinothiazoles [40] and 2-hydrazino-1,3,4-thiadiazoles [41], are intermediates in these transformations. The XI → II transformation occurs in acetic acid when the mixture is heated to 100° [41]. The yields are, as a rule, high. Excess ortho ester frequently also serves as the solvent [24, 27, 28, 42-44], but alcohols are somtimes added [33]. The possibility of cyclization of hydrazines I by means of ortho esters to the corresponding triazoles II has been demonstrated in the case of benzimidazole (70-80% yield [5, 45], thiazole (20% yield) [6], benzothiazole (76-82% yield) [5, 45], pyrazine (55-78% yield) [45-50], quinoxaline (85-94% yield) [14], 1,3,4-thiadiazole (70-90% yield) [41], pyrimidine (30-77% yield) [24, 27, 28, 33, 42-44, 51], quinoline (60% yield) [5, 22, 52], isoquinoline (40-84% yield) [19, 53], 1,4-benzodiazepine [54], and thieno[2,3-e]-1,4-diazepine [55]. According to the data in [47], cyclization with ortho esters occurs with greater ease, the lower the basicity of hydrazine I. If alternative cyclization pathways are possible, as a rule, both are realized. For example, two isomers were obtained from unsymmetrically substituted 2-pyrimidylhydrazines [24, 42, 43], although instances in which only one isomer was isolated have been described [33, 42]. Diethoxymethyl acetate has recently been frequently used in place of ethyl orthoformate [56-58]. Acetic anhydride has been successfully used in the cyclization of 3-pyridazinylhydrazine (the products are obtained in up to 80% yields) [11, 58], whereas in the case of 3-hydrazino-1,2,4-triazine, condensation in a neutral medium with ethylformate led to a mixture of isomeric (with respect to the position of the substituent) XII and XIII [39]. Compound XII is unstable and slowly (very rapidly when it is refluxed in formic acid) undergoes Dimroth rearrangement to give a derivative of the (5,1-c) isomer, whereas XIII is completely stable.



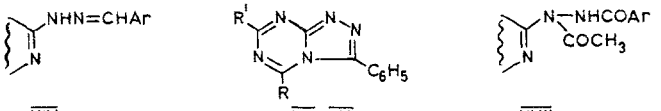
R	XII : XIII
H	1
CH_3	0,25

XII XIII

In addition to carboxylic acids, ortho esters, or esters, ethoxyacetylene [59] and diethylamino-1-propyne [60] have been used for the cyclization of 2-pyridylhydrazines. In this case triazoles II, where R = CH_3 and C_2H_5, were obtained.

Condensed Triazoles of the II (R = aryl, hetaryl) Type. Compounds of the III type, where R = aryl or hetaryl, are formed in the general case when α-hetarylhydrazines I are treated with the chlorides of substituted benzoic or hetaryl carboxylic acids in the presence of bases (pyridine and triethylamine). Hydrazines III can be converted to substituted II by refluxing in $POCl_3$ or phenol. The corresponding condensed 1,2,4-triazoles were obtained by this method from 2-pyridyl- [5, 22], 2-thiazolyl- [6], and 2-pyrazinylhydrazines [14, 46, 47, 61]. In some cases intermediates III are not isolated; thus, for example, triaolopyridazines were obtained in 27 to 76% yields when pyridinecarboxylic acid chlorides were refluxed in pyridine with 3-pyridazinylhydrazines [12, 60]. Similar cyclizations have been described for 1-phthalazinylhydrazones [62, 63] and 3-hydrazino-5,6,7,8-tetrahydrocinnoline [64].

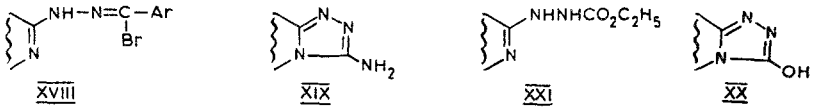
A convenient method for the preparation of 3-phenyl derivative II by fusion of 2-pyridylhydrazine with benzoic acid has been proposed [3, 65]. Imino esters [19] or phenyl esters [5] of aromatic acids can be used for the preparation of triazoles II.



XIV XV, XVI XVII

XV R = OCH_3, R' = H; XVI R = H, R' = OCH_3

A method for the oxidation of arylidenehydrazones of heterocyclic hydrazines XIV has found wide application. Nitrobenzene, ferric chloride III, lead tetraacetate, and bromine in acetic acid may serve as the oxidizing agents. As a rule, the products are obtained in no less than 40% yields. This method for the preparation of triazoles II has been tested for pyridine [22, 66], pyridazine [12, 67], pyrimidine [22, 31, 34], and 1,3,5-triazine [57] derivatives. In the oxidation of compounds of the XIV type, obtained from 2-pyrimidylhydrazine, it was established that cyclization proceeds at the 3-N atom when there is a hydroxyl group in the 4 position [31]. The reaction is carried out in inert solvents [34], since the use of acetic acid may lead to isomerization [22]. Both 3,5- (XV) and 3,7-disubstituted (XVI) triazolotriazines are formed in a ratio of 1 : 2.5 in the oxidation of 2-benzylidenehydrazino-4-methoxy-1,3,5-triazine [57]. However, only isomer XVI was obtained in the oxidation of 2-arylidenehydrazino-4-methyl- and -4-methylthio-1,3,5-triazines [57]. The product of oxidation of N-benzylidene-N'-(3-phenyl-1,2,4-triazol-5-yl)hydrazine with lead tetraacetate was called "diphenyl-sym-triazolo-sym-triazole" without establishment of the structure [22], but it has been shown by alternative synthesis that this compound is 3,6-diphenyl-5(7)H-1,2,4-triazolo[5,1-c]-1,2,4-triazole [68, 69]. Substituted N-acetylhydrazide XVII may be formed along with condensed 1,2,4-triazole II in the oxidation of arylidenehydrazones of the XIV type with lead tetraacetate in acetic acid [70, 71]. Thus the chief products of oxidation of 2-arylidenehydrazinobenzothiazole [72] and 5-arylidenehydrazino-1(or 2)-methyltetrazole [73] are the corresponding hydrazides XVII. The corresponding II are formed in 41-58% yields when various hydrazides XVII are refluxed in phenol [72]. Arylidene derivatives of 2-hydrazino-1,3,4-oxadiazole and 5-hydrazinotetrazole are readily converted to XVIII on treatment with bromine; XVIII give 2,5-diaryl-1,2,4-triazolo[3,4-b]-1,3,4-oxadiazoles [74, 75] and two series of isomeric 1H- and 3H-1,2,4-triazolo[4,3-b]tetrazoles [76-78], respectively, on solvolysis in aqueous acetone or dioxane and on refluxing in benzene in the presence of excess triethylamine.



