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Condensed Tetrazoles

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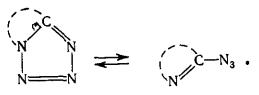
The present review surveys the literature on the methods of synthesis and chemical properties of condensed tetrazoles. The bibliography includes 125 references.

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I. INTRODUCTION

During the last 15 years, numerous studies dealing with the structure and properties of condensed tetrazoles have been published, the reason being that the tetrazole ring condensed via the $N_{(1)}-C_{(5)}$ bond with other rings exhibits a number of characteristic features in relation to non-condensed 1,5-disubstituted tetrazoles. Conversions into isomeric 2-azido-derivatives of nitrogen-containing heterocycles, which frequently occur on heating solutions of the test substance and sometimes in the crystalline state after prolonged storage, are characteristic of such condensed systems:



An equilibrium is then frequently established between the isomeric tetrazole and azido-forms, the position of which depends on the electronic nature of the condensed ring and its substituents, the polarity of the solvent, the pH of the medium, the reaction temperature, and the nature of the reagent employed[1].

Certain methods for the synthesis and the properties of individual examples of this interesting type of compound have been described in reviews dealing with the azide–tetrazole tautomerism[1-6], but a review in which methods for the synthesis of condensed tetrazoles and the relations between their properties and structures are surveyed and described systematically is lacking. The literature data on this problem are discussed in the present article (including publications in 1973).

II. METHODS FOR THE SYNTHESIS OF CONDENSED TETRAZOLES

The majority of the reactions leading to condensed tetrazoles proceed via the formation of isomeric α-azido-derivative of nitrogen-containing heterocycles as intermediates. In this case the group

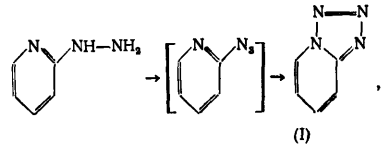


may be compared with the azidoazomethine group $R_2-N=C-N_3$ in linear systems, which isomerises irreversibly
|
R_1

to the thermodynamically more stable tetrazole ring. Calculations carried out by Roberts[7] have shown that an appreciable expenditure of energy is not required for the formation of the tetrazole ring on formation of a bond between the azido-group and a nitrogen atom in an open chain or a ring.

If the azidoazomethine group is part of a heterocycle, the formation of a bond between the azido-group and the nitrogen atom of the heterocycle and the consequent formation of a condensed system do not always occur. Depending on the nature of the nitrogen-containing ring and the electronic nature of the substituents, the reaction product may be isolated in the form of a condensed tetrazole isomeric with the azido-derivative or in the form of an equilibrium mixture of both tautomeric forms.

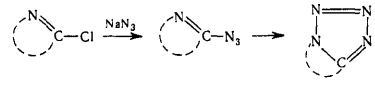
One of the most widely used methods for the synthesis of condensed tetrazoles involves the interaction of α-hydrazino-derivatives of nitrogen-containing heterocycles with nitrous acid. Tetrazolo[5,1-*a*]pyridine (I) was obtained for the first time by this procedure in 1915[8]:



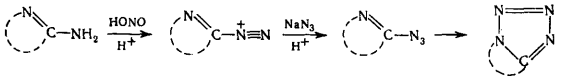
(I)

and subsequently compounds were synthesised in which the tetrazole ring is condensed with isoquinoline[9], quinoxaline[10-12], *s*-triazine[13], pyrimidine[14-18], phthalazine[19-22], naphthothiazole[23], pyridazine[24-26], pyrazine[26], pyridine[27], naphthyridine[28-35], uracil[36], quinoline[37,38], quinazoline[10,39,40], purine[41,42], thiazole[43-45], and benzoselenazole[46,47].

Condensed tetrazoles are frequently obtained by the interaction of α-chloro-derivatives of nitrogen-containing heterocycles with nitrous acid or sodium azide in a solvent (alcohol, acetonitrile, dimethylformamide). α-Chloroderivatives of benzothiazole[48], pyridine[49-53], quinoline[54], pyridazine[25,26,55-57], pyrimidine[14,15,58,59], quinazoline[14,22,40,60-62], phthalazine[19-22], quinoxaline[10,19], pyrazine[63], triazine[26], and naphthyridine[30,32] have been introduced into this reaction:



A convenient modification of this method involves the diazotisation of **α**-amino-derivatives of nitrogen-containing heterocycles followed by treatment of the resulting diazonium salts with sodium azide in an acid medium[48,64-66]:

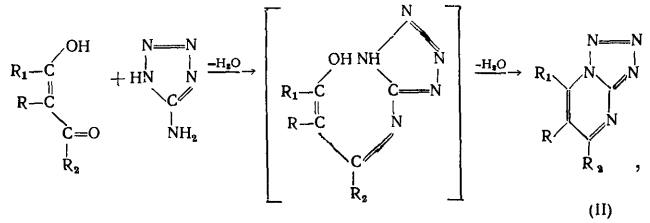


Although the yield of tetrazoles is lower in this case than in the synthesis by the procedures described above, the amino-derivatives are sometimes more readily available than the chloro- or hydrazino-derivatives. Furthermore, certain condensed tetrazoles cannot be formed at all by the first two methods. Thus, instead of the expected thiazolo[2,3-*e*]tetrazole, the interaction of 2-hydrazinothiazole with nitrous acid led to the isolation of 2,2′-dithiazolyltriazene[14]. On the other hand, the required product can be readily obtained from 2-aminothiazole[67]. Consequently this method was later used by Carboni and coworkers to synthesise tetrazolonaphthyridines[31,35].

Condensed tetrazoles can also be obtained by carrying out the Schmidt reaction with cyclic ketones. 1,5-Pentamethylenetetrazole[68], adamantane derivatives[69], methylcyclohexanone and camphor derivatives[70-72], and others[69] have been obtained by this method. Ruzicka and coworkers applied this reaction to higher cyclic ketones—cyclopentanone, cyclooctanone, cyclopentadecanone, and civetone[73,74]. The reaction of nitrous acid with 2-methoxy-Δ^1-pyrroline, as a result of which a compound which is probably trimethylenetetrazole was isolated, has been reported[75].

By treating 3,3-dihalogenoazocycloalkan-2-ones with phosphorus pentachloride and subsequent treatment of the resulting intermediate iminochlorides with nitrous acid, 8,8-dichloro- and 8,8-dibromo-tetrahydrotetrazolo[1,5-*a*]pyrimidines, 9,9-dichloro- and 9,9-dibromo-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepines, and 10,10-dichloro-5,6,7,8,9,10-hexahydrotetrazolo[1,5-*a*]azocine have been obtained[76].

Several examples of the synthesis of condensed tetrazoles using non-condensed tetrazoles as the starting materials have been described. Derivatives of tetrazolo[1,5-*a*]pyrimidine (II) have been obtained by the reaction of 5-aminotetrazole with β-diketones or β-keto-acids[77]:



(II)

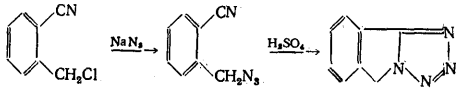
where

R=H, R_1=CH_3, R_2=OC_2H_5;
R=H, R_1=R_2=CH_3; R=H, R_1=C_6H_5, R_2=CH_3,
R=R_1=R_2=CH_3.

The mechanism of this reaction has been studied by Temple and Montgomery[16], who showed that the intermediate may be isolated as the sodium salt. Other tetrazolopyrimidines have been obtained by the same procedure[17,78,79].

