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The Azidoazomethine-Tetrazole Tautomerism

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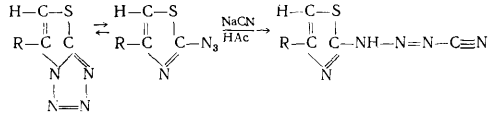
The review deals with the literature on the azidoazomethine-tetrazole tautomerism of condensed tetrazoles with a detailed consideration of the influence of the structure of the condensed tetrazoles, the nature of the substituents, solvents, and temperature on the state of the azidoazomethine-tetrazole equilibrium.
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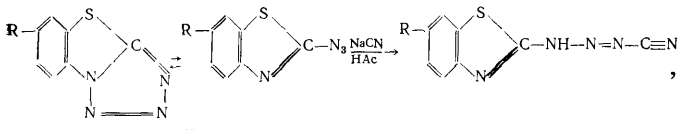
I. INTRODUCTION

A number of studies have been carried out since 1951 on the synthesis and properties of certain condensed tetrazoles[1-24]. The chemistry and fine structure of tetrazolo[5,1-*b*]benzothiazoles and thiazolo[2,3-*e*]tetrazoles were investigated in greatest detail. The studies led to the conclusion that the tetrazole ring condensed with an aromatic heterocycle via the $N_{(1)}-C_{(5)}$ bond is as a rule less stable than 1,5-disubstituted tetrazoles. In many cases it is opened at the $N_{(1)}-N_{(2)}$ bond with formation of the isomeric azidoazomethine derivative. Similar transformations in the series of tetrazolo[5,1-*b*]benzothiazoles and thiazolo[2,3-*e*]tetrazoles frequently occur on heating or dissolution of the substance and following the introduction of electron-accepting substituents into the heterocycle. Therefore, while retaining the properties of 1,5-disubstituted tetrazoles, they enter into reactions characteristic of azides, which was first demonstrated in a number of investigations[1,4,7-10,13,16,18,19,21]. For example, like azides, tetrazolo[5,1-*b*]benzothiazoles and thiazolo[2,3-*e*]-tetrazoles condense with sodium or potassium cyanide to form benzothiazol-2-yl- and thiazol-2-yl-cyanotriazenes respectively[4,19]:



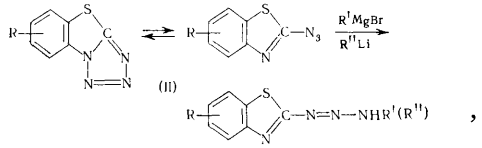
(I)

where R = Me or Ph;



(II)

where R = H, Me, MeO, EtO, F, Cl, or Br. A very interesting relation between condensed tetrazoles and organomagnesium halides and organolithium compounds has been described[1,4,7,13,18,19,21]. It was found that all tetrazolo[5,1-*b*]benzothiazoles, with the exception of the 8-methyl derivative, readily react (like azides) in ether with phenylmagnesium bromide and phenyllithium with formation of phenyl(benzothiazol-2-yl)triazenes:



(II)

where R = H, 6-Me, 6-Cl, 4-Cl, or 6-MeO, R′ = Ph, Bu, Me, or $PhCH_2$, and R″ = Ph or Bu.

8-Methyltetrazolo[5,1-*b*]benzothiazole does not react with phenylmagnesium bromide and phenyllithium. Alkylmagnesium halides and alkyl-lithium compounds are not involved in the formation of aliphatic-aromatic triazenes even on refluxing the reaction mixture in benzene solution. Under these conditions, the initial tetrazoles were isolated in almost quantitative yields[19,21].

On the other hand, 2-azido-4-chlorobenzothiazole, which is isomeric with 8-chlorotetrazolo[5,1-*b*]benzothiazole, forms triazenes with organomagnesium halides regardless of the nature of the organic group[19].

Thiazolo[2,3-*e*]tetrazoles form the corresponding triazenes with phenylmagnesium bromide, phenyl-lithium, and alkylmagnesium halides readily only in the case of the 6-phenyl derivatives[19].

It is interesting that the replacement of the electronegative phenyl group in 6-phenylthiazolo[2,3-*e*]tetrazole by the electropositive methyl group leads to the loss of capacity for the formation of triazenes in the reaction with organometallic compounds.

It has been shown that tetrazolo[5,1-*a*]pyridine does not form triazenes when acted upon by organometallic compounds or sodium and potassium cyanides[19,21]. On the other hand, it has been stated[25] that pyrido[5,1-*a*]tetrazole reacts with triphenylphosphine like azides[18], forming triphenylphosphazo-compounds. The behaviour of tetrazolo[5,1-*b*]benzothiazole and thiazolo[2,3-*e*]tetrazole in relation to phosphines is similar[26].

The reaction of tetrazolo[5,1-*a*]benzothiazoles with 3-methyl-1-phenylpyrazol-5-one and its derivatives has been described[9] and it has been shown that these reactions proceed similarly to the reactions of phenyl azide.

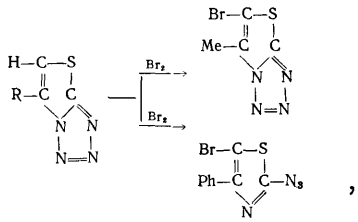
On the other hand, condensed tetrazoles are much more resistant to chemical agents (concentrated acids, oxidising agents) and to light than azides[1,7,10,16,17]. The oxidation of tetrazolo[5,1-*b*]benzothiazole derivatives does not

involve the tetrazole ring. For example, the oxidation of 6-methyltetrazolo[5,1-*b*]benzothiazole leads to the formation of tetrazolo[5,1-*b*]benzothiazole-6-carboxylic acid[10,17].

Dissolution of thiazolo[2,3-*e*]tetrazoles and tetrazolo-[5,1-*b*]benzothiazoles in concentrated inorganic acids leads to the protonation of the tetrazole ring, and, when they are treated with alkylating agents, quaternary tetrazolium salts are formed[14,17].

The isomerisation of 2-azido-4-chlorobenzothiazole to 8-chlorotetrazolo[5,1-*b*]benzothiazole on treatment with sulphuric acid or dimethyl sulphate has been noted[14,17].

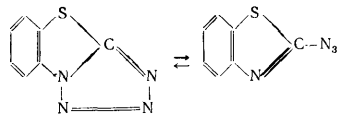
Avramenko, Pochinok, Skopenko, and others[10,17,20,23,24] investigated the halogenation, sulphonation, chlorosulphonation, nitration, and substitution with thiocyanate of thiazolo[2,3-*e*]tetrazoles and tetrazolo[5,1-*b*]benzothiazoles. The halogenation of 6-methylthiazolo[2,3-*e*]tetrazole and its substitution with thiocyanate involve the 5-position of the condensed system and lead to the formation of 5-bromo-6-methyl- and 6-methyl-5-thiocyanato-thiazolo[2,3-*e*]tetrazoles. The corresponding reactions with 6-phenylthiazolo[2,3-*e*]tetrazole proceed similarly at the 5-position. However, the tetrazole ring is opened under the influence of the electronegative phenyl substituent and the reaction products are the isomeric azido-derivatives:



where R = Me or Ph.

The sulphonation, chlorosulphonation, and nitration of 6-phenylthiazolo[2,3-*e*]tetrazole also proceed at the 5-position. The introduction of powerful electron-accepting substituents results in the formation of the isomeric 2-azido-derivatives[17,20,24]. It has been shown[23] that nitration of tetrazolo[5,1-*b*]benzothiazole takes place at the 7-position of the condensed system and the nitration product has the structure of 2-azido-5-nitrobenzothiazole.