XVIII XIX XXI XX

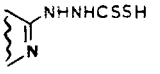
Condensed Triazoles of the II ($R = NH_2$) Type. A general method for the preparation of condensed 1,2,4-triazoles with an amino group in the triazole portion (XIX) is reaction of α-hetarylhydrazones I with cyanogen bromide in alcohol or aqueous alcohol solution. This method has been successfully used for the cyclization of 2-hydrazino-1,3,4-thiadiazoles [79, 80], 3-hydrazino-1,2,4-triazoles [81, 82], 2-pyridyl- [2, 83], 2-quinolyl- [19, 50], and 3-pyridazinylhydrazines [84, 85], 3-hydrazino-5,6,7,8-tetrahydrocinnoline [64], 1-phthalazinyl- [62], 2-pyrimidyl- [86-88], 2-pyrazinyl- [47, 48, 89] and 2-thiazolylhydrazines [6], and 2-hydrazino-1,4-benzodiazepines [90]. Depending on the experimental conditions, the cyclization of derivatives of 5-substituted 3-hydrazino-1,2,4-triazoles may proceed at the 2-N and 4-N atoms of the triazole ring. Thus a mixture of 3-hydrazino-5R-1,2,4-triazole hydrochloride with cyanogen bromide in 85% aqueous methanol at room temperature gives XIX with cyclization exclusively at the 4-N atom. As the length of group R increases, the yield of

the [3,4-c] isomer decreases, and the yield of the [5,1-c]isomer (cyclization at the 2-N atom) increases [82]. By changing the experimental conditions, one can obtain either 3-amino-1,2,4-triazolo[4,3-c]pyrimidines or their isomerization products – 2-amino-1,2,4-triazolo[1,5-c]pyrimidines – in the cyclization of 4-pyrimidylhydrazines by means of cyanogen chloride [56, 91, 92]. 1-Isoquinolinylhydrazines react with cyanogen bromide to give only cyclization products in ~10% yield [93]. The use of S-methylisothiourea sulfate and N-dichloromethylenebenzamide for the cyclization of 1-isoquinolinylhydrazine is discussed in [19, 50]. 2-Alkyl(aryl)amino-1,2,4-triazolo[1,5-c]pyrimidines can be synthesized from substituted 1-(4-pyrimidyl)semicarbazides or their thio analogs [94].

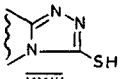
Condensed Triazoles of the II (R=OH) Type (XX). The reaction of α-hetarylhydrazines with ethyl chlorocarbonate is widely used for the preparation of hydroxy derivatives (XX) of 1,2,4-triazoles. The intermediate esters (21) of carbazic acid, which undergo cyclization when they are heated, can be isolated in some cases. Thus 2-hydroxy-1,2,4-triazolo[1,5-c]pyrimidine – the product of Dimroth rearrangement – is formed when N-(4-pyrimidyl)carbazic acid is heated, whereas 3-hydroxy-1,2,4-triazole[4,3-c]pyrimidine is formed when the acid is heated in o-dichlorobenzene [56, 94]. 3-Hydroxy-1,2,4-triazolo[3,4-a]phthalazines were obtained in [63] by the action of ethyl chloroacetate on 4-phthalazinylhydrazines in the presence of bases; however, these results have not been confirmed [62].

Fusion of 2-pyridyl- [2, 3, 83] and 4-phthalazinylhydrazine [62] with urea gives cyclization products in high yields. The reaction of hydrazines I with phosgene is also used to obtain 1,2,4-triazoles XX [48, 89, 94-96]. The reaction of phosgene with 2-pyrazinyl [48, 89], 4-pyrimidyl- [94], and 2-pyridylhydrazine has been studied [95]. In [5, 52], it was shown that 1-(2-pyridyl)-4-phenylsemicarbazide is formed as an intermediate in the reaction of 2-pyridylhydrazine with phenyl isocyanate; aniline and a cyclization product were isolated by fusion of this intermediate. 3-Hydroxy derivatives of 1,2,4-triazolobenzothiazole were obtained (in 63% yields) as a result of cyclization of 2-hydrazinobenzothiazoles with phenyl isocyanate [5]. 1-(5,6-Diphenyl-1,2,4-triazin-3-yl)semicarbazide undergoes cyclization at the 2-N atom when it is heated [97].