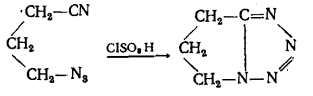
A series of chemical transformations led to the conversion 1-(*o*-carboxyphenyl)-5-phenyltetrazole into 1-(*o*-aminophenyl)-5-phenyltetrazole, which yields tetrazolophenanthridine on treatment with nitrous acid[54]. Certain tetrazolopyridines and isoquinolines have been synthesised by the dehydrogenation of 1-(α-pyridyl)-3-aryltriazine with tribromophenyl bromide in acetic acid at room temperature[36].

When azidonitriles are treated with concentrated acids, condensed tetrazoles are also formed[80-82]. Thus 5*H*-tetrazolo[1,5-*a*]isoindole (III)[82] has been obtained by the reaction of *o*-chloromethylbenzonitrile with sodium azide in aqueous alcoholic medium followed by the treatment of the resulting *o*-azidomethylbenzonitrile with concentrated sulphuric acid while cooling the mixture:



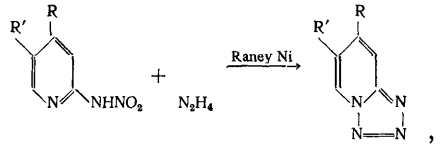
(III)

When chlorosulphonic acid is allowed to react with γ-azidobutyronitrile, trimethylenetetrazole is formed[81] (IV):



(IV)

A method has been proposed for the preparation of substituted hydrogenated derivatives of (I) from nitraminopyridines and hydrazine in the presence of Raney nickel[83]:



R=R′=H; R=CH_3, R′=H; R=H, R′=CH_3 .

III. THE PROPERTIES OF CONDENSED TETRAZOLES

The reactions in which condensed tetrazoles participate may involve the condensed tetrazole ring or the isomeric azidoazomethine group, the heterocycle with which the tetrazole ring is condensed, or a substituent in the heterocycle.

The chemical properties of condensed tetrazoles depend on the stability of the tetrazole ring, the type of reactant, and the reaction conditions. The first stage of these reactions frequently involves the opening of the tetrazole ring and the formation of the isomeric azidoazomethine derivative under the influence of heat, the solvent, or another reactant. The condensed tetrazole then reacts like an aromatic or heterocyclic azide. The reaction may be accompanied by the evolution of nitrogen and the subsequent recombination of the nitrene radicals formed (photolysis and thermolysis). Interaction with nucleophilic reagents leads to the substitution of the azido-group (reactions with sodium cyanide and organometallic compounds). Reactions which proceed via the cycloaddition of the azido-group formed have also been described.

If the tetrazole ring shows no tendency towards isomerisation or is stabilised under the reaction conditions, it is preserved.

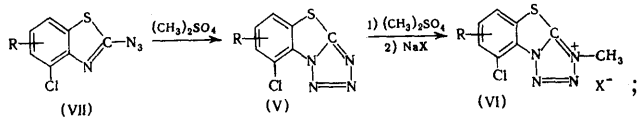
1. The Effect of Inorganic Acids and Alkylating Agents

The effect of inorganic acids on condensed tetrazoles depends on the nature of the nitrogen-containing heterocycle with which the tetrazole ring is condensed. Strong

inorganic acids and trifluoroacetic acid at room temperature sometimes increase the stability of the tetrazole ring and displace the azide–tetrazole equilibrium towards the cyclic form. At the same time the electron-accepting tetrazole ring is protonated.

Thus Pochinok and coworkers [84] showed that tetrazolo-[5,1-*b*]-benzothiazole (V), thiazolo[3,3-*e*]tetrazole, and their derivatives with electron-donating substituents dissolve in concentrated sulphuric acid without decomposition, the dissolution being accompanied by protonation. When the solution is diluted with water, the initial tetrazoles are recovered almost quantitatively. Furthermore, when certain isomeric 2-azido-derivatives, for example 2-azido-4-chloro-benzothiazole, are dissolved in inorganic acids, they isomerise to condensed tetrazoles with subsequent protonation of the resulting ring [84]. The increase of the stability of the tetrazole ring of tetrazolo[5,1-*a*]pyridine (III) in an acid medium has also been reported by Boyer et al. [85] This compound does not decompose even on heating in concentrated acid up to 120°C.

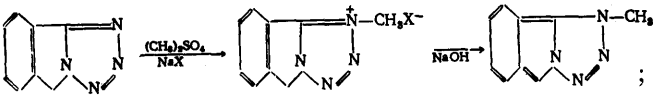
When tetrazolo[5,1-*b*]benzothiazoles (V) react with dimethyl sulphate or triethyloxonium fluoroborate, the condensed tetrazole ring is alkylated with formation of quaternary tetrazolium salts (VI) and not the isomeric azidinium salts [84]. For example, alkylation of 2-azido-4-chlorobenzothiazole (VII) proceeds via the preliminary isomerisation to the 8-chloro-derivatives (V) under the influence of polar dimethyl sulphate:



(VII) (V) (VI) X = I, ClO_4 ;

By subsequent treatment with a saturated alcoholic solution of sodium iodide or sodium perchlorate, the *N*-methyltetrazolium methyl sulphates were converted into the corresponding methiodides or methoperchlorates.

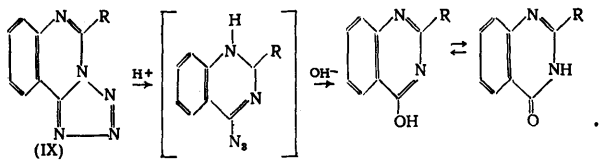
Under analogous conditions compound (III) has been converted into a quaternary salt, from which the base (VIII) was obtained on treatment with alkali [82]:



(III) (VIII) X=ClO_4, I .

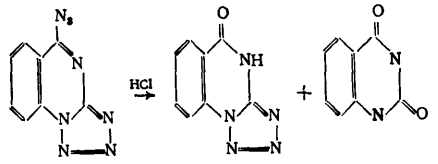
If the nitrogen-containing heterocycle can be protonated, electrons are withdrawn from the tetrazole ring, the stability of the latter decreases sharply, and the azide–tetrazole equilibrium in the system is displaced towards the isomeric azido-form [15,16,26,31,34,52,85] in which the azido-group plays the role of the electron donor.

On heating in acids, the azido-group produced is hydrolysed and replaced by the hydroxy-group. Postovskii and coworkers showed [40,56,62] that heating of 5-substituted tetrazolo[1,5-*c*]quinazolines (IX) in hydrochloric acid leads to the formation of 2-substituted 4-quinazolinones. This process can be assumed to involve a stage in which the condensed tetrazole ring is opened with subsequent hydrolytic abstraction of the azido-group via a nucleophilic mechanism:



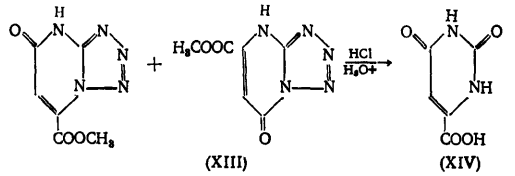
(IX)

When the 5-azido-derivative (X), in which the tetrazole ring is somewhat more stable, is heated in hydrochloric acid, a mixture of tetrazolo[1,5-*a*]quinazolin-5-one (XI) and quinazoline-2,4-dione (XII) is formed:



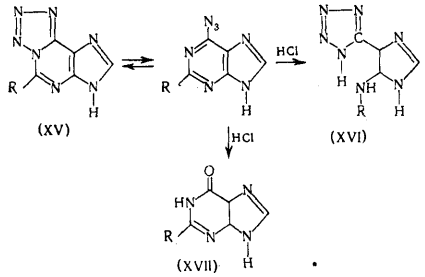
(X) (XI) (XII)

It has been found [87] that, when a mixture of the isomers of methoxycarbonyloxodihydrotetrazolo[1,5-*a*]pyrimidine (XIII) is refluxed with hydrochloric acid, 1,5-dipolar opening of the tetrazole ring also takes place with subsequent nucleophilic substitution of the azido-group and the formation of 6-carboxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (XIV):



(XIII) (XIV)

Temple et al. [42] found that the unsubstituted 6-azidopurine system (XV, R = H) is converted preferentially into 5-substituted tetrazole (XVI) on treatment with concentrated hydrochloric acid:



(XV) (XVI) (XVII)

When an amino- or chloro-group is present in the 2-position [compounds (XV, R = NH_2 or Cl)], the system is resistant to the action of hydrochloric acid at room temperature, but hydrolyses on heating to guanine or xanthine (XVII).

