Chemistry of Heterocyclic Compounds, Vol. 31, No. 2, 1994

DIHYDROAZOLOPYRIMIDINES WITH A NODAL NITROGEN ATOM: SYNTHESIS, REACTIONS, TAUTOMERISM (REVIEW)

S. M. Desenko

The published data on methods of synthesis of dihydro derivatives of azolopyrimidines with a nodal nitrogen atom are generalized; their applicability is comparatively analyzed. The chemical properties of dihydroazolopyrimidine systems are examined; the intra- and intermolecular factors that determine the position of imine—enamine tautomeric equilibrium are analyzed.

Despite the exceptional role of dihydroazines in cellular bioenergy engineering ($NAD \cdot H \rightarrow NAD^+$, etc.) and the widely known importance of azolopyrimidine systems in the body's vital activity, dihydro derivatives of azolopyrimidines with a nodal nitrogen atom were virtually not investigated until recently. Studies on directed synthesis of compounds of this class first appeared in the mid-1980's [1-6] and in particular demonstrated the high physiological activity of many of them (primarily with respect to the cardiovascular system). Synthetic approaches to dihydroazolopyrimidine systems were subsequently developed and some of their chemical properties, molecular structure, and imine—enamine tautomeric equilibrium were investigated.

The currently available data on the chemistry of dihydroazolopyrimidines containing a nodal nitrogen atom are systemized in the present review.

1. METHODS OF SYNTHESIS

1.1. Cyclocondensation of Aminoazoles with Carbonyl Compounds

Cyclocondensation of aminoazoles with α,β-unsaturated carbonyl compounds or Mannich bases is the most common method of synthesis of dihydroazolopyrimidines with a nodal nitrogen atom [1-15]. Various alkyl- and aryl-substituted dihydropyrazolo[1,5-*a*]- (I), dihydroimidazo[1,2-*a*]-(II), dihydrotriazolo[1,5-*a*]- (III), dihydrotetrazolo[1,5-*a*]pyrimidine (IV), and dihydropyrimido[1,2-*a*]benzimidazole (V) were prepared in this way.

In contrast to the analogous reaction of amines with β-diketones, reaction 1 is characterized by high regioselectivity, which makes it possible to obtain compounds with $R \neq R^3$ even with a low degree of differentiation of the electronic properties of these substituents. Formation of the pyrimidine nucleus corresponds to the reaction of an enone atom with the nitrogen atom of the aminoazole ring and a carbonyl group with an amino group ("anti-Skraup" direction). If there are several nonequivalent reaction sites in the ring, the more nucleophilic one (for example, the $N_{(2)}$ atom in 1,2,4-triazole and pyrazole amino derivatives [7, 8]) usually participates in formation of the pyrimidine nucleus. The reaction of 3-amino-1,2,4-triazole with dibenzoylethylene is an exception [16]. The first stage — alkylation with unsaturated ketone — takes place at all possible reaction sites

Khar'kov State University, Khar'kov 310077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 147-159, February, 1995. Original article submitted May 11, 1994.

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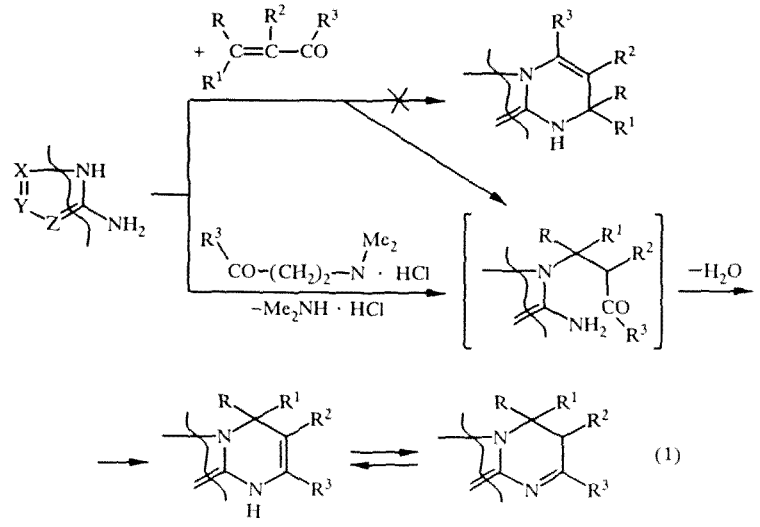
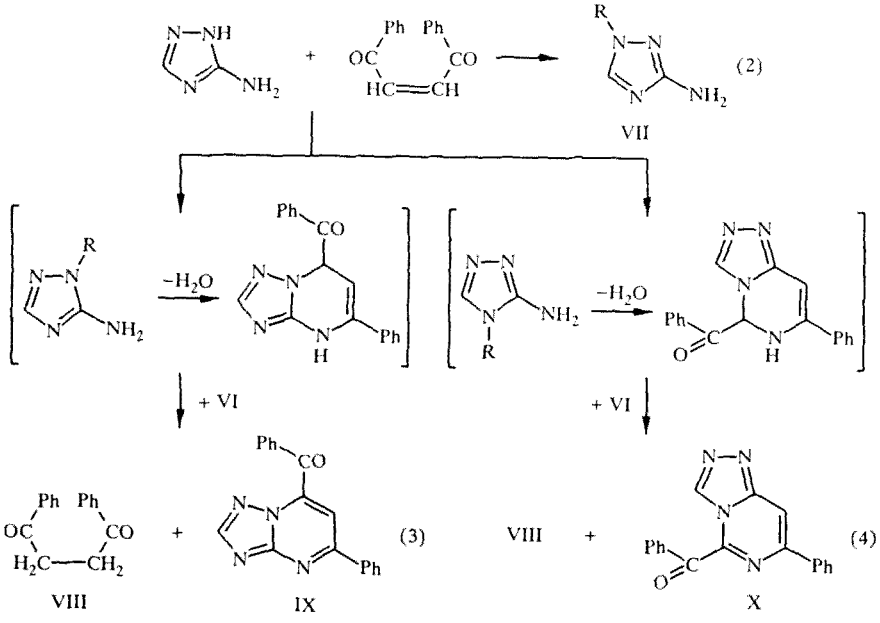