In view of the dual nature of the condensed tetrazoles investigated (on the one hand they exhibit the properties of azides and on the other they are much more stable than organic azides and behave like true tetrazoles), Pochinok[2,3] suggested for the first time in 1956 the occurrence of the azidoazomethine–tetrazole tautomerism for condensed tetrazoles:



(II)

It follows from the reactions of various condensed tetrazoles with organometallic compounds, sodium or potassium cyanide, and phosphines that the course of the reaction depends on the state of the azidoazomethine–tetrazole equilibrium, which is influenced by the nature of the substituent in the heterocycle and by the chemical nature of the reagent acting upon the condensed tetrazole.

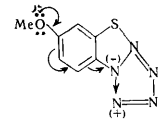
Subsequently the phenomenon of the azidoazomethine–tetrazole tautomerism was demonstrated exactly with the aid of physical research techniques, particularly infrared and NMR spectroscopy.

In 1959 Reynolds et al.[27] and also Boyer and Miller[28] concluded on the basis of spectroscopic studies on condensed tetrazoles that the azidoazomethine–tetrazole tautomerism is possible for some condensed tetrazoles. Infrared spectroscopic data led Boyer and Miller[28] to the hypothesis that tetrazolo[5,1-*b*]benzothiazole is a condensed system in the crystalline state, while in solution it is an equilibrium mixture of the azide and tetrazole forms. In 1961 Sheinker et al.[29] published the results of an infrared spectroscopic study of tetrazolo[5,1-*b*]benzothiazole, which confirmed the earlier conclusions. Furthermore, they observed for the first time that the tetrazolo[5,1-*b*]-benzothiazole ⇌ 2-azidobenzothiazole equilibrium occurs also in the melt[29].

Separate studies on the azidoazomethine–tetrazole tautomerism of tetrazolo[5,1-*b*]benzothiazole, thiazolo[2,3-*e*]tetrazole, and their derivatives were also carried out by infrared spectroscopy[10,11,16,17,20]. The phenomenon of the azidoazomethine–tetrazole tautomerism was likewise observed for other condensed tetrazoles. There are literature data for the azidoazomethine–tetrazole tautomerism of tetrazolopyridine[28,30,31], tetrazolopyrimidines[32-35], tetrazoloquinazoline[36,37], etc.

Condensed tetrazoles have been described in a number of reviews dealing with the chemistry of tetrazoles[38-40]. The reviews by Tisler[41] and Butler[42] on certain aspects of the azidoazomethine–tetrazole tautomerism were published in 1973.

It has been shown[11,14,17,20,33,34] that the state of equilibrium between the azide and tetrazole forms depends on the electron density at the nitrogen atom common to the two rings. In this case the chemical nature of the substituents is of decisive importance. The presence of electron-donating substituents facilitates the closure of the condensed tetrazole ring and increases its stability by enhancement of the electron density at the common nitrogen atom. Electron-accepting substituents stabilise the azido-form:



The study of the azidoazomethine–tetrazole tautomerism has acquired practical importance.

Emulsion-photographic studies have been made[5,12,15,17,22] of tetrazolo[5,1-*b*]benzothiazoles, thiazolo[2,3-*e*]tetrazoles, and certain others. It has been shown that tetrazolo[5,1-*b*]benzothiazole and its derivatives are excellent stabilisers of silver chloride photographic emulsions.

It has been found that the stabilising effect of condensed tetrazoles depends on the state of the azidoazomethine–tetrazole equilibrium. Only those condensed tetrazoles which can give rise to azido-forms with an increased electron density at the heterocyclic nitrogen atom exhibit stabilising properties:

Thus tetrazolopyridine does not stabilise silver chloride emulsions, while 5-nitrotetrazolopyridine is an effective emulsion stabiliser. Infrared spectroscopy of these compounds showed that the former exists only in the tetrazole form in both the crystalline state and in solution. The latter exists in solution as an equilibrium mixture of the azido- and tetrazole forms. For this reason, alkyl

derivatives of thiazolo[2,3-*e*]tetrazole are not stabilisers, while 6-phenylthiazolo[2,3-*e*]tetrazole exhibits a fairly pronounced stabilising effect on the photographic emulsion.

II. METHODS FOR THE INVESTIGATION OF THE AZIDO-AZOMETHINE–TETRAZOLE TAUTOMERISM

The phenomenon of the azidoazomethine–tetrazole tautomerism has been studied in systems where the tetrazole ring is condensed with five- and six-membered aromatic nitrogen-containing heterocycles. The influence of the heterocycle and the electronic nature of its substituents, the polarity of the solvent, the pH of the medium, and temperature on the stability of the condensed tetrazole ring, its isomeric azido-derivative, or the state of the azidoazomethine–tetrazole equilibrium between them has been studied.

The possibility of the annelation of the tetrazole ring to thiazole[4,6,10-12,16,17,20-23,43], 1,2,4-triazole[44,45], thiadiazole[43], tetrazole[46], benzothiazole[1,2,4,6,9-12,14,16,17,19,21,22,24,27-29,47-51], benzoselenazole[27], benzoxazole[27], benzimidazole[26,52], naphtho[2,1-*d*]thiazole[53], naphtho[1,2-*d*]thiazole[53], pyridine[27,28,30,31,47,48,54-64], pyridazine[48,65-77], pyrimidine[27,33-35,47,48,63,69,70,78-87], pyrazine[48,67,79,88], 1,2,4-triazine[47,67,89,90], *s*-tetrazine[91,92], quinoline[93-96], isoquinoline[95], phthalazine[27,77,97,98], quinazoline[36,69-84,85,96,98-110], quinoxaline[96,97,101,111,112], 1,8-naphthyridine[113-122], pyrido[3,4-*d*]pyridazine[72,123,124], pyrido[2,3-*d*]pyridazine[123], 4*H*-pyridazino[6,1-*e*]-1,2,4-triazine[74,75], pyrazino[2,3-*d*]-pyridazine[125], phenanthridine[96,126,127], pyrrolo[1,2-*a*]quinoxaline[129], thieno[3,2-*d*]pyrimidine[129,130], imidazo[1,2-*o*]pyridazine[74,129,131], pyrazolo[1,5-*a*]pyrimidine[132,133], purine[134-137], *s*-triazolo[4,3-*b*]pyridazine[67,71,74,138,139], and *s*-triazolo[4,3-*b*]-*as*-triazine[67,140] has been examined in greatest detail.

The hypothesis of the occurrence of an equilibrium between the azido- and tetrazole forms was put forward on the basis of a study of the chemical properties of these compounds[2]. In certain cases the study of the chemical properties of condensed tetrazoles combined with infrared or NMR spectroscopy can be useful for a quantitative assessment of the equilibrium system. Thus Carboni and coworkers[114,116-118,120] established by a chemical method the proportions of the isomeric 8-azidotetrazolo[1,5-*a*]-1,8-naphthyridines in solutions. The method is based on the different chemical properties of the condensed tetrazole ring and the azido-group. In reduction reactions and in the interaction with nucleophilic agents the azido-group exhibits a higher reactivity. Consequently, in determining the structures and compositions of the products in the reaction mixtures, it is possible to estimate quantitatively the proportions of the isomers in solution.

It is sometimes possible to demonstrate the occurrence of the azidoazomethine–tetrazole equilibrium or even to separate the tautomers by paper and thin-layer chromatography.

In 1959 Boyer and Miller[28] used paper chromatography for the first time in the separation of tetrazolo[5,1-*b*]benzothiazole and 2-azidobenzothiazole and showed that the intensity of the luminescence in the ultraviolet of the two spots on the chromatogram depends on temperature, but no quantitative estimates were made for the equilibrium.