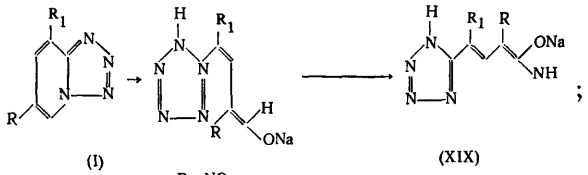
2. The Effect of Alkalis and Alkoxides

Condensed tetrazoles, which as a rule readily undergo ring opening under the influence of acids, are more stable in alkalis and do not interact with them [31,34]; the nitrogen-containing heterocycle is cleaved [16,42,88,89].

Carboni and coworkers [31,34] showed that in the hydroxy- and amino-derivatives of substituted tetrazolo[1,5*a*][1,8]-naphthyridines (XVIII) the tetrazole formed is stabilised by alkalis. When the acetamido-derivative (XVIII) is hydrolysed with sodium hydroxide, the amino-derivative is formed in satisfactory yield, the tetrazole ring being unaffected [29-33].

Derivatives of tetrazolo[5,1-*a*]pyridine (I) with electron-donating substituents in the 6- and 8-positions readily

dissolve in alkalis, alkoxides, or organic bases[88]. The pyridine ring is then opened with formation of the 5-substituted tetrazole (XIX) and its subsequent *cis–trans* isomerisation:

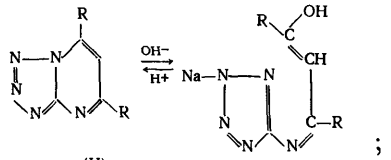


(I) (XIX)

$R=NO_2$.

The cleavage of the nitrogen-containing heterocycle in condensed tetrazoles under the influence of alkali has been described for tetrazolo[1,5-*a*]pyrimidines[16] (II), tetrazolo[1,5-*a*]quinazolines (X)[89], and the 6-azidopurine (XV) system[42].

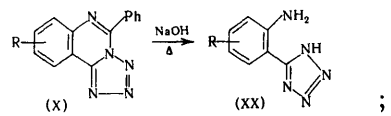
When compound (II) or its dimethyl derivative is dissolved in 0.1 *N* aqueous solution of alkali, the product is an equilibrium system which is reconverted into (II) on cautious acidification[16]:



(II)

$R=H, CH_3$.

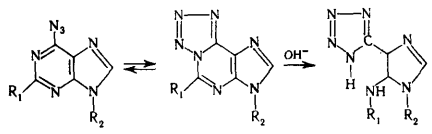
Golomolzin and Postovskii[89] described the alkaline cleavage of 5-phenyl-7(9)-R-tetrazolo[1,5-*c*]quinazolines (X), which results in the formation of 5-[2-amino-3′(5′)-R-phenyl]tetrazoles (XX):



(X) (XX)

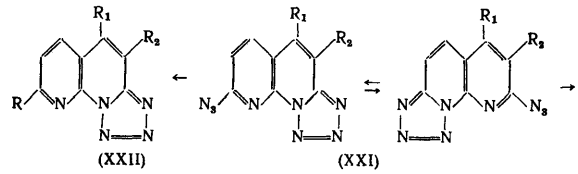
R = H, OCH_3, CH_3, Cl, Br .

The pyrimidine ring is opened similarly when the system (XV) substituted in the 2-position is treated with aqueous solutions of alkali[42]:

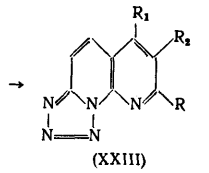


(XV) (XVII)

The tetrazole ring is also retained in the azido-derivatives of condensed tetrazoles 6-azidotetrazolo[1,5-*b*]pyridazine[25], 6-azidotetrazolo[1,5-*a*]phthalazine[99], 6-azidopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine[91], 6-azidopyrido[3,2-*d*]tetrazolo[1,5-*a*][naphthyridine[29-33], 6-azidopyrazino[2,3-*d*]tetrazolo[4,5-*b*]pyridazine[92], and 5-azidotetrazolo[1,5-*a*]quinazoline[62] on heating with aqueous or alcoholic solutions of alkalis, alkoxides, ammonia, and organic bases. The azido-group is activated under the influence of the electronegative tetrazole ring and readily becomes involved in a nucleophilic substitution reaction, which results in the formation of the corresponding hydroxy-, alkoxy-, amino-, and hydrazino-derivatives of the condensed tetrazoles. Mixtures of the isomeric hydroxy- and alkoxy-derivatives (XXII) and (XXIII) are formed from substituted 8-azidotetrazolo[1,5-*a*][1,8]-naphthyridines (XXI), which exist in solution in the form of two isomeric species in equilibrium[29-33]:



(XXII) (XXI)



(XXIII)

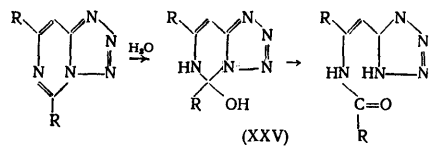
R=OH, OC_2H_5, NH_2

$R_1=R_2=H$; $R_1=CH_3$, $R_2=H$; $R_1=C_6H_5$, $R_2=H$; $R_1=H$, $R_2=CH_3$

3. Covalent Hydration

The condensation of the electron-accepting tetrazole ring with pyrimidine, purine, or quinazoline leads to the withdrawal of electrons from the carbon atom in the 5-position as a result of which there is a possibility of the formation of covalent hydrates involving the $N_{(6)}$–$C_{(5)}$ bond. The covalent hydration process competes with the cleavage of the nitrogen-containing ring, leading to the formation of 5-substituted tetrazoles, the former process predominating. The stability of covalent hydrates is greatly influenced by the pH of the medium, the electronic nature of the substituents in the nitrogen-containing heterocycle, and temperature.

Thus it has been shown[58] that tetrazolo[1,5-*c*]pyrimidine (XXIVa) readily reacts with water to form the covalent hydrate (XXVa), which cannot be dehydrated even on heating *in vacuo* to 120°C. The 5,7-dimethyl derivative (XXIVb) forms a covalent hydrate even at room temperature, but this involves the opening of the pyrimidine ring and the formation of the substituted tetrazole (XXVIb)[15]:

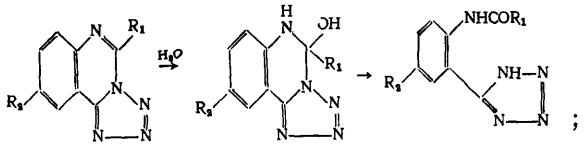


(XXIV) (XXV) (XXVI)

(a) R=H; (b) $R=CH_3$.