(1)

I–V

I X = N, Y = CR^4, Z = CH; II X = CH, Y = CR^4, Z = N; III X = Z = N, Y = CR^4; IV X = Y = Z = N; V X, Y = *o*-C_6H_4, Z = N; I—V R = H, Alk, Ar; R^1 = H, Alk; R^2 = H, Alk, COR^5, COOEt, CN; R^3 = Alk, Ar; R^4 = H, NH_2, Alk, Ar; R^5 = Alk, Ar

(reactions 2-4). In addition, the relatively higher ability of dibenzoylethylene to act as a hydride ion acceptor was manifested by the fact that 1,2,4-triazolopyrimidine dihydro derivatives were not obtained in this reaction, and triazole (VII), dibenzoylethane (VIII), and triazolopyrimidines (IX) and (X) were the products.



(2)

VII

(3)

VIII + IX

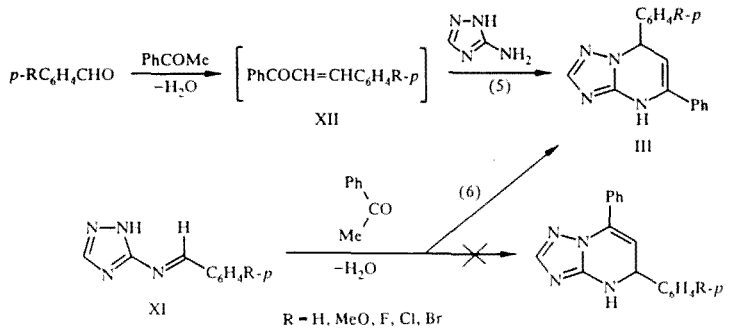
(4)

VIII + X

R=CHCOPhCH$_2$COPh

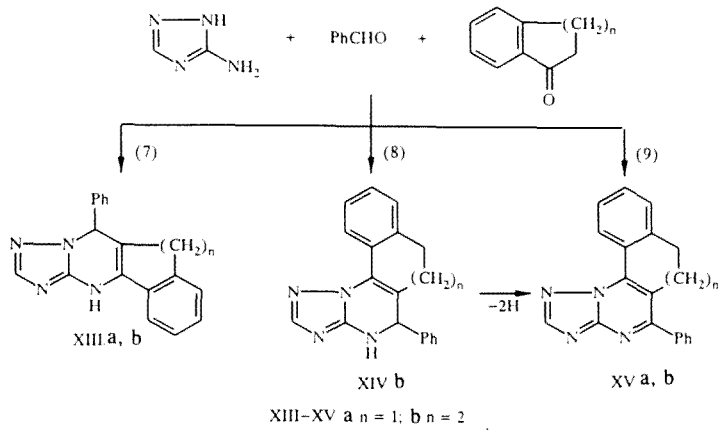
Heteroaromatization is also observed in the reaction of aminoazoles with nitrochalcones [10], arylidenecycloalkanones [13], and in reactions involving 3,5-diaminotriazole [11]. In many cases, in conducting cyclocondensation in conditions of free access of atmospheric oxygen, it can be complicated by oxidation of dihydroazolopyrimidines into their hydroxy-substituted derivatives [15] (reaction 19, Chapter 2).

The possible formation of dihydroazolopyrimidines III directly in the reaction of 3-amino-1,2,4-triazole with synthetic precursors of chalcones — substituted benzaldehyde and acetophenone (reaction 5) or in condensation of acetophenone with azomethines (XI) (reaction 6) — was established in [17, 18].