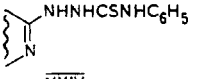
Condensed Triazoles of the II (R=SH) Type. Hetarylhydrazines I react with carbon disulfide to give the corresponding compounds of the XXIII type. The intermediates – dithiocarbazic acid derivativex XII – have been isolated in some cases [89, 98-100]. The reaction with 5,6-diphenyl-2-pyrazinylhydrazine does not lead to the corresponding XXIII but stops at the step involving the formation of compounds of the XXII type [89]. Difficulties with the XXII → XXIII transformation most frequently arise if CS_2 is used in the absence of bases. α-Hetarylhydrazines I of the thiazole [45, 100], benzimidazole [22, 46, 101], benzoxazole [98], 1,3,4-thiadiazole [80], 1,2,4-triazole [81, 82], pyridazine [64, 84], 1,2,4-triazine [97, 102], pyrimidine [103], pyrazine [47, 48], pyridine [19, 100], and 1,4-benzodiazepine [90] series are used to obtain compounds of the XXII type in the reaction with CS_2. 4-Pyrimidinylhydrazines react with CS_2 in butanol to give 2-mercapto-1,2,4-triazolo[1,5-c]-pyrimidines as a result of Dimroth rearrangement whereas they give the normal cyclization products in the presence of triethylamine [94, 104]. In addition to carbon disulfide, the reaction of α-hetarylhydrazines I with phenyl isothiocyanate is used for their cyclization to compounds of the XXIII type. In this case the initial products are 1,4-disubstituted thiosemicarbazides XXIV, which undergo cyclization to mercapto derivatives XXIII when they are heated to temperatures near their melting points. This method has been tested with thiazolyl-2-benzimidazolyl-, 2-benzoxazolyl- [5], 3-pyridazinyl- [105], 2-pyridyl- [5], 2-pyrimidinyl- [24, 42, 103], and 2-quinolylhydrazine [106, 107]. As a rule, the compounds are obtained in high yields.



XXII



XXIII

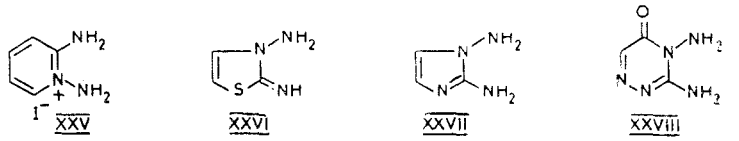


XXIV

In addition to the methods listed above, the reaction of thiophosgene or potassium trithiocarbonate can be used for hydrazines I and pyridine [53, 100, 108] and 1,4-benzodiazepine [90, 109] derivatives.

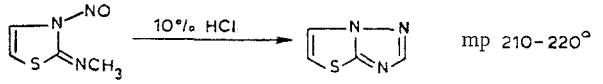
Annelation of the 1,3,4-Triazole Ring to Heterorings by Other Methods

From 1,2-Diaminoheterocycles. Compounds with two adjacent amino groups that are capable of reacting with carboxylic acids or acid anhydrides (or chlorides) with closure to a 1,2,4-triazole ring can be used for the preparation of cyclic systems containing a 1,2,4-triazole ring. Thus 2-alkyl(aryl, hetaryl)-1,2,4-triazolo[1,5-a]-pyridines are formed in good yields (61-70%) when salt XXV is heated with carboxylic acids, acetic anhydride, or acid chlorides [110, 111]. 2-Hydroxy-5-methylthiazolo[3,2-b]-1,2,4-triazole is formed from XXVI and ethyl chlorocarbonate [112].



XXV XXVI XXVII XXVIII

Unsubstituted thiazolo[3,2-b]-1,2,4-triazole was obtained in 1891 by the following original transformation [113]:



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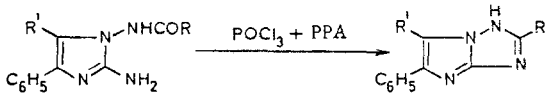
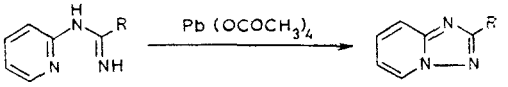
A large number of 2,5,6-trisubstituted 3H-imidazo[1,2-b]-1,2,4-triazoles have been obtained from 1,2-diaminoimidazoles XXVII, formed by cleavage with nitrogen bases of quaternary salts from 2-amino-1,3,4-oxadiazoles and substituted phenacyl bromides [114, 115]. Thus cleavage of these salts with benzamidine gives 1-acylamino-2-benzimidoylaminoimidazoles in low yields, which are converted to 2-phenyl-3H-imidazo[1,2-b]-1,2,4-triazole in high yield on refluxing in alcoholic HCl solution [114]. The cleavage of these salts with ammonia is more interesting in a preparative respect. In this case 2-amino-1-acylaminoimidazoles are formed in high yields [114, 115], and the products undergo cyclization to imidazo[1,2-b]-1,2,4-triazoles when they are heated in a mixture of $POCl_3$ and polyphosphoric acid (PPA).



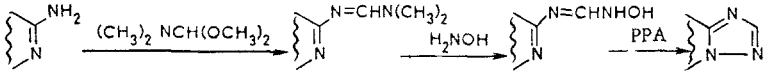
2-Amino-1-acylaminoimidazoles can be obtained from compounds of the XXVII type and carboxylic acids [115]. Diamines XXVII react with CS_2 in DMF to give 2-mercaptoimidazo[1,2-b]-1,2,4-triazoles [115]. Condensation of 3,4-diamino-1,2,4-triazines XXVIII with carboxylic acids has been successfully used for the synthesis of a number of derivatives of 1,2,4-triazolo[5,1-c]-1,2,4-triazines [116]. 4-Amino-3-anilino-6-phenyl-1,2,4-triazin-5-one can also be used in this reaction.

Method of Oxidation. 1,2,4-Triazolo[1,5-a]pyridines are formed in 72-90% yields in the oxidation of N-(2-pyridyl)amidines with lead tetraacetate [110, 119].



This method has been successfully used for the preparation of condensed isoquinolines (40-89% yields) [120, 121] and pyrazines (51-70% yields) [61, 122]. Attempts to extend this reaction to N-(5-phenyl-1,3,4-thiadiazol-2-yl)benzamidine [79] and N-(4-methyl-2-thiazolyl)acetamidine [6] were unsuccessful.