A similar process involving (XXIV) proceeds in an alkaline medium with formation of a salt. The 2-azidopurine system (XV) also undergoes covalent hydration[42]. It has been shown in a series of studies by Postovskii and coworkers[93-97] that the covalent hydration of tetrazolo-[1,5-*c*]quinazolines (X) takes place in a weakly acid medium, since the protonation of the $N_{(6)}$ heteroatom promotes an increase of δ^+ on the $C_{(5)}$ atom[96] and the yield of such interaction depends on the nature of the substituents. The unsubstituted tricyclic compound (Xa) is

hydrated more readily than the 5-methyl derivative (Xb), while the 5-phenyl analogue (Xc) is not hydrated at all:



(X) (XXVI)

(a) $R_1=R_2=H$; (b) $R_1=CH_3$, $R_2=H$; (c) $R_1=C_6H_5$, $R_2=H$; (d) $R_1=\gamma$-pyridyl, $R_2=H$; (e) $R_1=C_6H_5$, $R_2=COOH$; (f) $R_1=C_6H_5$, $R_2=Br$.

It may be that the steric hindrance associated with the phenyl group also plays a role here. The 5-γ-pyridyl derivative (Xd) behaves similarly[95,96]. The introduction of a carboxy- or bromo-group, which increase the positive charge on $C_{(5)}$, into the 9-position of compound (Xc) makes possible the hydration of compounds (X,e and f)[93,97]. The product of the hydration of (Xf) has the structure of 5-(2-acylamino-5-bromophenyl)tetrazole (XXVII) in the crystalline state[94].

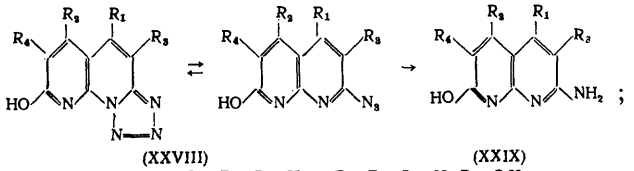
When the covalent hydrates are heated in 2 *N* hydrochloric acid, acid hydrolysis takes place with formation of 5-(2-acylaminophenyl)tetrazoles[95,96].

4. Reduction

The resistance of the condensed tetrazole ring to the action of reducing agents or catalytic hydrogenation depends in many respects on the reaction conditions, particularly on the pH of the medium. Boyer et al.[85], who investigated the catalytic hydrogenation of tetrazolo[5,1-*a*]pyridine (I), showed that in an acid medium, where the tetrazole form (I) is stabilised, only the pyridine ring is hydrogenated. 2-Aminopyridine is formed in an alkaline medium. In a neutral medium the reaction proceeds in two ways with formation of a mixture of products. They also observed that, when the 6-methyl-4-nitro-derivative of (I) is treated with stannous chloride in hydrochloric acid, only the nitro-group is reduced.

In those cases where a second nitrogen heteroatom in the nitrogen-containing heterocycle is protonated, the stability of the condensed tetrazole ring is reduced and acids and bases are found to have the opposite effects on the mode of catalytic hydrogenation.

Carboni and coworkers[31,34] showed that, in the case of the isomeric hydroxy-derivatives of 5(6)-phenyltetrazolo-[1,5-*a*][1,8]naphthyridine (XXVIII), the azido-form is stabilised (as a result of protonation) by acids and the tetrazole form is stabilised by alkalis. Accordingly, during the catalytic hydrogenation of (XXVIII, a – d) in acetic acid, amino-derivatives of naphthyridine (XXIX) are formed in acetic acid in 75–78% yield. After hydrogenation in an alkaline medium, the initial compounds (XXVIII), a – d) were recovered in an almost quantitative yield:

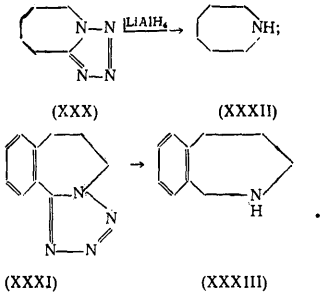


(XXVIII) (XXIX)

(a) $R_1=C_6H_5$, $R_2=R_3=R_4=H$; (b) $R_1=R_2=R_4=H$; $R_3=C_6H_5$; (c) $R_1=R_2=R_4=H$, $R_3=C_6H_5$; (d) $R_1=R_2=R_3=H$, $R_4=C_6H_5$.

Tetrazolo[1,5-*a*]pyrimidines behave similarly on hydrogenation in acetic acid[98].

The reduction of pentamethylenetetrazole (XXX) and 6,7-dihydro-5*H*-tetrazolo[4,5-*a*]benzo[*c*]azepine (XXXI) with lithium aluminium hydride in isopropyl ether, leading to the formation of the perhydroazepine (XXXII) and 1,2,3-tetrahydrobenzo[*c*]azepine (XXXIII) has been described[72]:

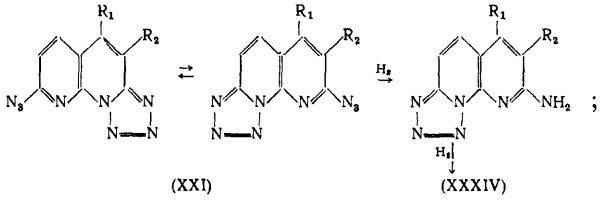


(XXX) (XXXII)

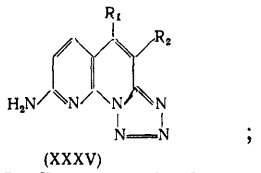
(XXXI) (XXXIII)

The study of the reduction and catalytic hydrogenation reactions of azido-derivatives of condensed tetrazoles has shown that the azido-group is converted into the amino-group much more readily than the condensed tetrazole ring. Thus, hydrogenation, treatment with hydrogen sulphide, or heating in ethylcellosolve of 6-azidotetrazolo-[1,5-*b*]pyridazine[22,25] and heating of 6-azidotetrazolo-[1,5-*a*]phthalazine in tetralin[22] leads to the formation of the corresponding aminotetrazoles.

Catalytic hydrogenation of the unsubstituted 8-azidotetrazolo[1,5-*a*][1,8]naphthyridine (XXIa) results in the formation of the 8-amino-derivative and a very small amount of the 8-hydroxy-analogue[29]. Under these conditions, the 5-methyl and 5-phenyl derivatives (XXI, b and c) are preferentially converted into the corresponding amines (XXXIV, b and c) and their 4-methyl and 4-phenyl analogues (XXI, d and e) are converted into the amines (XXXV, d and e)[31-34]:



(XXI) (XXXIV)

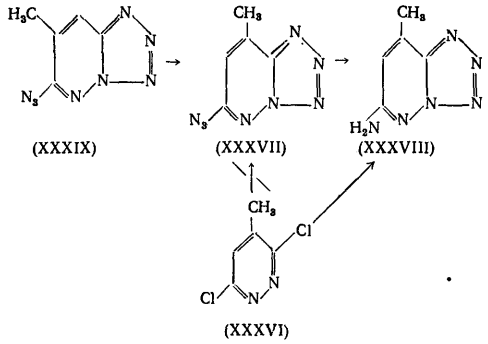


(XXXV)

(a) $R_1=R_2=H$; (b) $R_1=CH_3$, $R_2=H$; (c) $R_1=C_6H_5$, $R_2=H$; (d) $R_1=H$, $R_2=CH_3$; (e) $R_1=H$, $R_2=C_6H_5$.