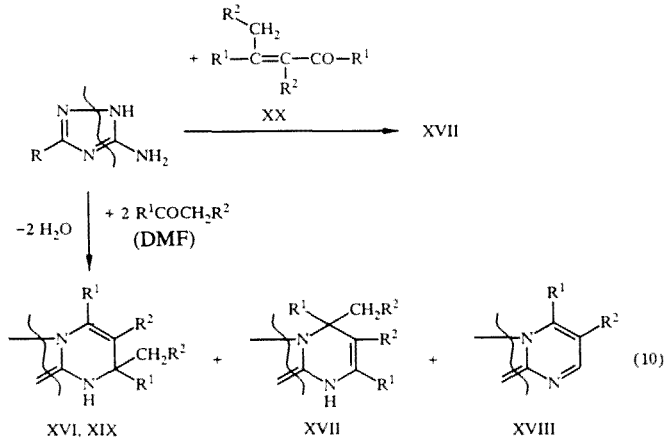


However, it was shown that in the first case, the method of synthesis of compounds III is not independent but involves preliminary formation of unsaturated ketones (XII) and their subsequent reaction with 3-amino-1,2,4-triazole.

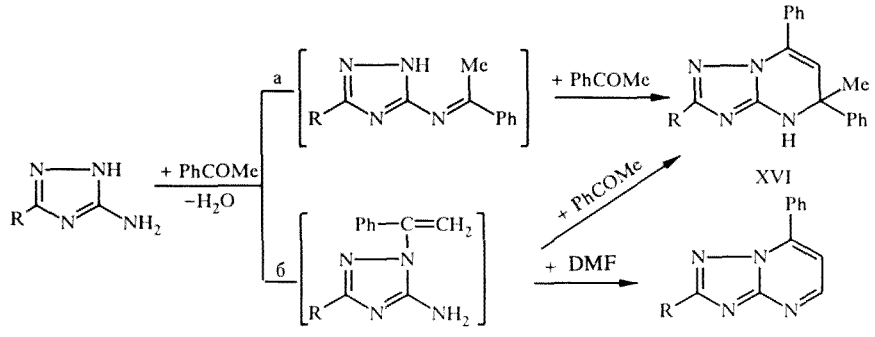
A slightly different picture is observed in the reaction of 3-amino-1,2,4-triazole with benzaldehyde and benzocycloalkanones [17]: in addition to the basic products — derivatives of 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (XIII) (reaction 7), isomers (XIV) and/or products of dehydrogenation of these isomers (XV) are formed with yields of 15-25%. The structure of compounds XIV and XV corresponds to the opposite direction of cyclocondensation (reactions 8, 9).



As a result of the reaction of 3-amino-1,2,4-triazole with methyl aryl ketones ($ZnCl_2$ catalyst, reaction 10), mixtures of 4,5- and 4,7-dihydro isomers (XVI) and (XVII) were obtained [19]. Only 4,5-dihydro derivatives XVI and compounds XVIII (in the last case of the second carbonyl component of condensation, dimethylformamide was used as the solvent) were obtained in the reaction of 3-amino- and 3,5-diamino-1,2,4-triazole with acetophenone in the presence of acetic or mineral acids [20]. The formation of compounds XIX exclusively was observed in reactions of aminotriazoles with cyclohexanone [21].



Since autocondensation of two moles of ketones cannot be the first stage of formation of 4,5-dihydrotriazolopyrimidines XVI and XIX (the reaction of unsaturated ketones (XX) with aminoazoles exclusively yields compounds XVII), two alternative mechanisms ("a" and "b") were proposed for this stage in [19, 20]. In the opinion of the investigators in [19], azomethines (path "a") are the key intermediates in formation of the dihydropyrimidine ring, while enamines are such intermediates (path "b") according to [20].

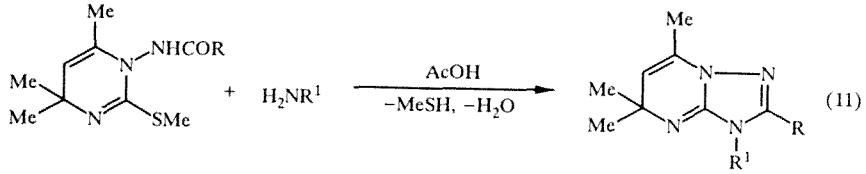


R = H, NH_2

In our opinion, mechanism "b" is more probable, since the formation of compounds XVII as one of the products of the reaction corresponds to cyclization of the indicated enamines and not azomethines. The fact that azomethines XI are not directly involved in cyclization in reacting with acetophenone (reaction 6) but only serve as sources of an aldehyde fragment is also indirect evidence against mechanism "a".