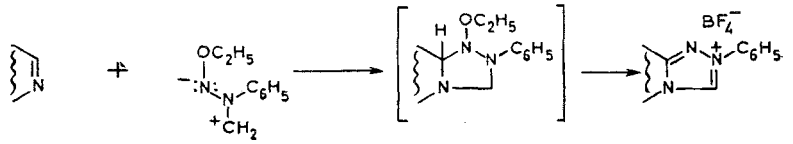
Tisler and co-workers have shown that condensed 1,2,4-triazoles XXXI can be synthesized from various α-aminoheterocycles (XXIX) via the following scheme [117, 118]:



XXIX XXX XXXI

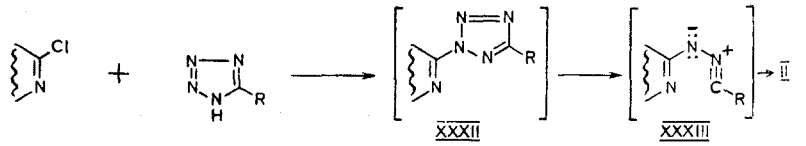
In the case of 2-amino-4-methylpyrimidine, the product of cyclization of XXXI at the 3-N atom is formed in greater amounts (by a factor of five) than the product of cyclization at the 1-N atom. The same transformation for 2-aminopyridine gives 2-pyridylurea, and this constitutes evidence for Beckmann rearrangement of the corresponding XXX.

Dipolar Addition. Pyridine and its benzo analogs, to the same extent as benzothiazole, sometimes react as cyclic Schiff bases (1, 2-dipoles) and undergo cycloaddition [123].



N-Iminopyridine [111] and N-iminoquinoline [124] behave like 1,3-dipoles in reactions with nitriles to give condensed 1,2,4-triazoles in moderate yields.

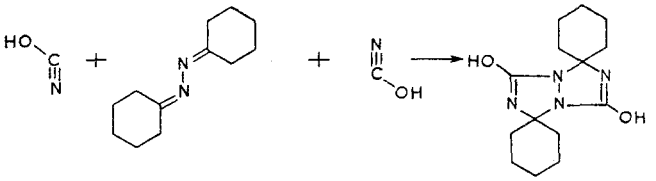
3-Phenyl(amino)-1,2,4-triazolo[4,3-a]pyridine or -isoquinoline are obtained in low yields in the reaction of 2-chloro-5-nitropyridine [125] and 1-chloroisoquinoline [93] with 5-phenyl(amino)tetrazole. Huisgen considers the mechanism of this reaction to be intramolecular cyclization of dipole XXXIII.



XXXII XXXIII

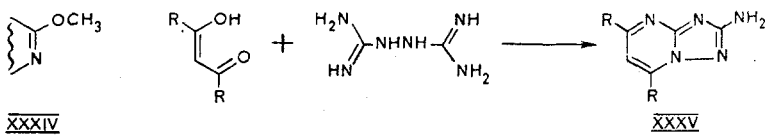
2-Hetaryl-1,2,3,4-oxathiadiazole S-oxides, obtained from 2-hetarylhydrazines and $SOCl_2$ [93], have been proposed as donors of 1,5-dipoles XXXIII that are more stable than tetrazole XXXII. When these compounds are melted, they evolve SO_2 to give the corresponding 1,5-dipole XXXIII, which immediately gives condensed 1,2,4-triazole.

An interesting type of condensed 1,2,4-triazole – 1H, 5H-1,2,4-triazolo[1,2-a]-1,2,4-triazole – is obtained in the dipolar cycloaddition of sodium thiocyanate to aldazines and ketazines in acetic acid and cyanic or thiocyanic acids and their esters [126, 127]. Thus 3,7-dimercapto-1,5-diphenyl-1H,5H-1,2,4-triazolo[1,2-a]-1,2,4-triazole has been obtained from benzalazine [128, 129]. The following variants of this reaction are possible: The use of an aqueous solution of thiocyanic acid [130, 131] or replacement of the prepared azine by a mixture of the carbonyl compound and hydrazine thiocyanate [132, 133]. Dihydroxy derivatives are formed in the reaction of azines with cyanic acid [127] or its esters [134]. Spiro derivatives of this system are obtained in the case of azines of alicyclic ketones [135].



Other Methods. Condensed 1,2,4-triazoles II can be obtained from derivatives of heterocycles containing lactim ester (XXXIV) fragments, which on condensation with carboxylic acid hydrazides form N-hetarylhydrazides III. Triazoles II are formed when hydrazides III are refluxed in phosphorus oxychloride or phenol. This method has been used in the case of isoindole [136] and 1,4- [137, 138] and 1,5-benzodiazepine derivatives [139] and also in the synthesis of 3,4-polymethylene-1,2,4-triazoles [140, 141]. The lability of the halogen atom in α-chloro azaheterocycles in reactions with carboxylic acid hydrazides makes it possible to obtain condensed 1,2,4-triazoles, where R = Ar, NH_2, OH. Thus condensation of benzhydrazides with α-halopyridines [5, 52] or 2-halobenzothiazoles [5, 45] in a mixture of phenol or sodium phenoxide gives the corresponding II (R = Ar) in 30-40% yields. As shown in [142], 3-amino-1,2,4-triazolo[4,3-a]pyridines are formed in good yields (no less than 60%) from α-halopyridine and thiosemicarbazide. 3-Hydroxy-6-chloro-1,2,4-triazolo[4,3-b]pyridazine is obtained by refluxing a mixture of 3,6-dichloropyridazine with semicarbazide hydrochloride in alcohol [143]. The reaction of 1,3-dihydro-2H-1,4-benzodiazepine-2-thiones with carboxylic acid hydrazides takes place in alcohols and dioxane and leads to the corresponding triazoles II [144, 145]. 5,6-Dihydro-4H-1,2,4-triazolo-[4,3-a]-1,5-benzodiazepines [146] and dibenzotriazoloazepines [147, 148] were similarly obtained.