It has been shown that, when 3,6-dichloro-4-methylpyridazine (XXXVI) is treated with sodium azide in ethylene glycol, the 8-amino-derivative (XXXVIII) is formed as a result of the reduction of the azido-group instead of the expected 6-azido-8-methyltetrazolo[1,5-*b*]pyridazine

(XXXVII).[91] When 6-azido-7-methyltetrazolo[1,5-*b*]-pyridazine (XXXIX) is heated in ethylcellosolve, it isomerises with subsequent reduction to the amino-derivative (XXXVIII):



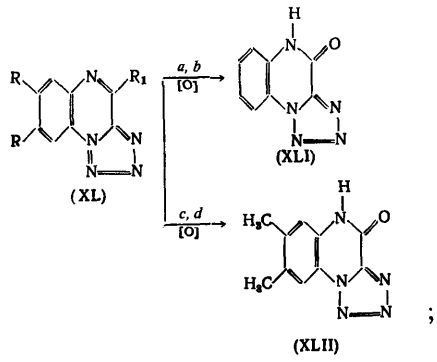
(XXXIX) (XXXVII) (XXXVIII)

(XXXVI)

5. Oxidation

Like 1,5-disubstituted tetrazoles, the condensed tetrazole ring sometimes exhibits an appreciable resistance to oxidation. Thus the oxidation of quinolino[1,2-*e*]tetrazole with a solution of potassium permanganate leads to the formation of tetrazole and the quantitative evolution of carbon dioxide[54]. Tetrazolo[1,5-*a*][1,8]-naphthyridines behave similarly[29,39].

Postovskii and coworkers[11] studied the action of various oxidants on tetrazolo[1,5-*a*]quinoxalines (XL), which resulted in the isolation of the tetrazolo[1,5-*a*]quinoxalinones (XLI) and (XLII):



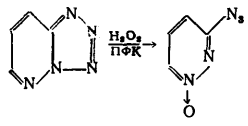
(XL) (XLI)

(XLII)

(a) R=R₁=H; (b) R=H, R₁=CH₃; (c) R=CH₃, R₁=H; (d) R=R₁=CH₃.

Oxidants decompose the tetrazole ring when the ring carbon atom carries a nitrogen-containing substituent. For example tetrahydrotetrazolo[1,5-*a*]quinazoline is oxidised by potassium permanganate to adipic acid and ammonia[99]. When 6-methyltetrazolo[1,5-*b*]benzothiazole and 9-methyl-5-phenyltetrazolo[1,5-*c*]quinazoline react with aqueous solutions of potassium permanganate, the methyl group is oxidised to the carbonyl group[67,93].

Treatment of tetrazolo[1,5-*b*]pyridazine (XLIII) with hydrogen peroxide in polyphosphoric acid leads to the simultaneous *N*-oxidation and opening of the tetrazole ring with formation of 3-azidopyridazine N-oxide (XLIV)[57]:

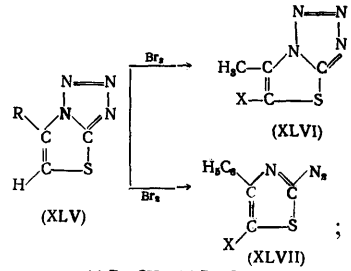


(XLIII) (XLIV)

6. Electrophilic Substitution Reactions

The structure of the products of electrophilic substitution reactions involving condensed tetrazoles depends in many respects on the stability of the tetrazole ring and on the electronic nature of the substituent introduced into the nitrogen-containing heterocycle. Powerful electron-accepting substituents or substituents with a negative inductive effect destabilise the condensed tetrazole ring and promote the formation of reaction products having the azide structure.

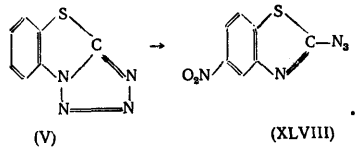
It has been shown that bromination and the introduction of thiocyanato-groups into 6-methylthiazolo[2,3-*e*]tetrazole (XLVa) take place in the 5-position of the condensed system with formation of the corresponding 5-bromo- and 5-thiocyanato-derivatives (XLVI). The reactions with the 6-phenyl-substituted derivative (XLVb) proceed similarly in the 5-position, but, owing to the lower stability of the tetrazole ring, the isomeric azido-derivatives (XLVII) are formed in this case[84,100]:



(XLV) (XLVI) (XLVII)

(a) R=CH₃; (b) R=C₆H₅; X=Br, CNS.

The sulphonation, chlorosulphonation, and nitration reactions of compound (XLVb) also involve the 5-position. The introduction of strong electron-accepting substituents promotes the opening of the tetrazole ring at the $N_{(1)}$–$N_{(2)}$ bond with formation of the isomeric 2-azido-derivatives[66,84]. Tetrazolo[5,1-*b*]benzothiazole is nitrated in the 7-position of the condensed system and the nitration product has the structure of 2-azido-5-nitrobenzothiazole (XLVIII):



(V) (XLVIII)

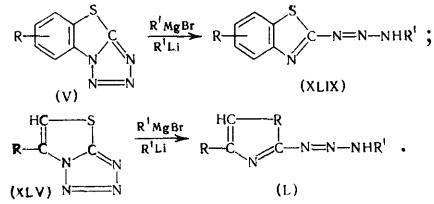
It has been observed[84] that the tetrazole ring is protonated in electrophilic substitution reactions carried out in the presence of inorganic acids and the tetrazolium salt reacts. In a concentrated acid, the reaction product retains the structure of the tetrazolium salt. When the reaction mixture is diluted with water, the salt is hydrolysed and the condensed tetrazole isomerises to the 2-azido-derivative in consequence of the introduction of an electron-accepting substituent into the thiazole or benzothiazole ring.

Sasaki et al.[86] showed that tetrazolo[5,1-*a*]pyridine (I) is nitrated and brominated in the 6-position with formation of the 6-nitro- and 6-bromo-derivatives.

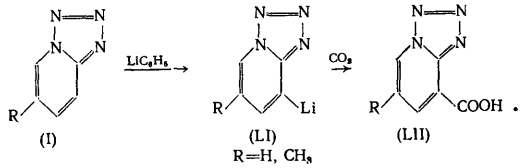
7. Reactions with Organometallic Compounds and Sodium Cyanide

It has been shown for derivatives of tetrazolo[5,1-*b*]-benzothiazole (V) and thiazolo[2,3-*e*]tetrazole (XLV) that

the course of the reactions with organomagnesium bromide and organolithium derivatives depends on the position of their azide–tetrazole equilibrium and the nature of the organometallic reagent[48,64,101,102]. In contrast to the 4-methyl derivative (V) and the 6-methyl derivative (XLV), which do not react with such organometallic reagents, compound (V) and its 6-methyl, 6-chloro-, 6-methoxy-, and 4-chloro-derivatives as well as the 6-phenyl derivative of compound (XLV) give rise respectively to benzothiazol-2-yl-triazenes (XLIX) and thiazol-2-yltriazenes (L)[48,64,101,102]. It is interesting that compound (V) and its 6-methyl- and 6-chloro-derivatives are converted into triazenes only in reactions with phenylmagnesium bromide and phenyl-lithium:

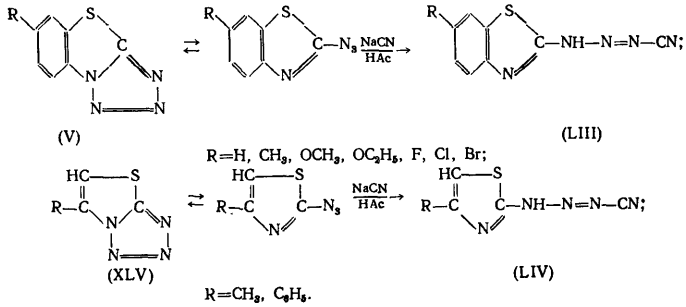


When tetrazolo[5,1-*a*]pyridine (I) and its methyl derivative are treated with phenyl-lithium, the pyridine ring is metallated, while the tetrazole ring remains unchanged. The lithio-derivatives (LI) obtained in this way were then converted into carboxylic acids (LII):



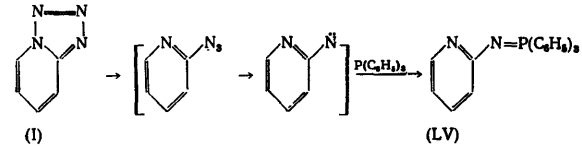
The reaction of the tetrazole ring with organometallic compounds probably requires a definite degree of electron-accepting capacity of the substituents in the condensed tetrazole and of the organic group linked to the metal.

Like aromatic azides, the tetrazoles (V) and (XLV) readily react with sodium cyanide, forming benzothiazol-2-ylcyanotriazenes (LIII) and thiazol-2-ylcyanotriazenes (LIV) respectively[64,102]:

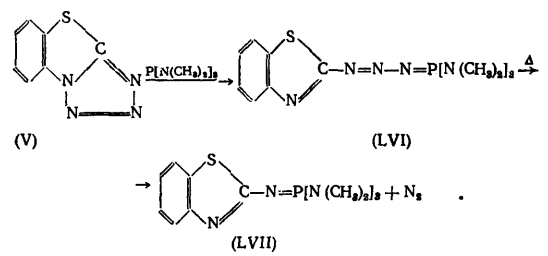


8. Reactions with Organophosphorus Compounds

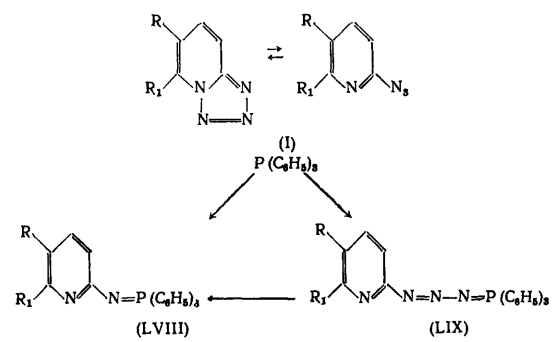
Aromatic azides are known to form aryliminophosphoranes on reaction with triphenylphosphine[103]. The interaction of condensed tetrazoles with triphenylphosphine was described for the first time by Sasaki and Kanematsu[107] with tetrazole (I) as an example. It is believed that under the reaction conditions the tetrazole isomerises to the azido-derivative, which is followed by a thermally induced loss of nitrogen and the interaction of 2-pyridylnitrene with triphenylphosphine, the product being 2-triphenylphosphazopyridine (LV):



Zhmurova et al.[105] studied this reaction with certain tetrazolo[5,1-*b*]benzothiazoles (V) and thiazolo[2,3-*e*]-tetrazoles (XLV). Since the reaction proceeds under mild conditions (in benzene at 50–60°C), the formation of benzothiazol-2-yl- and thiazol-2-yl- nitrenes as intermediates is doubtful. The authors suggested that the reaction of these tetrazoles with triphenylphosphine is due to the presence in the solution of azido-forms and that it involves the usual oxidative imination of tertiary phosphines by organic azides. This hypothesis was confirmed indirectly by the isolation of the intermediate phosphazide (LXI) in the reaction of compound (V) and phosphorous hexamethyltriamide. The phosphazide subsequently decomposes with formation of the phosphazo-compound (LVII):

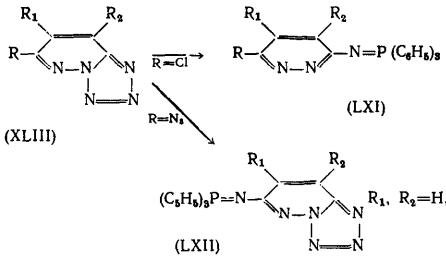


Sasaki et al.[106] investigated the interaction of compound (I) and some of its derivatives with triphenylphosphine in various solvents and at different temperatures. They showed that the reaction is of second order and that its rate and mechanism depend on the electronic nature of the ring substituents, on the type of solvent, and temperature. Thus, substituents promoting ring opening and the formation of the isomeric azido-form accelerate the formation of the iminophosphoranes (LVIII) via the intermediate triazenophosphoranes (LIX). A decrease of solvent polarity and an increase of reaction temperature act in the same direction.



In the absence of the reactive azido-form from the solution, the reaction involves the $N_{(1)}$ or $N_{(3)}$ atoms of the tetrazole ring, after which the ring is cleaves with subsequent loss of nitrogen and the formation of compound (LVIII).

Tetrazolodiazines[107], i.e. tetrazolo[1,5-*b*]pyridazine (XLIII) and tetrazolo[1,5-*a*]pyrazine (LX) and their derivatives, also form iminophosphoranes on reaction with triphenylphosphine. Electron-accepting substituents in the pyridazine and pyrazine rings facilitate this reaction, while electron-donating substituents stabilise the tetrazole ring and preclude the reaction:



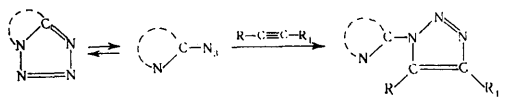
(XLIII) (LXI) (LXII)

Thus, the unsubstituted compound (XLIII) and its 5-methoxy-derivative do not interact with triphenylphosphine even on refluxing in chlorobenzene, while the 5-chloro-derivatives form the corresponding iminophosphoranes.

The 5-azido-derivative (XLIII) reacts with an excess of triphenylphosphine only via the azido-group, forming monoiminophosphoranes (LXII). Evidently, the iminophosphorane group formed behaves as an electron-donating substituent and stabilises the tetrazole ring. The reaction mechanism depends on the position of the azide–tetrazole equilibrium in solution also in the case of tetrazolopolyazines. If only the tetrazole forms (XLIII, R = Cl) and (LX) are present, the $N_{(1)}$ and $N_{(3)}$ atoms of the tetrazole ring are subjected to nucleophilic attack by triphenylphosphine. If only the azido-isomer of the 5,6-diphenyl derivative of compound (LX) is present in acetic acid under the reaction conditions, the reaction involves the formation of triazenophosphorane. When both tautomeric forms of compound (LX) are present in the reaction mixture in chloroform, the reaction proceeds in both ways.

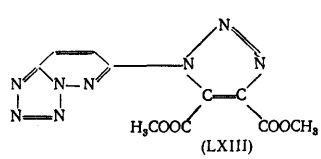
9. Cycloaddition Reactions and Others

It has been shown that tetrazolo[5,1-*a*]pyridine (I)[108] and its 5-chloro-, 6-bromo-, and 6-nitro-derivatives[86], 5,7-dimethyltetrazolo[1,5-*a*]pyrimidine[108], and 7,8-diphenyltetrazolo[1,5-*a*]pyrazine[26] undergo cycloaddition reactions with propiolate and acetylenedicarboxylate esters and diphenylacetylene, forming the corresponding substituted triazoles:



R = H, R_1 = $COOCH_3$; R = R_1 = $COOCH_3$; R = R_1 = C_6H_5.