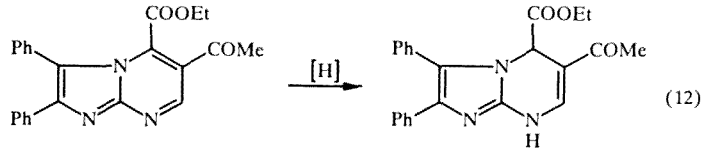
1.2. Alternative Methods of Synthesis of Dihydroazolopyrimidines

Despite the broad possibilities for formation of azolopyrimidine systems by cyclization of substituted pyrimidines, there are only isolated examples of the use of this approach in synthesis of their dihydro derivatives in the literature. Formation of dihydrotriazolopyrimidines (XXI) in condensation of dihydropyrimidinethiol derivatives with amines (reaction 11) was communicated in [22].

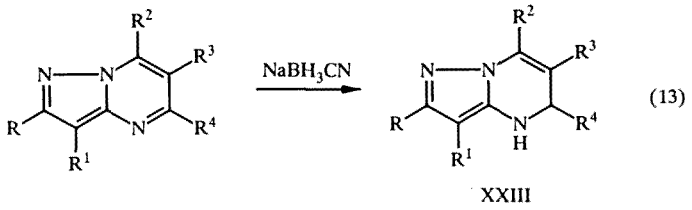


R = Me, Et, Bu; R^1 = Me, *i*-Pr, Ar

Methods of synthesis of dihydroazolopyrimidines from their heteroaromatic analogs have become much better known. Dihydroimidazopyrimidine XXII was obtained directly by catalytic hydrogenation of the corresponding imidazopyrimidine (reaction 12) [23].

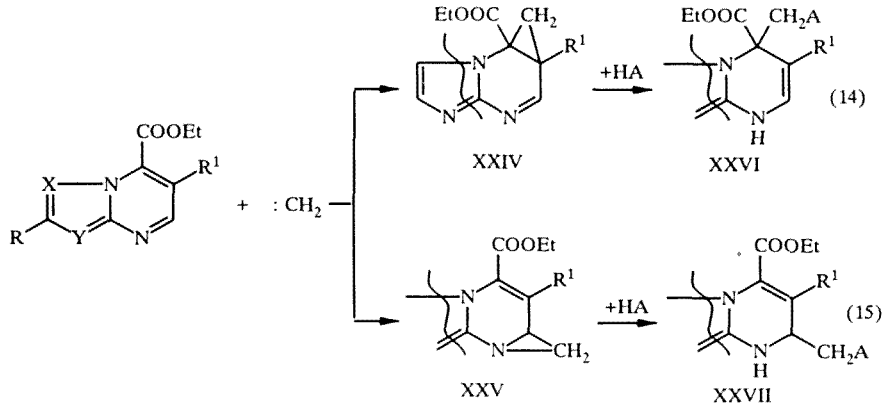


Ordinary methods of catalytic hydrogenation have not been widely used, probably due to the difficulty of stopping reduction in the stage of formation of dihydro derivatives. Directed synthesis of 4,5-dihydropyrazolo[1,5-*a*]pyrimidines (XXIII) from their heteroaromatic precursors was conducted using soft hydrogenating agents (reaction 13) [24].



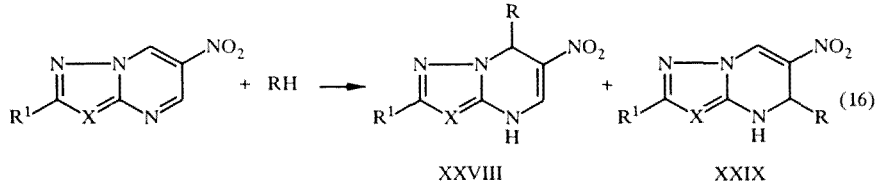
R, R^3, R^4 = H, Alk; R^1 = H, Cl, $CONH_2$, COOH, COOEt; R^4 = H, Alk, Ar

Heteroaromatic azolopyrimidines can undergo cyclopropanation under the effect of diazomethane [23, 25]. The products of this reaction (XXIV, XXV) can be rearranged in acid media with formation of dihydroazolopyrimidines (XXVI, XXVII) (reactions 14 and 15). This process usually takes place in parallel with ring expansion reactions.



A = Cl, OAc; X, Y = N, CR^2; R, R^2 = H, CN, Ph; R^1 = MeCO, COOEt

Nucleophilic addition to nitro-substituted pyrazolo- and triazolopyrimidines (reaction 16) is now the most common method of synthesis of dihydroazolopyrimidines from their heteroaromatic analogs.



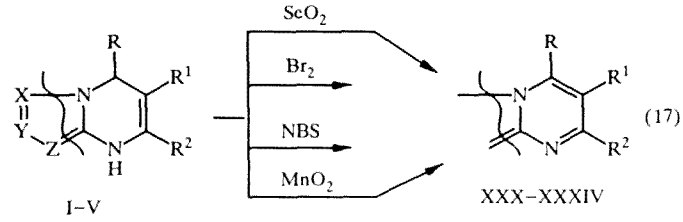
X = N, CR^2; R^1 = H, Me, Ph, SMe; R^2 = NO_2, CN, COOEt

Water and alcohols [26, 27], polyphenols [28, 29], and dimethylaniline [30], pyrrole [31] and indole [32, 33] derivatives have been investigated as nucleophilic reagents.