In order to study the azidoazomethine–tetrazole equilibrium and to separate the tautomers in the *s*-tetrazino[2,3-*e*]tetrazole-3-azido-*s*-tetrazine system, Ershov and Postovskii[91] used thin-layer chromatography on alumina.

A detailed study of the phenomenon of the azidoazomethine–tetrazole tautomerism and quantitative estimation of the composition of the equilibrium mixture became possible as a result of the wide-scale application of physical research techniques, primarily infrared and NMR spectroscopy.

The application of infrared spectroscopy is based on the fact that the azido-group has characteristic ν_{as} absorption bands in the range 2100–2200 cm^{-1} and ν_s bands in the range 1100–1350 cm^{-1}. The vibration bands of the tetrazole ring are more difficult to identify and they must be sought at 760, 1212, 1390, 1465, and 1480 cm^{-1}. By measuring the infrared spectra of the compounds in the crystalline state and in solution in polar and non-polar solvents, it is possible to detect the azido- or tetrazole forms of the compounds or both forms simultaneously. Similar measurements at elevated temperatures reveal a change in the intensities of the absorption bands of the azido-group and the tetrazole ring. The heat of the tetrazole–azide transformation can be determined from the temperature variation of the intensities of the absorption bands. It amounts to 4.65 and 0.98 kcal $mole^{-1}$ for the tetrazolo[5,1-*b*]benzothiazoles $\rightleftharpoons$ 2-azidobenzothiazole system in pyridine and dioxan respectively[29,51]. It has been shown that the transformation of the tetrazole into the azide is an endothermic process.

The application of NMR is based on the different effects of the azido-group and the tetrazole ring on the positions of the protons signal in the NMR spectra of the test compounds. These different effects are associated with the greater (in relation to the azido-group) electronegativity of the tetrazole ring. Therefore the proton signals referring to the tetrazole tautomer should occur in the region of lower fields compared with the proton signals due to the azido-tautomers. The nearest protons should be influenced most. The NMR spectra at elevated temperatures reveal an increase of the intensities of the signals of the protons belonging to the azido-form of the compound. This may be regarded as evidence for the validity of the assignment of the proton signals belonging to different tautomeric forms of the compounds.

Quantitative studies of the NMR spectra at different temperatures led to the calculation of the equilibrium constants for various tautomeric systems and to the determination of the heats of the tetrazole–azide transformations in different solutions[33,34,61,72,123,135,136]. These heats for tetrazolo[1,5-*a*]pyridine, tetrazolo[1,5-*a*]pyrimidine, tetrazolo[1,5-*a*]purine, and tetrazolo[5,1-*b*]purine are in the range 2.5–7.0 kcal $mole^{-1}$.

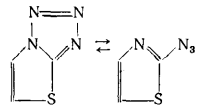
Until recently electronic spectroscopy was not used to investigate the azidoazomethine–tetrazole tautomerism, because the tetrazole ring does not absorb in the ultraviolet and the azido-group gives rise to low-intensity bands at 280 nm. Ershov and Postovskii[91] were the first to employ the ultraviolet spectra to investigate the influence of solvent polarity and to examine the time variation of the tautomeric equilibrium in the *s*-tetrazino[2,3-*e*]tetrazole $\rightleftharpoons$ 3-azido-*s*-tetrazine system. This became possible because the authors separated the tautomers and isolated one of them in a pure form.

III. INFLUENCE OF THE NATURE OF THE NITROGEN-CONTAINING HETEROCYCLE ON THE STABILITY OF CONDENSED TETRAZOLES

The stability of the condensed tetrazole ring is to a large extent determined by the nature of the nitrogen-containing heterocycle to which it is annelated. The

tetrazole ring condensed with saturated heterocycles (trimethylene-[28], tetramethylene-[141,142], and pentamethylene-tetrazoles[142,143], as well as other derivatives[141,144-147], and the nitrogen analogue of trimethylenetetrazole–tetrazoloimidazolidine[28,141]) do not differ in their stability from the 1,5-disubstituted tetrazoles. In the crystalline state and in solution they have cyclic structures.

However, the condensation of the tetrazole ring with a five-membered aromatic heterocycle (thiazole, triazole, tetrazole) leads to a sharp decrease of the stability of the former. The nature and number of heteroatoms in the five-membered heterocycle influence appreciably the stability of the tetrazole ring. Thus in the crystalline state the equilibrium in system (I)

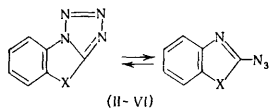


(I)

is almost completely displaced towards thiazolo[2,3-*e*]-tetrazole. However, the tetrazole ring in the latter compound is relatively unstable and tends to be converted into the isomeric azido-form even on dissolution.[20]

It has also been reported that the pyrazole[27], triazole[44], thiadiazole[43], and tetrazole[46] rings destabilise the tetrazole ring condensed to them. For example, 5-azidotetrazole and 5-aryl-3-azido-1,2,4-triazole do not undergo ring closure to the corresponding tetrazoles.

It has been shown[10,11] that tetrazolo[5,1-*b*]benzothiazole (II) is more stable than thiazolo[2,3-*e*]tetrazole (I), as can be seen from the effect of the same solvents on these compounds (see below):

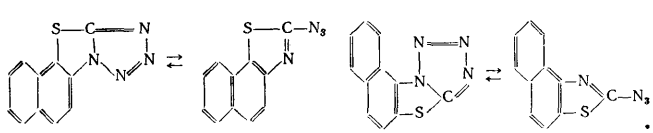


(II–VI)

where X = S (II), Se (III), O (IV), NH (V), and SO_2 (VI).

In systems (II)–(VI) the states of the azidoazomethine–tetrazole equilibrium and the stability of a particular isomeric form depends to a large extent on the electronegativity of the atom X[27]. When X = S or Se, compounds (II) and (III) have the structures of condensed tetrazoles, although they are much less stable than the 1,5-disubstituted tetrazole and exist in solution in equilibrium with the isomeric azido-forms[10,11,16,17,20,27-29]. The replacement of the sulphur atom in the tetrazole (II) by the sulphone group (VI) leads to an increase of the stability of the azido-form and precludes its ring closure[27]. The attempts to obtain tetrazole rings condensed with benzoxazole or benzimidazole rings also did not lead to the desired results. The compounds synthesised had the structures of 2-azido-derivatives of benzoxazole (IV) and benzimidazole (V).

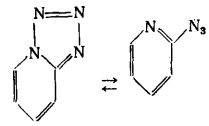
The condensation of the thiazole ring in (I) with the naphthalene ring [systems (VII) and (VIII)] reduces the stability of the corresponding tetrazole forms relative to tetrazolo-[5,1-*o*]benzothiazole (II):



(VII) (VIII)

Even in the crystalline state tetrazolo[1,5-*b*]naphtho-[1′,2′-*d*]thiazole (VII) and tetrazolo[1,5-*b*]naphtho[2′,1′-*d*]thiazole (VIII) exist in equilibrium with the isomeric azido-derivatives and in the latter case the equilibrium is displaced towards the azido-form. The authors attribute this decrease of stability to the fact that naphthothiazoles have more pronounced electron-accepting properties than benzothiazoles[53].

In the crystalline state tetrazolo[5,1-*a*]pyridine (IX) has a cyclic structure and is not converted into the isomeric azido-derivative in polar and non-polar solvents[27,61,48,63]:

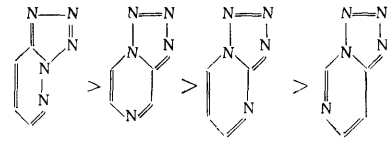


(IX)

However, under severe conditions (in pyrolysis) it can give rise to the reactive azido-form and can enter into reactions characteristic of azides[62,63,47,147].