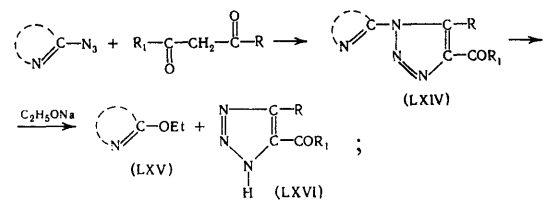
All these reactions proceed via the preliminary isomerisation to the azido-form and the yield of the triazole under the reaction conditions depends on the rate of isomerisation. It has been noted[26] that even in boiling toluene 6-azidotetrazolo[1,5-*b*]pyridazine reacts with dimethyl acetylenedicarboxylate only via the azido-group, forming the product (LXIII):



(LXIII)

while the tetrazole ring does not react. On the other hand, 7,8-diphenyltetrazolo[1,5-*a*]pyrazine takes part in this reaction at a temperature as low as 62°C in chloroform, which indicates a greater tendency of the tetrazole ring towards isomerisation in the latter compound.

Triazoles are not always the final products of such reactions. Several instances have been described where cycloaddition with formation of triazoles is an intermediate stage. Under the reaction conditions, the triazoles may be cleaved, which leads to the formation of secondary reaction products. Thus it has been reported[109] that the interaction of tetrazolo[5,1-*b*]benzothiazole and tetrazolo[1,5-*b*]1,2,4-triazine with compounds of the type $R-C(=O)-CH_2-COR$ (where R = CH_3 or C_6H_5) proceeds with formation of the corresponding cycloaddition products (LXIV), which are relatively unstable under the reaction conditions and are cleaved at the C–N bond between the heterocyclic rings with formation of 2-ethoxy-derivatives of the corresponding heterocycles (LXV) and substituted triazoles (LXVI):

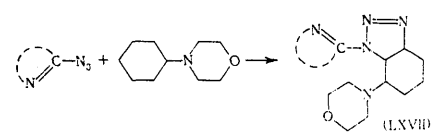


(LXIV) (LXV) (LXVI)

R = CH_3, R_1 = C_6H_5; R = R_1 = CH_3.

When the same tetrazoles react with ethylbenzoyl acetate, the stable sodium salt of the corresponding cycloaddition product may be isolated; on acidification with hydrochloric acid, the sodium salt is hydrolysed with evolution of nitrogen and carbon dioxide and formation of 2-aminobenzothiazole and ω-chloroacetophenone.

Fusco et al.[110] found that, like azides, condensed tetrazoles react with *N*-(α-cyclohexenyl)morpholine, also forming 1,2,3-triazole derivatives (LXVII):

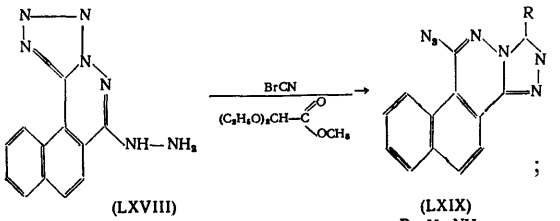


(LXVII)

The cycloaddition of 4,5-dimethyltetrazolo[1,5-*a*]pyrimidine and tetrazolo[5,1-*a*]pyridine to norbornene proceeds in a similar manner[108]. The interactions of these tetrazoles with cyclohexene, 1,2-dihydronaphthalene, indene, *trans*-stilbene, 1,1-diphenylethylene, and dimethyl maleate and fumarate have been investigated[108] and it has been found that the cycloaddition products are the corresponding triazoles, which are cleaved under the reaction conditions with subsequent formation of enamines and the evolution of nitrogen.

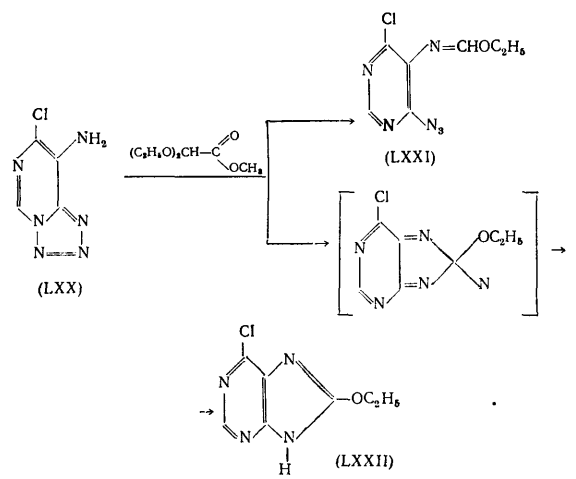
Stanovnik and Tišler[20,21] studied the interaction of 6-hydrazino-7,8-dihydrobenzo[*h*]tetrazolo[5,1-*a*]phthalazine (LXVIII) with diethoxymethyl acetate or bromocyanogen and found that this involves the destabilisation and opening of the tetrazole ring with formation of the azido-derivative. As a result, a new condensed triazole ring

(LXIX) is formed, destabilising the tetrazole ring and converting it into the azido-form:



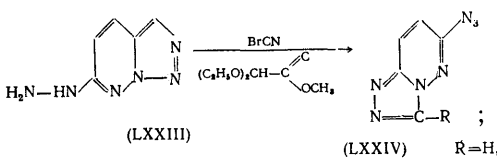
(LXVIII) (LXIX) R=H, NH_2 .

The interaction of diethoxymethyl acetate with 8-amino-7-chloro-tetrazolo[1,5-*c*]pyrimidine (LXX) at room temperature, leading to the formation of the corresponding ethoxymethylene derivative (LXXI), has been described[111]. The tetrazole ring is ruptured in this process. On heating in anisole, 6-chloro-8-ethoxypurine (LXXII) is formed:



(LXX) (LXXI) (LXXII)

The attempts to obtain a tricyclic derivative by treating 6-hydrazinotetrazolo[1,5-*b*]pyridazine (LXXIII) with diethoxymethyl acetate or bromocyanogen led to the opening of the tetrazole ring and the formation of 3-R-6-azido-*s*-triazolo[4,3-*b*]pyridazine (LXXIV)[20,21]:



(LXXIII) (LXXIV) R=H, NH_2 .

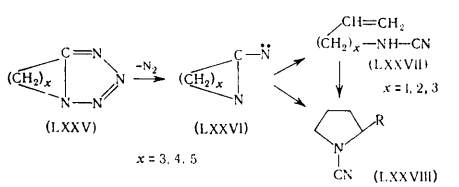
10. Thermolysis and Photolysis

Many condensed tetrazoles are known to be converted into the isomeric azido-derivatives even at room temperature or on slight heating. Therefore it was to be expected that even condensed tetrazoles which do not exhibit a tendency towards the azide–tetrazole tautomerism might be converted into azides at high temperatures and might undergo thermal decomposition of the azide type.

The behaviour of condensed tetrazoles on heating has been investigated for polymethylenetetrazoles[112], tetrazolo[5,1-*a*]pyridine[51,52,86,88,113-117], tetrazolo[5,1-*a*]-quinoline[60], tetrazolo[1,5-*a*]pyrimidine[113,118-120], tetrazolo[1,5-*c*]pyrimidine[119], tetrazolo[1,5-*a*]quinoxaline[60], tetrazolo[1,5-*a*]pyrazine[26,119], tetrazolo[1,5-*a*]pyridazine[26,53,119,121], tetrazolophenanthridine[60], tetrazolo-[1,5-*c*]quinazoline[60], and certain others.