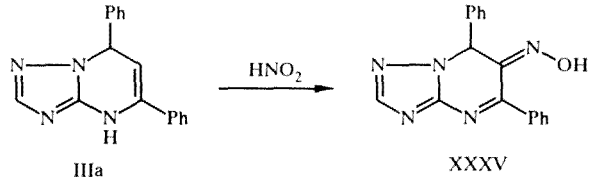
Primarily 4,7-dihydro derivatives (XXVIII) are the products of this reaction; compounds (XXIX) are either not formed at all or are minor products. The selectivity of addition can also be a function of the conditions of the reaction [30]. We note that despite the relatively general character of the reaction, the possibilities of varying both substituent R and the azolopyrimidine fragment in the target compounds are very limited, since only RH nucleophiles with an excess of electrons and only nitro derivatives with sufficient π-deficiency of the annelated azole ring can enter into the reaction [30].

2. REACTIONS OF DIHYDROAZOLOPYRIMIDINES

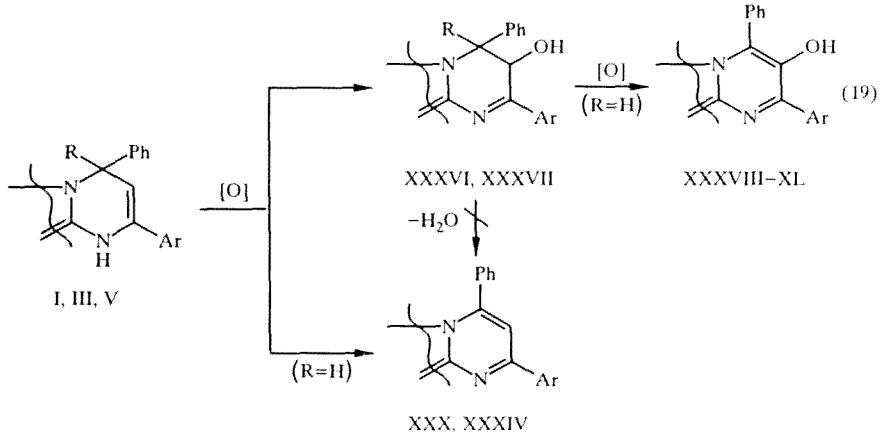
Their capacity for heteroaromatization (reaction 17), which takes place under the effect of such reagents as N-bromosuccinimide (NBS), Br_2/HOAc, SeO_2, and MnO_2, is a common property of azolopyrimidine dihydro derivatives [7-12, 25, 34]:



(17)



(18)



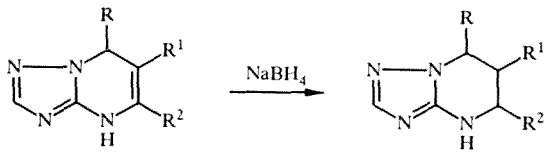
(19)

I, XXX, XXXVI, XXXVIII X = N, Y = CR^3, Z = CH; II, XXXI X = CH, Y = CR^3, Z = N; III, XXXII, XXXIX X = Z = N, Y = CH; IV, XXXIII X = Y = Z = N; V, XXXIV, XXXVII, XL X,Y = *o*-C_6H_4, Z = N
R, R^1 = H, Alk, Ar; R^2 = Alk, Ar; R^3 = H, Alk, Ar

At the same time, it was shown in [34] that compound IIIa forms oxime (XXXV) in the conditions of the widely used method of heteroaromatization of dihydroazines — the effect of acid solutions of $NaNO_2$ (reaction 18). The elevated stability of dihydrotriazolo- and dihydrotetrazolo[1,5-*a*]pyrimidine III and IV dihydro systems was manifested by their resistance to atmospheric oxygen (in neutral media) and trinitrobenzene [7, 8, 35].

In alcohol solutions of bases, preliminary ionization facilitates oxidation of dihydroazolopyrimidines III; formation of hydroxy-substituted compounds XXXIX (reaction 19) is observed together with heteroaromatization [34]. The capacity for conversion into the corresponding hydroxy derivatives is even more pronounced in dihydropyrazolo[1,5-*a*]pyrimidines I and dihydropyrimido[1,2-*a*]benzimidazoles V, and holding solutions of them (in $CHCl_3$, DMF, or alcohol) in conditions of exposure to atmospheric oxygen results in the corresponding compounds XXXVI, XXXVII as the basic (together with derivatives XXX, XXIV) or only products of the reaction [15, 36]. We note that hydroxy-substituted XXXVI and XXXVII unexpectedly exhibited resistance to dehydrating reagents when R = H, probably due to the geometry of the CH—COH fragment of the dihydropyrimidine ring which is unfavorable for this process (close to cisoid) [15, 36].