It follows from a series of studies by Temple and coworkers[33-35], Wentrup[48,70,82], Stanovnik[74,75], and others[65,88] that the replacement of the methine group in the six-membered nitrogen-containing heterocycle by a second electronegative atom (nitrogen) causes some decrease of the stability of the $N_{(1)}$–$N_{(2)}$ bond in the condensed tetrazole ring. In the crystalline state tetrazolo[1,5-*b*]pyridazine (X)[48,65], tetrazolo[1,5-*a*]pyrazine (XI)[48,70,88], and tetrazolo[1,5-*a*]pyrimidine (XII)[33-35,48] have cyclic structures. Tetrazolo[1,5-*c*]pyrimidine (XII) is in equilibrium with the isomeric 4-azidopyrimidine even in the crystalline state[35]. In polar and non-polar solvents compounds (X)–(XIV) exist in both tautomeric forms, but on heating they behave like azides.

Thus the state of the azidoazomethine–tetrazole equilibrium involving the above heterocycles depends on the relative positions of the two nitrogen atoms in the heterocycle and in compounds (XII) and (XIII) also on the bond of the pyrimidine ring to which the tetrazole ring is attached. These compounds can be arranged in the following sequence in terms of the stability of the condensed tetrazole ring:



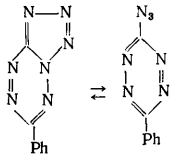
(X) (XI) (XII) (XIII)

This relation is manifested particularly clearly when the influence of temperature and solvent on the state of the azidoazomethine–tetrazole equilibrium is examined.

An increase in the number of nitrogen heteroatoms in the six-membered ring leads to a further destabilisation of the tetrazole ring condensed to it and to an increase of the stability of the azido-form. Ershov and Postovskii[91] carried out calculations for the azido-forms of a number of phenylazines and showed that, with increase of the number of nitrogen atoms in the ring, the π-electron density at the bridgehead nitrogen atom diminishes, which leads to an increase of the energy of the transition to the tetrazole form and to an increase of the stability of the azido-form.

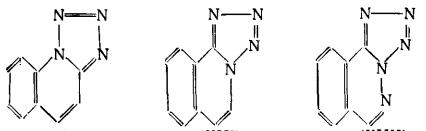
Unsubstituted azidotriazines and azidotetrazines or their isomeric condensed tetrazoles have not been described in the literature. The structures of their derivatives depend on the electronic nature of the substituents and confirm indirectly the calculations of Ershov and Postovskii[91].

Ershov and Postovskii showed that 6-phenyltetrazolo-[5,1-*b*]-*s*-tetrazine (XIV) cannot be isolated in a pure state because of the exceptional ease of its conversion into the azido-form owing to the latter's greater stability[91]:



(XIV)

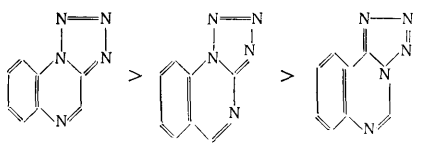
The benzo-analogues of compounds (IX)–(XIII) and (XV)–(XX) contain more stable tetrazole rings. Thus tetrazolo-[1,5-*c*]quinoline (XV) and its analogue tetrazolo[5,1-*a*]isoquinoline (XVI) exist only in the cyclic form[95].



(XV) (XVI) (XVII)

Under severe conditions (380–510°C/10^{-3}–10^{-2} mmHg), they isomerise, like compound (IX), to the corresponding azides. The existence of tetrazolo[1,5-*a*]phthalazine (XVII), but not of its isomeric 1-azidophthalazine, has been reported[27,77,97,98]. Tetrazolo[1,5-*e*]quinazoline (XX) is more stable than the related tetrazolo[1,5-*c*]pyrimidine (XIII). Thus in the crystalline state compound (XX) exists only in the cyclic form[103] and compound (XIII) is present in equilibrium with the azide[35]. Tetrazolo[1,5-*a*]quinoxaline (XVIII) is more stable than tetrazolo[1,5-*a*]pyrazine (XI). This is confirmed by the cyclic structure of compound (XVIII) even in trifluoroacetic acid, in contrast to compound (XI).[101]

Compounds (XVIII)–(XX) can be arranged in the following sequence in terms of the stability of the condensed tetrazole ring:

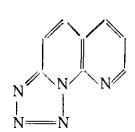


(XVIII) (XIX) (XX)

,

which is analogous to the series (XI) > (XII) > (XIII) discussed above. Thus, in contrast to compound (XVIII), the tetrazoloquinazolines (XIX) and (XX) are converted into the corresponding azides in trifluoroacetic acid[69,101]. The greater stability of tetrazolo[1,5-*a*]quinazolines (XIX) compared with tetrazolo[1,5-*c*]quinazolines (XX) is confirmed by the gradual transformation, observed by Postovskii and coworkers, of certain derivatives of (XX) into the isomeric azido-derivatives in the crystalline state[100,109], which is not observed for compounds of type (XIX).[36]

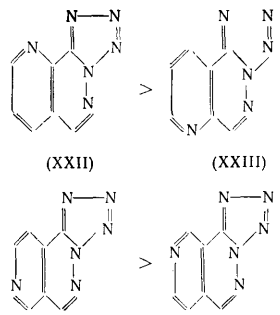
The replacement of the benzene ring in the condensed tetrazoles (XV) and (XVII) by pyridine leads to the somewhat less stable tetrazolo[1,5-*a*]-1,8-naphthyridine (XXI)[114,122]:



(XXI)

and also to the pyridotetrazolopyridazines (XXII)–(XXV)[72,73,123,124]. The stability of the tetrazoles (XXII)–(XXV) depends on the position of the nitrogen atom in the pyridine ring relative to the condensed tetrazole ring.

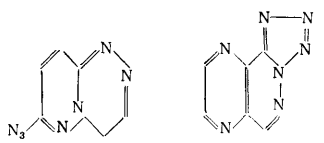
This can be inferred indirectly from the ability of 6-azidopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine and 6-azidopyrido[3,4-*d*]tetrazolo[1,5-*b*]pyridazine to isomerise to the thermodynamically more stable 6-azidopyrido[2,3-*d*]-tetrazolo[5,1-*b*]pyridazine and 6-azidopyrido[4,3-*d*]tetrazolo[1,5-*b*]pyridazine respectively[72,123,124]. It follows from these data that compound (XXII) is more stable than compound (XXIII) and compound (XXIV) is more stable than compound (XXV):



(XXII) (XXIII) ;

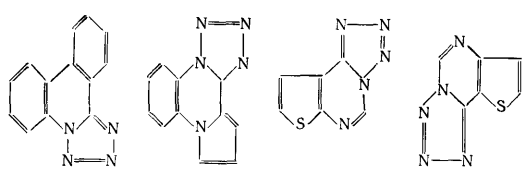
(XXIV) (XXV)

It has been shown in a series of studies by Stanovnik and Tisler[74,75] that the condensation of the pyridazine ring to heterocycles containing two nitrogen atoms leads to the formation of the azido-derivative (XXVI) instead of the isomeric condensed tetrazoles. On the other hand, compound (XXVII) exists in the cyclic form:



(XXVI) (XXVII)

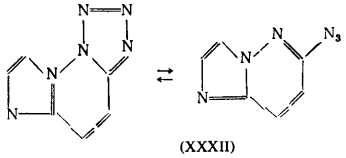
It has been reported[96,126,127] that the condensation of the 9,10-phenanthridine ring with the tetrazole ring leads to the stable tetrazolo[1,5-*b*]-9,10-phenanthridine (XXVIII). Pyrrolo[1,2-*a*]tetrazolo[1,5-*c*]quinoxaline (XXIX) has also been described[87]:



(XXVIII) (XXIX) (XXX) (XXXI)

The systems (XXX) and (XXXI), derived from tetrazolo[1,5-*c*]pyrimidine (XIII) in which the pyrimidine ring is in its turn condensed to a five-membered ring (thiophen) have been described[128,130]. The substances are said to have a cyclic structure in the crystalline state.