Triazolopyrimidines XXXV were obtained in high yields (76-86%) by reaction of hydrazine-N,N'-dicarboxylic acid diamidine with β-dicarbonyl compounds [87, 88, 149].



XXXIV XXXV

It is assumed that the initial product in the condensation is 3-amino-1,2,4-triazolo[4,3-a]pyrimidine, which subsequently undergoes isomerization to the [1,5-a] isomer.

2,5,7-Trifluoromethyl-3H-imidazo[1,2-b]-1,2,4-triazole was obtained as a result of the reaction of trifluoroacetonitrile with sodium cyanamide in dimethylformamide (DMF) [150].

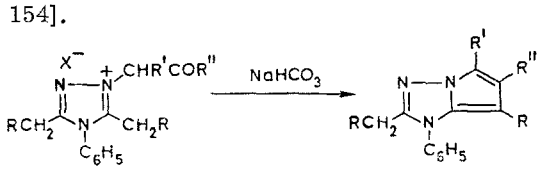
3,6,7-Triamino-1,2,4-triazolo[5,1-c]-1,2,4-triazole is formed in the reaction of triaminoguanidine with two equivalents of BrCN [81, 82].

Synthesis of Condensed Systems from 1,2,4-Triazole Derivatives

1H- and 4H-1,2,4-Triazoles. Owing to the activity of the methyl and methylene groups in quaternary salts obtained from 3,5-dialkyl-4-aryl-4H-1,2,4-triazoles and α-halo ketones, it has been found to be possible

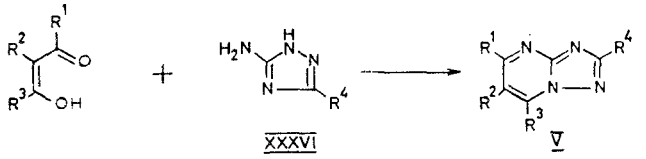
to realize intramolecular cyclization and to demonstrate the possibility of building up the pyrrole ring to give a 4H-1,2,4-triazole ring. The 1H-pyrrolo[1,2-b]-1,2,4-triazoles formed in this case were obtained in 40-70% yields [151, 152].

The isomeric 1H-pyrrolo[2,1-c]-1,2,4-triazoles have been synthesized via a similar scheme from 1H-1,2,4-triazolium salts. It has been established that the formation of a pyrrole ring occurs with the participation of the 5-CH_3 group. When this group is absent 1,2,4-triazolium ylids are formed from the quaternary salts under the influence of bases [153, 154].

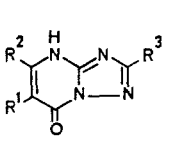


3(5)-Amino-1,2,4-triazoles. One of the most important methods for the construction of heterocyclic systems including a 1,2,4-triazole ring is the utilization on the amidine fragment of 3(5)-amino-1,2,4-triazole XXXVI in cyclization reactions. In this case, if β-dicarbonyl compounds are used, triazolopyrimidines are formed, and imidazotriazoles can be obtained from α-halo ketones.

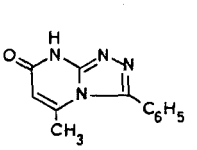
The principal method for the preparation of 1,2,4-triazole[1,5-a]pyrimidines V, discovered in 1909 by Bulow and Haas [155], is the reaction of β-dicarbonyl compounds with amines XXXVI. 5,7-Disubstituted V are formed in good yields (70-90%) when symmetrically substituted β-diketones, tetraethoxypropane, and β-keto aldehyde acetals are used. The fact that the 2-N ring atom of XXXVI undergoes cyclization with β-dicarbonyl compounds was proposed by Bulow and was proved after 50 years by subsequent studies [28, 44].



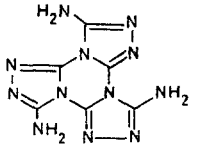
When $R^1 \neq R^3$, the formation of two isomeric (with respect to the position of the substituent) V is possible [27, 156]. In fact, this is not always observed [155]. It should be noted that this problem has not been thoroughly analyzed. The reaction with β-diketones proceeds under various conditions, and acetic acid or alcohols are most often used as the solvent. Amines XXXVI do not react with 1,1,3,3-tetraethoxypropane in the presence of alkali metal alkoxides [157]. The use of acetoacetic ester or diketene in reactions with aminotriazoles XXXVI leads to the formation of only one of the four possible isomers – triazolopyrimidine XXXVII [23, 24, 159-161, 242]. The reaction proceeds without a condensing agent (the products are obtained in 30-95% yields), most frequently when the aminotriazole is heated with excess acetoacetic ester or in a solvent (alcohols, acetic acid, nitrobenzene, etc.). An exception to this is XXXVI ($R = C_6H_5$), which forms lactam XXXVIII with acetoacetic ester [36]. 1,2,4-Triazoles substituted in the 1 or 4 positions of the XXXVI molecule also react with β-keto esters to give, as a rule, mixtures of isomeric 5- and 7-oxo-1,2,4-triazolo[1,5-a]pyrimidines [162, 163]. Various derivatives of malonic ester, in the presence of alkali metal alkoxides, have been introduced as β-dicarbonyl compounds in reactions with amines XXXVI [164, 166]. Ethyl cyanoacetate reacts with amines XXXVI to give biologically active 7-amino-1,2,4-triazolo[1,5-a]pyrimid-5-(4H)-ones. The reaction proceeds only in the presence of sodium ethoxide [164-168]. It has been proposed [25, 26, 157] that ethyl esters of substituted propiolic acids be used as β-dicarbonyl compounds. The most important difference between this transformation and the preceding transformations consists in the fact that the reaction products are mixtures of derivatives of [4,3-a]- and [1,5-a]-1,2,4-triazolopyrimidines rather than mixtures of isomeric (with respect to the position of the substituents) V [26]. Substituted β-akloxyacrylic esters react with amines XXXVI as β-dicarbonyl compounds with a fixed enol form and, depending on the polarity of the solvent, form either 5(4H)-oxo- or 7(4H)-oxo-1,2,4-triazolo[1,5-a]pyrimidines. Exclusively 7-oxo isomers are formed in acetic acid, whereas the 5-oxo isomer is formed in the presence of alkali metal alkoxides in alcohol [169]. The mechanism of the formation of 5-hydroxy-1,2,4-triazolo[1,5-a]pyrimidine in an alcohol solution of sodium ethoxide includes the intermediate formation of carbethoxyacetals from β-akloxyacrylic esters [157]. 4R-Derivatives XXXVI react with β-alkoxyacrylic esters to give isomeric (with respect to the substituents) 1,2,4-triazolo[1,5-a]pyrimid-7(or 5)-ones [34, 158]. Alkoxymethylenemalononitriles and dimers of nitriles [170] also react with amines XXXVI. In the first case, the reaction takes place by refluxing in acetic acid, whereas in the second case fusion at 160-200° is required. 7-Amino-1,2,4-triazolo[1,5-a]pyrimidine is obtained in both cases. α-Acyl-β-alkoxyacrylic esters do not react with amines XXXVI at the carbethoxy group but rather at the acyl group to give 6-carbethoxy-1,2,4-triazolo[1,5-a]pyrimidines [27, 31].