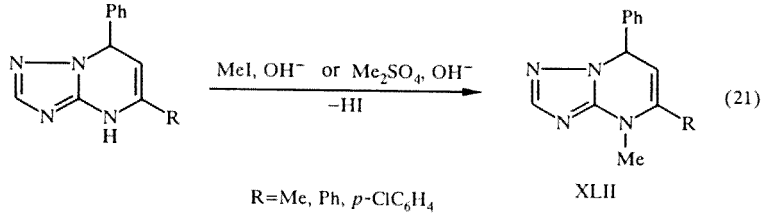
Reduction of dihydrotriazolopyrimidines III with sodium borohydride (reaction 20) results in tetrahydro derivative XCI, and only one of the possible geometric isomers is formed in all cases (*cis*- for R^1 = H, *cis-cis*- for R^1 = CH_3) [34, 37].



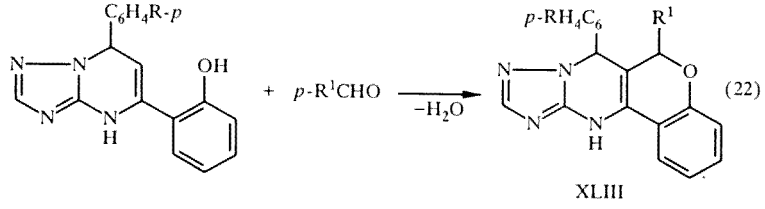
(20)

R = R^2 = Me, Ph; R^1 = H, Me

Reactions (21-24) of alkylation, hydrolysis, and heterocyclization of dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines are presented below. We note that alkylation takes place at the $N_{(4)}$, but not at the $C_{(6)}$ atom when both soft (MeI) and harsh (Me_2SO_4) reagents are used [34]. On the other hand, heterocyclization of *o*-hydroxyphenyl-substituted compounds of this series with aldehydes leads to formation of a benzopyran but not a benzoxazine ring (reaction 22 [18, 38]). In acid media and with *p*-nitrobenzaldehyde, dihydrotriazolopyrimidines decompose with formation of unsaturated ketones and aminotriazole (or azomethine on its base) [18, 34] (reactions 23, 24).

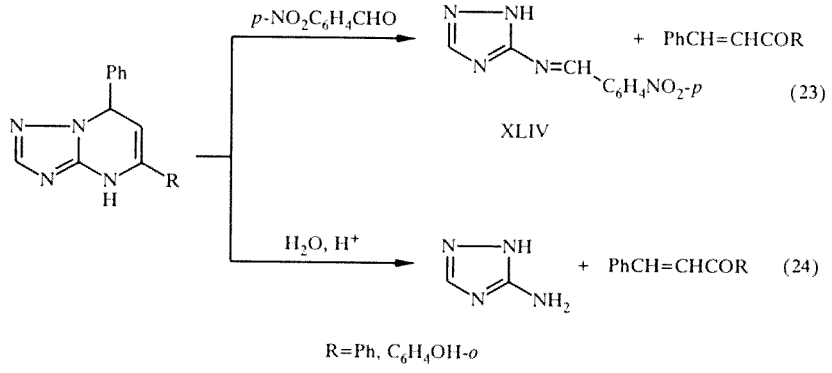


R=Me, Ph, *p*-ClC_6H_4 XLII



XLIII

R=H, MeO, Me_2N, F, Cl; R^1=H, C_6H_4R-*p*

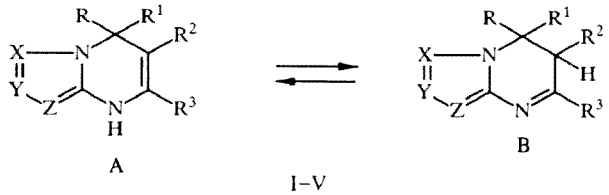


R=Ph, C_6H_4OH-*o*

XLIV

3. IMINE—ENAMINE TAUTOMERIC EQUILIBRIUM IN THE DIHYDROAZOLOPYRIMIDINE SERIES

Formation of mixtures of enamine (A) and imine (B) tautomeric forms in solutions in comparable concentrations is a widespread phenomenon in many dihydroazolopyrimidines with a nodal nitrogen atom.