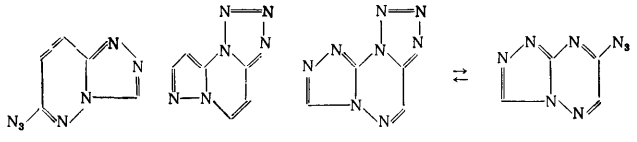
The condensation of tetrazolo[1,5-*b*]pyridazine (X) with a five-membered nitrogen-containing ring (imidazole) leads to the destabilisation of the tetrazole ring in imidazo[1,2-*b*]tetrazolo[5,1-*f*]pyridazine (XXXII):



(XXXII)

It has been stated that even in the crystalline state compound (XXXII) exists in equilibrium with a small amount of the isomeric azido-form[131]. The accumulation of nitrogen atoms in the five-membered ring precludes the closure of the tetrazole ring. 6-Azido-*s*-triazolo[4,3-*b*]-pyridazine (XXXIII), which does not isomerise to the corresponding tetrazole, has been described[67,71,74,138,139].

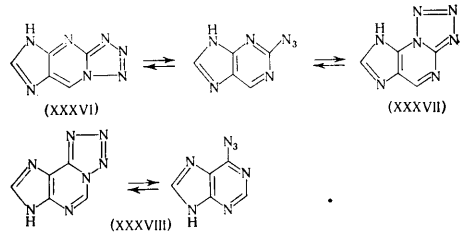
On the other hand, the condensation of tetrazolo[1,5-*c*]-pyrimidine (XIII), which is less stable than compound (X), with the pyrazole ring leads to the formation of the stable pyrazolo[1,5-*a*]tetrazolo[1,5-*c*]pyrimidine (XXXIV), which has only the cyclic structure in the crystalline state[132]:



(XXXIII) (XXXIV) (XXXV)

In the crystalline state the equilibrium in system (XXXV) is fully displaced towards the cyclic form, while in solution there is an equilibrium between both tautomers[67,140].

The condensation of the pyrimidine ring in the tetrazolopyrimidines (XII) and (XIII) with the imidazole ring leads to the formation of the tetrazolopurines (XXXVI), (XXXVII), and (XXXVIII) in which the stability of the tetrazole ring is sharply reduced compared with the related tetrazolopyrimidines:



(XXXVI) (XXXVII)

(XXXVIII)

The studies of Temple and coworkers[134-136] have shown that tetrazolo[5,1-*b*]purine (XXXVIII) exists in the crystalline state in equilibrium with 6-azidopurine, while in the system (XXXVI)–(XXXVII) the equilibrium is almost completely displaced towards 2-azidopurine. However, under certain conditions the azido- and two tetrazole forms can be in equilibrium. These compounds can be arranged in the following sequence in terms of the stability of the tetrazole ring: (XXXVIII) > (XXXVI) > (XXXVII).

IV. INFLUENCE OF SUBSTITUENTS

The electronic nature of the substituent in the nitrogen-containing heterocycle has a considerable influence on the possibility of the formation of the condensed tetrazole ring and its stability and also on the state of the azidoazomethine–tetrazole equilibrium in the system. As a rule, the introduction of powerful electron-donating substituents, which increase the electron density at the nitrogen heteroatom, promotes the formation of condensed tetrazoles in chemical reactions, increases the stability of the condensed tetrazole ring, and shifts the azidoazomethine–tetrazole equilibrium towards the cyclic form. The introduction of powerful electron-accepting substituents, which reduce the electron density at the nitrogen heteroatom, leads to an appreciable decrease of the stability of the condensed tetrazole ring and to a shift of the equilibrium in the tetrazole ⇌ azide system towards the azido-tautomer. A powerful electron acceptor introduced into the nitrogen-containing heterocycle sometimes precludes altogether ring closure by the azido-group via the nitrogen atom and the formation of a condensed tetrazole ring is not observed.

In systems containing a tetrazole ring condensed with five-membered nitrogen-containing heterocycles this phenomenon has been studied in greatest detail for thiazolo[2,3-*e*]tetrazoles (I) and tetrazolo[5,1-*b*]benzothiazoles (II). Thus Pochinok and coworkers[10,14,16,20,23,24] studied the influence of substituents on the possibility of the annelation of the tetrazole ring to the thiazole and benzothiazole rings and the state of equilibrium in systems (I) and (II). It has been shown that electron-donating substituents in the thiazole and benzathiazole rings facilitate the closure of the condensed tetrazole ring and increase its stability. Thus thiazolo[2,3-*e*]tetrazole (I) and its 5-methyl, 6-methyl, 5,6-dimethyl, 6-phenyl, 6-*p*-tolyl, 6-*p*-bromophenyl, 6-*p*-chlorophenyl, 5-bromo-6-methyl, and 6-thiacyanato-derivatives are condensed tetrazoles in the crystalline state. The introduction of the electron-accepting nitro-, sulpho-, chlorosulphonyl, aminosulphonyl, thiacyanato-, or bromo-groups in the 5-position of 6-phenylthiazolo[2,3-*e*]tetrazole (I) decreases appreciably the electron density at the nitrogen atom of the thiazole ring and therefore ring closure by the azido-group via this atom becomes impossible; such derivatives of (I) exist in the azido-form even in the crystalline state. When substituents such as methyl and the bromo-group, methyl and the thiacyanato-group, or the bromo- and thiacyanato-groups are combined in a derivative of (I), the stability of the tetrazole ring also diminishes. However, the presence of the electropositive methyl group in such molecules imparts a certain stability to the tetrazole forms of these compounds in the crystalline state, although in solution (in chloroform, carbon tetrachloride, and acetonitrile) the equilibrium in these systems is almost completely displaced towards the isomeric azides.

Similar relations are observed in systems (II). Tetrazolo[5,1-*b*]benzothiazole and its 6-methyl, 8-methyl, 6-methoxy-, 8-methoxy-, 6-acetamido-, 6-chloro-, 6-bromo-, and 6-fluoro-derivatives are condensed tetrazoles in the crystalline state. The introduction of chlorine in the 4-position of the benzothiazole ring leads to the formation of the isomeric 2-azido-4-chlorobenzothiazole instead of the tetrazole, which is a consequence of the greater influence of the negative inductive effect of the chlorine in the 4-position of the benzothiazole ring compared with the chlorine in the 6-position. The chlorine atom in the 4-position does not give rise to steric hindrance, which might interfere with the formation of the condensed tetrazole, while the analogous compound with the CH_3 group in the 4-position has the cyclic structure.

The introduction of an electron-accepting substituent (the nitro-group) in the 4-, 5-, 6-, and 7-positions of the

benzothiazole ring leads to the existence of stable 2-azido-derivatives even in the crystalline state.

6-Carboxy-derivatives of (II) exist in equilibrium with the azido-form even in the crystalline state, which can be accounted for by the approximately identical electron-accepting properties of the carboxy-group and the tetrazole ring[148,149]. The formation of salts via the carboxy-group results in a decrease of the electron-accepting properties of the substituent and therefore the sodium salt exists as the tetrazole tautomer in the crystalline state.