XXXVII

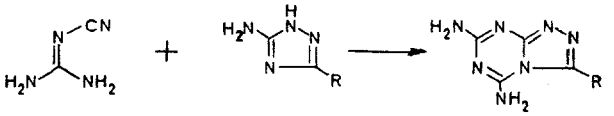


XXXVIII



XL

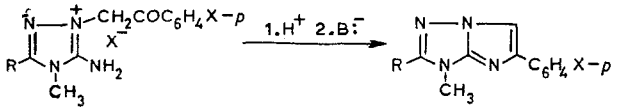
Guanazole (i.e., XXXVI, where R = NH_2) reacts with dicyanodiamide to give guanazoguanazole (i.e., XXXIX, where R = NH_2), and the latter is converted to pyrroguanazole XL when it is heated to high temperatures [171-173]. Hofmann and Pellizzari correctly assigned XXXIX (R = NH_2) and XL structures to the 1,2,4-triazolo-1,3,5-triazine derivatives, but the present structures of these compounds were established later [174, 175]. The reaction of amino-triazoles XXXVI with dicyanodiamide is general in character:



XXXVI R = CH_3, C_6H_5, NH_2 XXXVI XXXIX

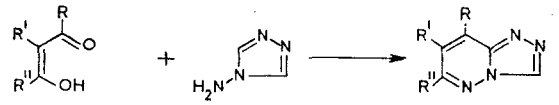
After suitable modification (for example, guanylation) the XXXVI molecule gives a series of intermediates, which can, in turn, be successfully converted to condensed systems. Thus 5-azaadenine (i.e., 7-amino-1,2,4-triazolo[1,5-a]-1,3,5-triazine) was obtained in the reaction of N,N'-bis(1,2,4-triazol-3-yl)formamidine with potassium cyanamide in DMF [176]. The preparation of 5-azaadenine derivatives from substituted 1-guanyl-1,2,4-triazoles is discussed in [177]. The reaction of 1-carbonylamino-5-amino-1,2,4-triazole with ethyl orthoformate gives 5-aza hypoxanthine [i.e., 7(6H)-oxo-1,2,4-triazolo[1,5-a]-1,3,5-triazine] [176, 178, 179]. 7-Oxo-5-thio(4H, 6H)-1,2,4-triazolo[1,5-a]-1,3,5-triazine is formed when 3-(3-ethoxycarbonylureido)-1,2,4-triazole is heated in pyridine [178] or aqueous sodium carbonate solution [179], and the isomeric 7-thio derivative is formed when 5-amino-1-ethoxycarbonylaminothiocarbonyl-1,2,4-triazole is heated with sodium ethoxide in alcohol [179]. The reaction of amine XXXVI with methyl isocyanate in DMFA at room temperature gives 6-methyl-7(6H)-thio-1,2,4-triazolo[1,5-a]-1,3,5-triazine [179]. 5-Amino-1-N-methylthiocarboxy-1,2,4-triazole is an intermediate in this case.

The reaction of guanazole (XXXVI, R = NH_2) with acyloins in acidic media gives 2-amino derivatives of 7H-imidazo[1,2-b]-1,2,4-triazoles in low yields [180]. 4-Substituted 3-amino-1,2,4-triazolium derivatives react with α-halo ketones to give quaternary salts, which undergo cyclization to imidazo[1,2-b]-1,2,4-triazoles (in 53-95% yields) on heating with a mixture of anhydrous acetic acid and H_2SO_4, 48% HBr, and a mixture of glacial acetic and perchloric acids [181].

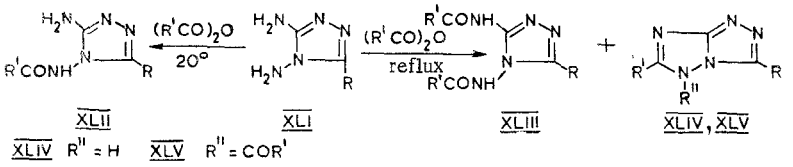


Isomeric imidazo[2,1-c]-1,2,4-triazoles were similarly synthesized from 1-substituted 5-amino-1,2,4-triazolium quaternary salts (in 65-90% yields) [182, 183]. The highest yields were obtained by cyclization in a mixture of anhydrous acetic and perchloric acids.