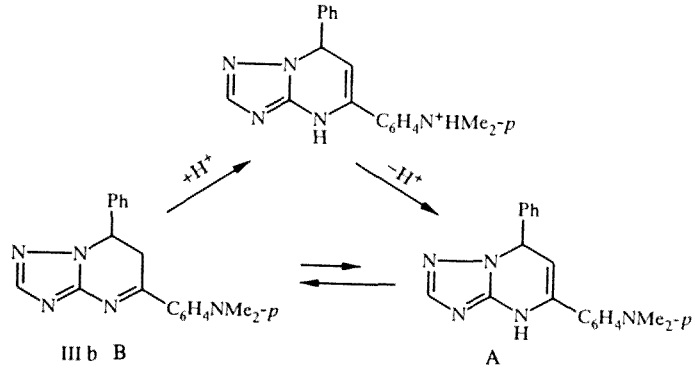


A I–V B

Quantum chemical calculations (AM1 [39]) show that these forms have similar thermodynamic parameters. As a consequence, even insignificant structural changes can significantly affect the equilibrium position, and this makes dihydroazolopyrimidines useful models for studying this type of tautomerism, together with the relative ease of experimental determination of the concentration of tautomeric forms in the solutions (primarily by comparing the integral intensities of the corresponding groups of signals in the PMR spectra).

It is useful to consider the character of the change in the equilibrium composition in variation of one to two and constancy of the remaining structural fragments of the molecule for analyzing the factors that determine the position of tautomeric equilibrium in the dihydroazolopyrimidine series. The data from [7-10, 12-15, 35, 40-43] grouped in this way are selectively reported in Tables 1-4.

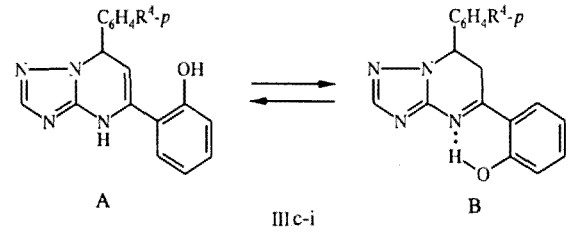
The data in Table 1 illustrate the important dependence of the equilibrium tautomeric composition of compounds I-V with $R^1 = R^2 = H$, and $R^3 = C_6H_4R^4$-*p* on the character of the azole ring and R^4 substituent. In many dihydro derivatives of 1,2,4-triazolo-, tetrazolo[1,5-*a*]pyrimidines and pyrimido[1,2-*a*]benzimidazoles, there is a pronounced tendency toward relative stabilization of forms B with an increase in the electron-donor character of R^4. In [7-10, 13, 14], this was correlated with the effects of conjugation of R^4 with an electron-acceptor azomethine group and the azole fragment of the molecule, possible in form B. This feature was used to separate the individual tautomers of compound IIIb [44]. This substance crystallizes from alcohol and chloroform in the form of imine form B, which predominates in these solutions. In solutions in CF_3COOH, the dimethylamino group is protonated and takes on an electron-acceptor character, so that almost total conversion of compound IIIb into form A is observed, and form A can also be crystallized after rapid neutralization of the solution.



IIIb B A

The effect of the nature of the annelated azole ring on the ratio of tautomers of compounds I-V is manifested by a regular shift in the tautomeric equilibrium to form B and levelling of the effect of substituent R^4 with a decrease in the electron-acceptor effect of the azolyl fragment on the remaining π-system of the molecules (see Table 1).

In dihydrotriazolopyrimidine derivatives IIIc-i ($R = C_6H_4R^4$-*p*, $R^1 = R^2 = H$, $R^3 = C_6H_4OH$-*o*) containing an *o*-hydroxyaryl substituent, the intramolecular hydrogen bond [40, 42, 43, 45], whose conditions of formation are preferred in this tautomer, is a significant factor that additionally stabilizes the imine form. The pronounced effect of the nature of the solvent on the equilibrium composition is also a manifestation of the effect of this factor (see Table 2). Competition of the H bond of the molecules of the heterocycle and the molecules of the solvent with an intramolecular hydrogen bond is undoubtedly the basic cause of the shift in the tautomeric equilibrium to form A in going from $CDCl_3$ to *i*-PrOH and DMSO-D_6. However, the lack of a symbatic change in the composition of the tautomers of compound IIIc with the proton-acceptor power of the solvent in the DMSO, DMF, and pyridine series observed in [42] indicates the significant role of nonspecific solvation in the observed phenomenon. Solvation effects have been used for separating both forms of compounds IIIc, e, g-h by crystallization of tautomer B from alcohols and chloroform or tautomer A from DMSO [40, 45].



A IIIc-i B

IIIc $R^4 = H$, d $R^4 = Me$, e $R^4 = MeO$, f $R^4 = Me_2N$, g $R^4 = F$, h $R^4 = Cl$, i $R^4 = Br$

As Table 2 shows, tautomeric equilibrium is not very sensitive to the electronic character of the R^4 substituents; only a weak tendency to shift to form B with strengthening of the electron-donor character of R^4 is observed. A similar phenomenon is also observed in the 7-aryl-5-(4-dimethylaminophenyl)-1,2,4-triazolopyrimidine series [46]. At the same time, the data from [14, 41] in Table 3 indicate the marked effect of the bulk of substituent R, incorporated in position 7 of the dihydrotriazolopyrimidine bicycle, on the position of tautomeric equilibrium.