Boyer and coworkers[28,30] showed that the introduction of hydroxy- and amino-groups into tetrazolo[5,1-*a*]pyridine (IX) does not destabilise the tetrazole ring and the resulting 6- and 8-hydroxy- and 8-amino-derivatives of (IX) have a cyclic structure in both the crystalline state and in solutions (in dimethylformamide, alcohol, and chloroform). The introduction of the electron-accepting nitro-group into the 6-position of compound (IX) reduces the stability of the condensed tetrazole ring, which leads to the formation under certain conditions of an equilibrium system containing both tautomers[28,65,88]. The chlorine atom introduced into the α-position of the pyridine ring acts similarly[61,95]. It has been found that the introduction of chlorine in the 5-position of compound (IX) destabilises the tetrazole form and shifts the equilibrium towards the azide.

It has also been reported[115,117-120,122] that tetrazolo[1,5-*a*]-1,8-naphthyridines (XXI) with electron-donating substituents have only the cyclic structure in the crystalline state with the exception of 8-hydroxy-5-phenyltetrazolo[1,5-*a*]-1,8-naphthyridine[74], which is an azide in the crystalline state. The phenyl substituent decreases the stability of the condensed tetrazole ring in compound (XXI) when it is in the 5-position, evidently because it attracts electrons to itself. This can explain the presence of the $\nu_{as}(N_3)$ band in the infrared spectrum of 8-hydroxy-5-phenyltetrazolo[1,5-*a*]-1,8-naphthyridine in the crystalline state[117] (although under certain conditions the pure tetrazole form can be isolated). On the other hand, when the phenyl substituent is in the 4-position, it stabilises the condensed tetrazole ring as a result of conjugation with the latter.

Similar features were observed in the series of substituted tetrazolo[1,5-*a*]pyrimidines (XII)[33,34,48]. The introduction of two methyl groups, a methyl and a methoxy-group, or a methyl and a methylthio-group into the pyrimidine ring stabilises the condensed tetrazole ring in such systems in relation to the unsubstituted compound (XII).

The introduction of chlorine, which exhibits a stronger negative inductive effect, as a substituent in the 5-position leads to an appreciable destabilisation of the ring compared with the unsubstituted compound (XII). The chloro-derivative of (XII) can be isolated in a pure state when solutions in $CHCl_3$ or CF_3COOH are evaporated and remains metastable for several weeks. However, after prolonged storage it is gradually converted into the more stable tetrazole form. The same process takes place rapidly when compound (XII) is heated above its melting point. Thus both isomers were isolated for the first time in a pure form.

The introduction of the electron-donating amino-group or the methyl group, which exhibits a powerful positive inductive effect, in the 8-position of tetrazolo[1,5-*c*]pyrimidine (XIII) stabilises the tetrazole ring. Thus 5,7,8-trimethyltetrazolo[1,5-*c*]pyrimidine is more stable than the 5,7-dimethyl derivative[14]. 8-Amino-7-chlorotetrazolo-[1,5-*c*]pyrimidine exists in the crystalline state as the tetrazole form. Acylation of the amino-group in the 8-position (with acetic or trifluoroacetic acid) or the introduction of the ethoxymethyleneamino-group in the 8-position leads to the occurrence of the tetrazole $\rightleftharpoons$ azide equilibrium even in the crystalline state, the equilibrium being displaced towards the azido-tautomers[35,86]. When the electron-donating substituent is in the 7-position, its influence on the stability of the tetrazole rings may be various. Thus Postovskii and Smirnova[87] investigated the influence of cycloalkylamino-residues in the pyridine ring on the state of the tetrazole $\rightleftharpoons$ azide equilibrium in system (XIII). It was found that the electron-donating cycloalkylamino-substituents with related structures have different effects on the stabilities of these compounds. When the ring contains morpholine and homopiperidine residues, the compounds exist in the form of azides even in the crystalline state. The pyrrolidino- and piperidino-derivatives are tetrazoles in the crystalline state. This difference between the structures cannot be related to the different basicities of the substituents, since the basicities of homopiperidine, pyrrolidine, and piperidine are approximately of the same order of magnitude. The authors suggested that the observed differences are probably due to the steric effect of the substituents.

It has also been reported[48] that the introduction of two-methoxy-groups into tetrazolo[1,5-*c*]pyrimidine (XIII) in the 5- and 7-positions precludes the formation of the condensed tetrazole ring, which cannot be accounted for by steric hindrance.

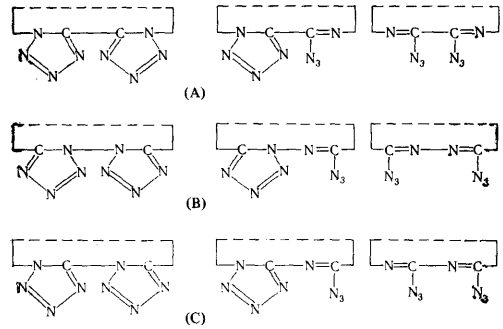
The introduction of the methyl, phenyl, γ-pyridyl, or α-furyl substituents in the 5-position of tetrazolo[1,5-*c*]-quinazoline (XX) does not destabilise the tetrazole form. These compounds have only the cyclic structure in both the crystalline state and in solutions[109]. The introduction of cycloalkylamino-residues into the 5-position of (XX) destabilises the cyclic form and makes possible its conversion into the isomeric azido-form even in the crystalline state after prolonged storage followed by the determination of the azideazomethine–tetrazole equilibrium position[36]. The rate of conversion of the tetrazole into the azide then depends on the basicity of the cycloalkylamino-residue. In contrast to compound (XX), tetrazolo-[1,5-*a*]quinazoline (XIX) with cycloalkylamino-groups in the 5-position has the cyclic structure in the crystalline state[99]. It has been shown[67] that the introduction of two phenyl groups in the 5- and 6-positions of tetrazolo[1,5-*a*]-pyrazine (XI) also leads to the destabilisation of the tetrazole ring.

The introduction of chloro- and methoxy-groups[25] in the 5-positions and cycloalkylamino-groups in the 6-position[68] of tetrazolo[1,5-*b*]pyridazine (X) does not evidently reduce the stability of the condensed tetrazole ring. The authors attribute the appearance of weak bands in the infrared spectrum of cycloalkylaminotetrazolo[1,5-*b*]pyridazine in the range 2100–2200 cm^{-1} to overtones or combination tones of the fundamental vibrations of the heterocycle in the region of the asymmetric vibrations of the azido-group[68].

Temple showed[36] that in purine systems the structure of azidotetrazole derivatives also depends on the presence of electron-donating or electron-accepting substituents. Thus 2-azidopurine exists almost completely in the form of the azide in the crystalline state. The introduction of the electron-donating hydroxy-group in the 6-position of 2-azidopurine leads to the appearance of one of the cyclic forms, which is completely converted into 2-azidopurine after only 30 min even after dissolution in trifluoroacetic acid (TFA)[136]. The amino-group has a similar effect, but in this case the two possible tautomers appear in d_6-DMSO. On the other hand, chlorine in the 2-position of 6-azidopurine appreciably stabilises the azido-form.

In the crystalline state and in solution in dimethyl sulphoxide (DMSO) the compound (XXVII) exists in the form of the azide, in contrast to unsubstituted 6-azidopurine.

Attempts have been made to synthesise compounds containing two condensed tetrazole rings in a single molecule or to condense two such rings with one nitrogen-containing heterocycle in a system of type (A)–(C):

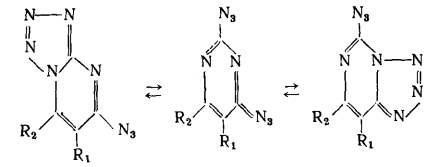


Behringer and Fischer[150] studied non-condensed linear systems of types (A) and (B) and showed that in type (A) systems there is isomerisation to the more stable bistetrazole with the same charge distribution on the nitrogen atoms of the two rings as in the unsubstituted tetrazole. Bistetrazoles of type (B) are as a rule extremely unstable and exist in the form of the isomeric diazides[150,151]. However, it proved possible to isolate 1,1-bis-(5-phenyl)-tetrazole in the crystalline state[150], while in solution the compound is in equilibrium with the isomeric diazide.