4-Amino-1,2,4-triazoles. In 1909 Bulow [184] showed that β-diketones react with 4-amino-1,2,4-triazole and assigned the 1,2,4-triazolo[4,3-b]-pyridazine structure to the resulting compound. The yields are close to quantitative [156, 184, 185]. 6-Methyl-1,2,4-triazolo[4,3-b]pyridazine is formed in low yield when 4,4-dimethoxy-2-butene is used [156, 185]. In his subsequent studies Bulow [186] extended this transformation to β-keto esters and, without proof, assigned the 6-substituted 8-hydroxy-1,2,4-triazolo[4,3-b]pyridazine structure to the products. Other researchers later arrived at the same conclusion of the basis of reliable data [32, 187]. The method underwent subsequent development in [32, 186, 188].



The acylation of 3,4-diamino-1,2,4-triazoles XLI with carboxylic acid anhydrides proceeds in a manner similar to the synthesis of benzimidazole from o-phenylenediamine and carboxylic acids [68]: Monoacyl derivative XLII is formed at 20°, whereas a mixture of XLIII-XLV is almost always formed in refluxing anhydride. Acyl derivative XLV is usually formed when diamine XLI is refluxed for 15 min in the anhydride, and saponification of XLV with a weak alkali solution is a better method for the preparation of triazolotriazole XLIV [68].

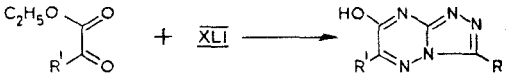


XLII XLI XLIII XLIV, XLV

XLIV R'' = H XLV R'' = COR'

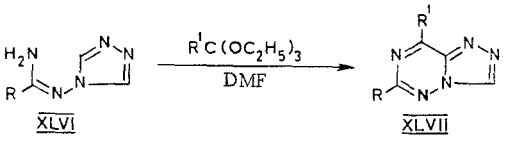
The action of excess benzoyl chloride on 4,5-diamino-3-phenyl-1,2,4-triazole leads to 5(7)H-1,2,4-triazolo[5,1-c]-1,2,4-triazole derivatives [68, 189].

Diamines XLI form 1,2,4-triazolo[4,3-b]-1,2,4-triazines when they are heated with aqueous alcohol solutions of α-diketones [189-192]. This transformation has been extended to α-keto acids and other unsymmetrical α-dicarbonyl compounds [102]. The reaction proceeds smoothly in glacial acetic acid with keto acids or their esters.



6,7-(5H,8H)Dioxo-3R-1,2,4-triazolo[4,3-b]-1,2,4-triazine is formed in high yield in the hydrolysis of a mixture of the ethyl ester of 3R-4-amino-5-oxalylamino-1,2,4-triazole and oxalic acid N,N'-bis(3R-4-amino-1,2,4-triazol-5-yl)amide, obtained from the diamine and diethyl oxalate [193].

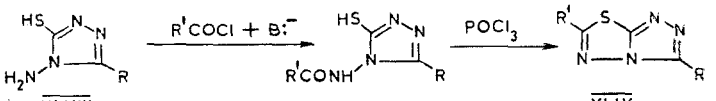
Derivatives of 1,2,4-triazolo[3,4-f]-1,2,4-triazines XLVII are obtained by condensation of N-(1,2,4-triazol-4-yl)amidines XLVI with ortho esters. The yields of compounds of the XLVII type are high (74-90%) when R = H, whereas the products are obtained in only 10% yield when R = C_6H_5.



XLVI XLVII

Somewhat higher yields of triazolotriazine XLVII (R = C_6H_5) are observed when amidine XLVI is heated with phenyl benzoate. The corresponding 8-hydroxy derivative XLVII is obtained when amidine XLVI is heated with ethyl chlorocarbonate [194].

The amino group in the 4-amino-5-mercapto-1,2,4-triazolo molecule XLVIII is in immediate proximity to the mercapto group, and this makes it possible to obtain a number of rings condensed with the 1,2,4-triazole ring by ordinary methods. Thus a number of 2-substituted XLIX systems are obtained when acyl derivatives of amines XLVIII are heated with phosphorus oxychloride [195]. Triazolothiadiazole XLIX (R = C_2H_5, R' = C_6H_5) was isolated as a result of the reaction of amine XLVIII (R = C_2H_5) with benzonitrile in the presence of $AlCl_3$ [99]. Attempts to cyclize amines XLVIII to XLIX derivatives by means of ortho esters were unsuccessful, since the reactions stopped at the step involving the formation of the anil [99]. 5,6-Dihydro derivative XLIX was obtained in low yield by the action of formaldehyde on amine XLVIII [99]. 2-Amino derivatives XLIX were obtained in 48-83% yields by heating alcohol or aqueous alcohol solutions of amines XLVIII with an equivalent amount of cyanogen bromide [79, 99, 196]. Prolonged refluxing of amines XLVIII with excess carbon disulfide in alcoholic alkali solutions gives mercapto derivatives XLIX (R' = SH) in high yields [79, 196].

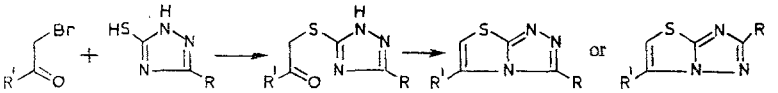


XLVIII XLIX

The reaction of amines XLVIII with α-halocarbonyl compounds is a method for the preparation of 7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazine derivatives [99, 197-199].

Attempts to use the reaction of 3-aminomethyl-1,2,4-triazoles with α-diketones for the synthesis of 1,2,4-triazolopyrazines [89] were unsuccessful.