TABLE 1. Concentration of Tautomers B (%) in Solutions of Compounds I-V ($R^1 = R^2 = H$, $R^3 = C_6H_4R^4$-*p*)

Compound	X	Y	Z	Solvent	R = H			R = Me		R = Ph				
					R^4			R^4		R^4				
					NO_2	H	MeO	H	MeO	NO_2	H	Me	MeO	Me_2N
I	N	C(Ph)	CH	DMSO-D_6		90				100	100	100	100	
II	CH	C(Ph)	N	DMSO-D_6		80		100		90	95	90	95	95
III	N	CH	N	DMSO-D_6	0	15	40	0	10	0	0	0	0	55
				CF_3COOH	0	50	90	45	90	0	15	35	60	0
IV	N	N	N	DMSO-D_6						0	0	0	0	40
				CF_3COOH						0	0	0	40	0
V	*o*-C_6H_4		N	DMSO-D_6	0	0	20	0	0	0	0	0	0	60
				CF_3COOH	5	55	80	70	90	0	50	70	90	0

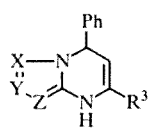
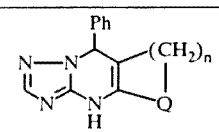
TABLE 2. Equilibrium Concentrations of Tautomer B (%) of Compounds IIIc-i (Y = CH; R = $C_6H_4R^4$-*p*, $R^1 = R^2 = H$, $R^3 = C_6H_4OH$-*o*) [40]

Solvent	Compound (R^4)						
	IIIc (H)	IIId (Me)	IIIe (MeO)	IIIf (Me_3N)	IIIg (F)	IIIh (Cl)	IIIi (Br)
i-PrOH	68	70	74	75	60	65	63
$CDCl_3$	100	100	100	100	100	100	100
DMSO-D_6	25	25	30	35	25	20	20

TABLE 3. Concentration of Tautomer B (%) in Solutions of Compounds III (Y = CH, $R^1 = R^2 = H$, $R^3 = C_6H_4R^4$-*p*)

Solvent	R			
	H	Me	*t*-Bu	Ph
	R^4 = H			
$CDCl_3$	20	20	0	0
DMSO-D_6	15	0	0	0
CF_3COOD	50	45	10	15
	R^4 = MeO			
$CDCl_3$	65	65	30	35
DMSO-D_6	40	10	0	0
CF_3COOD	90	90	65	60

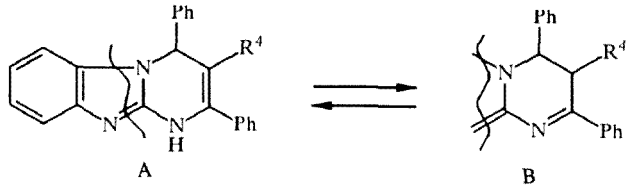
TABLE 4. Concentration of Tautomer B (%) in Solutions of Compounds I, III, V ($R^1 = R^2 = H$) and III [$R^1 + R^2 = -(CH_2)_nQ-$]

X	Y	Z	Solvent							
						Q = $(CH_2)_2$		Q = *o*-C_6H_4		
				R^3 = Me	R^3 = Ph	n = 1	n = 2	n = 1	n = 2	n = 3
N	C(Ph)	CH	DMSO-D_6	100	100	0	0	0	100	0
N	CH	N	DMSO-D_6	0	0	0	0	0	0	0
			CF_3COOH	0	15	0	0	0	0	0
o-C_6H_4		N	DMSO-D_6	0	0	0	0	0	0	0
			CF_3COOH	20	50	0	0	0	0	0

The difference in the features of the conformational behavior of 4,7- and 6,7-dihydroazolopyrimidines, namely the high conformational lability of form A, which allows the substituent to occupy a more favorable position than in form B, is the probable cause of the increase in the equilibrium concentration of tautomer A with an increase in the bulk of R [41].

The effect of steric factors is even more pronounced in the case of dihydrothiazolopyrimidines III, annelated at the pyrimidine nucleus by a hydrogenated carbocycle [12, 13]. As Table 4 shows, annelation is almost always accompanied by total conversion of the compounds into the enamine tautomeric form. This effect is less pronounced when Q = C_6H_4 and n = 2, since it is partially compensated by the stress that arises due to forced convergence of the imino group hydrogen atom and the *o*-hydrogen atom of the phenylene nucleus in this case.

The observed concentrations of tautomer A (C_A) in the series of compounds Va-c is probably also due to the effect of both steric and electronic factors of substituent R^4 [13, 36]: for Va, C_A = 100% in DMSO and 50% in CF_3COOH; for Vb, C_A = 100% in DMSO and CaenecF_3COOH; for Vc, C_A = 100% in DMSO.



V a-c

V a R^4 = H, b R^4 = Me, c R^4 = OH

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