Not one case where two tetrazole rings are present in the molecule simultaneously has been described for condensed systems. The attempts to condense the tetrazole ring with another tetrazole ring[46] or two tetrazole rings with pyridazine[65,67,72], pyrimidine[27,48,152–154], tetrazine[92], phthalazine[27,98], quinazoline[72,123], quinoxaline[27,98,103], pyrido[3,2-*d*]pyridazine[72,123], pyrido[4,3-*d*]pyridazine[123], naphthyridine[113,114,117–121], pyrazino[2,3-*d*]pyridazine[125], and purine[136,137] did not lead to the desired results. The reason for this is probably the powerful electron-accepting properties of the tetrazole rings and the consequent decrease of the basicity of the second nitrogen heteroatom. The second azido-group can play the role of a weak electron-donating substituent in such cases.

In most instances compounds of this kind exist as azidotetrazoles in the crystalline state. Azidoazomethine ⇌ tetrazole equilibrium systems arise in solutions and their tautomer content depend on the nature of the heterocycle and the substituents and also on the polarity of the solvent. Sometimes transitions of this kind occur after prolonged storage or heating of the compound.

Thus the structure of diazides was attributed in a number of studies[27,152–154] to 2,4-diazidopyrimidine and its derivatives (6-methyl, 5-methyl, 5,6-dimethyl, 6-phenyl, and 6-furyl) on the basis of an investigation of certain physical and chemical properties. Later studies by Wentrup[48] by NMR showed that at any rate methyl and dimethyl derivatives exist in the crystalline state as tautomeric mixtures of azidotetrazoles (XII, a-c) and (XIII, a-c) in which the more stable (XII, a-c) predominates.

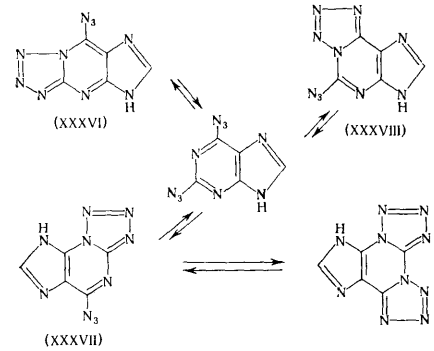


(XII) (XIII)

(a) R_1 = Me, R_2 = H; (b) R_1 = H, R_2 = Me; (c) R_1 = R_2 = Me.

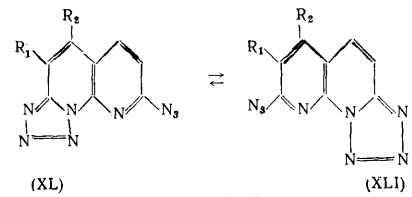
The diazido-forms of the methyl derivatives can be isolated in a pure state only under special conditions; they are metastable at room temperature. At the melting point such diazides are converted into a mixture of the isomeric tetrazoles (XII) and (XIII) which on further heating reforms the diazide. In chloroform solution all three isomers are in tautomeric equilibrium.

Smirnova and Postovskii[137] and Temple et al.[136] showed that, out of the five possible isomeric compounds in the 2,6-diazidopurine system, it is possible to detect 2,6-diazidipurine itself in the crystalline state (and in trifluoroacetic and acetic acids), while in DMSO solution two azidotetrazoles, probably (XXXVI) and (XXXVIII), can be detected in addition to the diazide.



(XXXVI) (XXXVIII) (XXXVII)

The introduction of substituents into the naphthyridine ring of azidotetrazolonaphthyridine leads to the formation of a series of isomeric substituted azidotetrazolonaphthyridines:



(XL) (XLI)

(a) R_1=Me, R_2=H
(b) R_1=H, R_2=Me
(c) R_1=Ph, R_2=H
(d) R_1=H, R_2=Ph

On the basis of a study of chemical properties and infrared spectra, Carboni and coworkers showed that such substances exist in the crystalline state in the form of only one tautomer whose structure was not established. On dissolution, the tautomeric equilibrium (XL) ⇌ (XLI, a-d) arises and the isomer content in such equilibrium is determined by the position of the substituent in the naphthyridine ring relative to the condensed tetrazole ring. When R_1 = Me or Ph, the tetrazole ring is stabilised as a result of conjugation and the isomers (XL, a and c) predominate in the system. When R_2 = Me or Ph, the tetrazole ring condensed with the unsubstituted ring is more stable and the isomers (XLI, b and d) predominate. In the crystalline

state these compounds probably have the structures (XL, a and c) and (XLI, b and d) respectively. Evidence is presented to show that the molecular ions derived from some of these compounds have the ditetrazole structure. Thus pyrolysis of 6-azidotetrazolo[1,5-*b*]pyridazines and 6-azidopyridotetrazolo[1,5-*b*]pyridazines results in the liberation of six nitrogen atoms, which indicates the existence of an intermediate ditetrazole structure[155].

V. INFLUENCE OF SOLVENTS AND TEMPERATURE

The state of the azidoazomethine–tetrazole equilibrium in solutions has been studied in most systems (I, II, VII–XIV, XIX–XXI, XXXVI, XXXVII) using various polar and non-polar solvents: DMSO, d_6-DMSO[33-35,48,61,67,72,86,123,-135,136], pyridine[29,33-35,51,87,91,120], acetone, deuterioacetone[33-35,61], dioxan[29,51,87], methanol, deuteriomethanol[33,-34,56], dimethylformamide[33,34,67,91,120,131], tetrahydrofuran[67], chloroform, deuteriochloroform[10,16,17,20,29,34,48,51,65,67,68,-70,87], carbon tetrachloride[10,16,17,20,29,51,53,87], benzene[29,51,-87,91], n-heptane[91], H_2O[70], D_2O[135], NaOD solution[135], acetic acid[114,135,136], TFA[33-35,48,61,65,67,69,101,117,120,135,136], $HF.SbF_5$,[48] and SO_2.[48]

In comparing the action of solvents on various condensed tetrazoles account must be taken in the first place of the stability of the system itself. However, apart from the nature of the annelated nitrogen-containing ring and the electronic structure of its substituents, in solution the stability of the condensed tetrazole ring and of the isomeric azido-derivative or the state of equilibrium between them is in addition greatly influenced by the polarity of the solvent. The dissolution of condensed tetrazoles is frequently but by no means always accompanied by ring opening. On the other hand, a polar solvent sometimes increases the stability of the condensed tetrazole or even promotes the cyclisation of the azide. The constants K_T for the same systems in different solvents are quoted in a review[42]. These data show that a decrease in solvent polarity destabilises the cyclic form and promotes its partial or complete isomerisation to the azide form. When the solvent interacts with the condensed system, for example protonates the second nitrogen atom in tetrazolopolyazines, the azide form is produced.