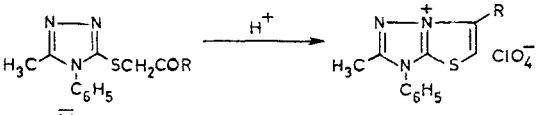
Thiazolo[3,2-b]- and -[2,3-c]-1,2,4-triazoles can be obtained from 3-mercapto-1,2,4-triazoles L and α-halo ketones [6]. The effect of the nature of substituent R on the cyclization of mercapto derivatives L has been studied [6]. Biologically active thiazolo[3,2-b]-1,2,4-triazoles have been synthesized from substituted phenacyl halides and mercaptans L containing 4-antipyran, 4-antipyrine, and 4-isoantipyrine residues in the 5 position [200].



L

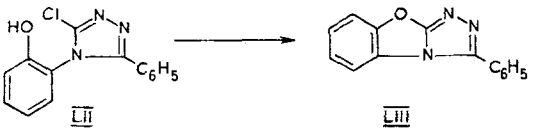
5-Hydroxy-2-methylthiazolo[3,2-b]-1,2,4-triazole was obtained by heating S-(3-methyl-1,2,4-triazol-5-yl)thioglycolic acid with acetic anhydride [201].

Alkylation of 3-methyl-4-phenyl-1,2,4-triazole-5-thione with α-halo ketones gives β-keto sulfides LI, which give 1H-thiazolo[3,2-b]-1,2,4-triazolium salts in good yields (> 60%) on cyclization in acidic media [202].



LI

A molecule of HCl is split out when triazole LII and its hydrobromide salt are refluxed in pyridine, and triazolobenzoxazole LIII is formed in good yield (62%) [203]. Compound LIII is obtained in 83% yield by refluxing the methyl ether of LII in pyridine in the presence of pyridine hydrochloride [203].

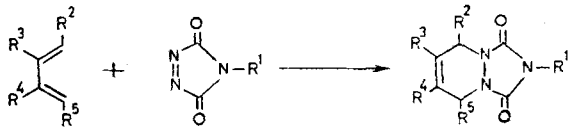


LII LIII

6-Aryl-substituted 5(7)H-1,2,4-triazolo[5,1-c]-1,2,4-triazoles can be obtained in good yields by heating 3-azido-4-arylideneamino-1,2,4-triazole [204, 205].

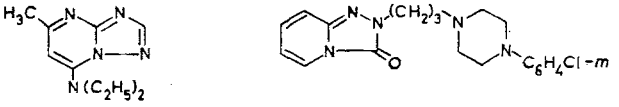
7H-1,2,4-triazolo[3,2-c]-1,2,4-triazines can be obtained in moderate yields from 3-oxo-5-(α-alkylhydrazino)-1,2,4-triazoles and α-halo ketones [206].

The high reactivities of 3,5-dioxo-1,2,4-triazolines as dienophiles have been used in Diels–Alder reactions for the synthesis of condensed 1,2,4-triazoles [207, 208]:



It was subsequently demonstrated that 3-oxo-5-aryl-1,2,4-triazoles [209] and urazole [210] can be used in the diene synthesis.

There are many indications in patents and papers regarding the possibility of the practical application of derivatives of condensed 1,2,4-triazoles. Thus it has been reported that derivatives of condensed 1,2,4-triazoles have antituberculous [211, 212], antiphlogistic [213-215], antivirus [216-218], psychotropic [219-221], analgesic [199, 222], antimicrobial [218, 223-225], antiblastic [166, 226, 227], hypotensive [228, 229], anxiolytic [230], antispasmodic [231], and tranquilizing [232, 233] activity. The vasodilator preparation "Rokornal" (LIV) [234] and the psychotropic preparation "Trazodont" (LV) [235] are being used abroad in medical practice.



LIV LV

Some derivatives [for example, 5-methyl-7(4H)-oxo-1,2,4-triazolo[1,5-a]pyrimidine [236, 237]] are used as photographic emulsion stabilizers. A number of preparations have been tested as agricultural fungicides and bactericides [238-241].

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POLAROGRAPHY OF NITRO AND CARBONYL DERIVATIVES OF ARYLFURANS IN ANHYDROUS DIMETHYLFORMAMIDE

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It is shown that the first reversible one-electron wave in the reduction of 5-arylfurans in anhydrous dimethylformamide (DMF) corresponds to the formation of an anion radical and that the subsequent waves are associated with cleavage of the C–Hal bond in the case of halo derivatives and with reduction of the anion radical and the arylfuran fragment. The character of the reduction of 5-(p-nitrophenyl)furan derivatives is determined by the ability of the substituent in the 2 position to delocalize the negative charge. In conformity with this, the first two reversible waves of carbonyl-substituted derivatives are one-electron waves and correspond to the formation of a stable dianion, the greatest contribution to the resonance hybrid of which is made by a p-quinoid structure. The second wave of 5-(p-nitrophenyl)furan and its 2-CH_2OH derivative is irreversible and corresponds to the transfer of three electrons. Lithium ions have a substantial effect on the height and $E_{1/2}$ value of the second reduction wave, and this effect is manifested more markedly, the less the substituent in the 2 position is capable of delocalizing the negative charge. The transmission factor of the furan ring is 0.48.

It has been previously established that furfural [1] and its 5-aryl derivatives [2] in aqueous alcohol buffered media are reduced on a dropping mercury electrode in conformity with the principles characteristic for the reduction of other aromatic aldehydes. The polarographic behavior of 5-(p-R-phenyl)furfurals (I), where R=H (a), CH_3 (b), OCH_3 (c), Cl (d), Br (e), and NO_2 (f), in anhydrous dimethylformamide (DMF) was investigated

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