It has been shown[14,17] that, on dissolution of tetrazolo[5,1-*b*]benzothiazole (II) in concentrated sulphuric acid, TFA, or dimethyl sulphate, the isomeric azido-form is not produced. It is interesting that 2-azido-4-chlorobenzothiazole is converted in the same solvents into the isomeric 8-chlorotetrazolo[5,1-*b*]benzothiazole. In acids this process is accompanied by the protonation of the condensed tetrazole ring and the formation of a tetrazolium salt. With decrease of solvent polarity, compound (II) and its derivatives with electron-donating substituents are partly (in pyridine, acetonitrile, dioxan, and chloroform) or fully (in carbon tetrachloride) converted into the azido-form. The state of tautomeric equilibrium in system (II) depends on the stability of the ring, which is determined by the electronic influence of the substituent and the polarity of the solvent. Thus compound (II) and its derivatives with methyl and methoxy-groups are in equilibrium with the azido-form in acetonitrile, dioxan, pyridine, and chloroform, while in carbon tetrachloride the equilibrium is fully displaced towards the azido-tautomer. The introduction of halogen atoms (F, Cl or Br) into the benzothiazole ring leads to the destabilisation of the tetrazole ring and the consequent full isomerisation to the azide even in acetonitrile[17]. Similar features are observed in the series of thiazolo[2,3-*e*]tetrazoles.

Tetrazolo[5,1-*a*]pyridine (IX) is converted in solutions into the isomeric 2-azidopyridine. However, the introduction in the 6-position of the nitro-group, which destabilises the cyclic system, affects the behaviour of the latter on dissolution. In chloroform, deuteriochloroform, trifluoroacetic acid, and acetone an equilibrium is established between the isomeric azido- and tetrazole forms[28,-61,65,88].

The tetrazoloazines (X)–(XIII), which are less stable than compound (IX), exist in solution in polar and non-polar solvents in equilibrium with azides and with decrease of solvent polarity the equilibrium is displaced towards the azido-form. Compound (X), which is the most stable in this series, exists in polar solvents almost completely in the cyclic form[48].

The equilibrium tetrazolo[1,5-*a*]pyrimidine ⇌ 2-azidopyrimidine (XII) is displaced in d_6-DMSO towards the tetrazole tautomer (K_T = 0.07) and with decrease of solvent polarity the content of the azido-form increases with a corresponding increase of the tautomeric equilibrium constant K_T, which is 0.37 in d_6-acetone. In chloroform, which is still less polar, only the azido-form (XII) exists[48].

Owing to the influence of the methyl groups, the stability of the condensed tetrazole ring in the 5,7-dimethyl derivative (XII) is somewhat greater. Therefore only the tetrazole form exists in d_6-DMSO[33,34,48]. With decrease of solvent polarity, there is a similar shift of the equilibrium towards the azide and an increase of K_T, which is 0.12 in d_6-methanol, 0.14 in pyridine, and 0.36 in deuteriochloroform[33,34]. The last value of K_T corresponds to the ratio tetrazole:azide = 1 : 3.[48] When a 6.8% chloroform solution of compound (XII) is diluted to 5.4% with the polar d_6-DMSO, K_T diminishes from 0.36 to 0.1 owing to the increase of the content of the tetrazole form in the system[33,34]. A similar influence of the solvent has been observed also for other substituted tetrazolo[1,5-*a*]pyrimidines[48].

It has also been shown[35,48] that in the tetrazolo[1,5-*c*]-pyrimidine ⇌ 4-azidopyrimidine (XIII) system with electron donating substituents in the pyrimidine ring the tetrazole ring is destabilised to a greater extent in the less polar d_6-acetone, pyridine and deuteriochloroform than in d_6-DMSO. For example, the ratio of the azide form (XIII) and the tetrazole form of the 7-methyl-5-methylthio-derivative is 1 : 16 in deuteriodimethyl sulphoxide and 5 : 1 in deuteriochloroform[48].

Postovskii and coworkers showed that in solutions in alcohol, dimethylformamide (DMF), and benzene 6-phenyltetrazolo[5,1-*c*]tetrazine (XIV) is in equilibrium with the azido-form (4 : 1, 1 : 1 and 2 : 3 respectively).[91] It has also been shown[47,67,90] that, on dissolution in chloroform, tetrahydrofuran, and trifluoroacetic acid, 5,6-diphenyltetrazolo[1,5-*c*]-1,2,4-triazine is in equilibrium with the azido-tautomer.

Temple's studies have shown that, on dissolving 2-azidopurine in d_6-DMSO, a system is produced in which the azido-tautomer is in equilibrium with two tetrazolopurines, (XXXVI) and (XXXVIII), in proportions of 3 : 6 : 1 respectively[94]. Similarly the dissolution of 6-amino-2-azidopurine in DMSO results in a system with the azido-form and the tautomers (XXXVI) and (XXXVIII) in proportions of 1 : 9.5 : 2.

In TFA the majority of tetrazoloazines exist in the azido-form or the latter predominates in the tautomer mixture, despite the fact that TFA can be classified as a polar solvent. This is probably a result of the protonation of the nitrogen atom of the heterocyclic base condensed

with the tetrazole ring or sometimes possibly of the substituent capable of being protonated. The positive charge is delocalised over the entire heterocycle and the electron-donating capacity of the latter, which favours the existence of the tetrazole form, diminishes.

Postovskii and coworkers[27] established that the hydrochloride and picrate of 7-piperidinotetrazolo[1,5-*c*]pyrimidine exist virtually as the azide in the crystalline state, while the base is in the tetrazole form. This example rules out the influence of solvation in this instance on the state of the azideazomethine–tetrazole equilibrium and apparently indicates an effect of protonation.

The studies of Postovskii and coworkers[29,51], Temple and coworkers[33-35,135], Sasaki et al.,[61] and Stanovnik and coworkers[72,123] showed that the transformation of the tetrazole form into the azido-form is an endothermic process and its heat is in the range 1–7 kcal mole^{-1}, a slight increase of temperature displacing the equilibrium towards the azido-form. This is indicated by the increase of the equilibrium constant, the increase of the intensity of the azide band observed in the infrared spectrum, and the decrease of that of the tetrazole bands. Similar features are shown also by the NMR spectra. The study of the pyrolysis of condensed tetrazoles in the gas phase by mass spectroscopy revealed that the first stage in the pyrolytic process is the tautomeric transformation of the tetrazole into the azide[48]. The opening of the tetrazole ring to form the azide with increase of temperature and ring closure to convert the azide into the tetrazole on reducing the temperature to the previous value can occur in both the crystalline state and in solution. The most stable tetrazolo[1,5-*a*]pyridine (IX) and tetrazolo[1,5-*b*]-pyridazine (X) do not isomerise to the corresponding azides on raising the temperature to 140°C.[48]

Postovskii and coworkers[29,51] showed for the first time that in the melt tetrazolo[1,5-*a*]benzothiazole (II) exists in equilibrium with the azido-tautomer. Wentrup[48] noted an interesting transformation of the azide at [above] its melting point into the [solid] tetrazole, which in turn is reconverted into the azide on fusion. On raising the temperature, the labile tautomeric azides, isolated under special conditions[48,133], undergo ring closure to the more stable tetrazole form (in solution or in the crystalline state).

Very low temperatures (obtaining in liquid SO_2) proved to be suitable for the preservation of the labile azido- and tetrazole tautomers[48].

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The tetrazole ring condensed with a nitrogen-containing heterocycle is in many instances readily cleaved at the $N_{(1)} - N_{(2)}$ bond with formation of the isomeric azidoazomethine derivative. Such transformations in the series of condensed tetrazoles do not require the expenditure of much energy. Therefore isomerisation frequently occurs on dissolution, heating, and sometimes after prolonged storage of condensed tetrazoles. A tautomeric equilibrium between the cyclic tetrazole and the open-chain azido-forms is frequently established as a result of such transformations and can occur in the crystalline state, in the melt, and in solution. The stability of the condensed tetrazole and the isomeric azido-form or the state of equilibrium between them is determined by the nature of the nitrogen-containing heterocycle with which the tetrazole ring is condensed and by the electronic nature of the substituent in the former, solvent polarity, pH of the medium, and temperature.

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