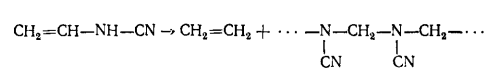
The reactions were carried out in the gas phase or in solvents, sometimes using copper acetylacetonate as the catalyst, which made it possible to reduce the thermolysis temperature (evolution of nitrogen) by approximately 100°C. In all the cases investigated the first stage of the thermolysis is the cleavage of the condensed tetrazole ring at the $N_{(1)}$–$N_{(5)}$ bond and the formation of the isomeric α-azido-derivative. The azide formed then loses nitrogen and gives rise to a nitrene radical, which is subsequently stabilised via several mechanisms, depending on the reaction conditions (solvent, temperature).

One important pathway to the stabilisation of the nitrene is its conversion into the corresponding α-amino-derivative as a result of the abstraction of hydrogen from the solvent and the formation of secondary amines as well (reaction with a neighbouring reactive group). Nitrenes can also undergo cycloaddition reactions with aromatic hydrocarbons, stilbenes, and nitriles. The cleavage of the ring and the formation of various unsaturated cyano-compounds or their polymerisation products are also possible (particularly at high temperatures in the gas phase). Ring contraction and the formation of various nitrogen-containing heterocyclic cyano-derivatives containing one carbon atom less frequently take place in the gas phase. It has been suggested that the latter process proceeds via the formation of ring cleavage products as intermediates with participation of nitrene nitrogen[115] or via the formation of bicyclic systems. Dimers are sometimes formed[60]. Thus polymethylenetetrazoles (LXXV), which do not exhibit a tendency towards isomerisation, under thermal decomposition in the gas phase at 450–675°C with formation of the nitrene (LXXVI), which then recombines with formation of alkenylcyanamides (LXXVII) (on ring opening) and 1-cyanopyrrolidine (LXXVIII) or its alkyl derivatives (on ring contraction[112]):



(LXXV) (LXXVI) (LXXVII) (LXXVIII)

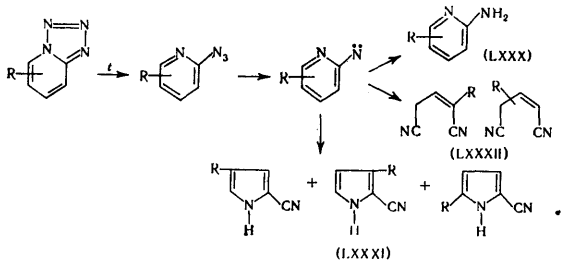
In the reaction involving trimethylenetetrazole, the propenylcyanamide formed evolves nitrogen and gives rise to poly-*N*-cyanoformamidine (LXXIX):



(LXXIX)

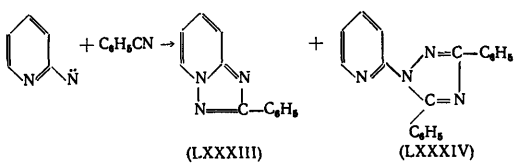
It is known that tetrazolo[5,1-*a*]pyridine (I) is not converted into the isomeric 2-azidopyridine even on heating to 120°C. However, under more severe conditions in the gas phase or in the presence of a catalyst, isomerisation does take place with formation of 2-pyridylnitrene accompanied by the evolution of nitrogen. The process also involves the formation of 2-aminopyridine (LXXX), 2-cyanopyrroles (LXXXI) on ring contraction, and the nitrile of glutaconic acid (LXXXII) on ring opening[26,113,117,118]. It has been shown[115-117] that 2-pyridylnitrene is converted into 2,7-diazatropylidene in the gas phase with ring expansion, the product being subsequently converted

into a cyanoazole following ring contraction. In the presence of a catalyst (copper acetylacetonate), there is no ring expansion with formation of diazepines:



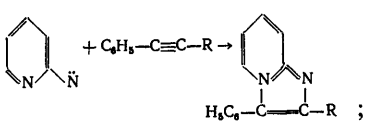
(LXXXI)

The thermolysis of tetrazolo[5,1-*a*]pyridine and its 6-bromo-, 6-nitro-, 8-nitro-, and 8-bromo-derivatives in solvents without a catalyst or in the presence of copper acetylacetonate[51,52,86,113] is accompanied by the interaction of 2-pyridylnitrene with solvents. In these cases the pyridine ring is preserved. The structure of the reaction products depends on the type of solvent. Thus, when the reaction is carried out in cyclohexane, cyclohexene[113], and toluene[86] in the presence of copper acetylacetonate, the main reaction product is 2-aminopyridine. In benzonitrile [3 + 2] cycloaddition takes place and 2-phenyl-3-triazolo[1,5-*a*]pyridine (**LXXXIII**) is formed with 2-(3,5-diphenyl-1,2,4-triazolyl)pyridine (**LXXXIV**) as an admixture[113]:



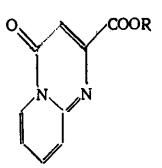
(LXXXIII) (LXXXIV)

Thermolysis in the presence of dienophiles (ethyl phenylpropiolate, diphenylacetylene) involves 3 + 2 cycloaddition of alkynes with formation of imidazopyridine derivatives (**LXXXV**):



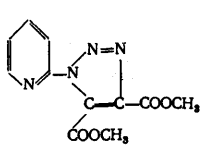
(LXXXV)

$R = C_6H_5$, $COOC_2H_5$;



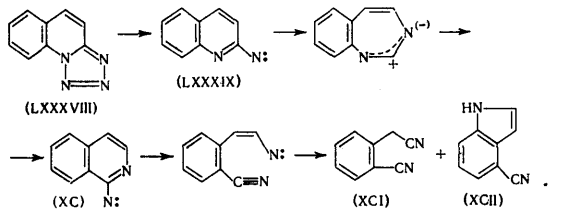
(LXXXVI)

Cycloaddition to fumaric acid[114] proceeds with formation of the analogous product (**LXXXVI**). However, in the presence of dimethyl acetylenedicarboxylate, compound (**LXXXVII**) is formed[86]:



(LXXXVII)

It has been shown[60] that the 2-quinolinylnitrene (**LXXXIX**) formed in the gas-phase thermolysis of tetrazolo[5,1-*a*]quinoline (**LXXXVIII**) is converted into 1-isoquinolinylnitrene (**XC**), possibly via preliminary ring expansion to azatropylidene followed by ring opening and the formation of compounds (**XCI**) and (**XCII**):

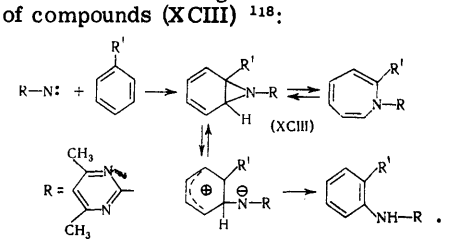


(LXXXVIII) (LXXXIX) (XC) (XCI) (XCII)

The thermolysis of tetrazolo[5,1-*a*]isoquinoline proceeds similarly[60].

The thermolysis of tetrazolo[1,5-*a*]pyrimidine and tetrazolo[1,5-*c*]pyrimidine in the gas phase also involves isomerisation to the azido-derivatives, the loss of nitrogen, and the formation of pyrimidin-2-yl- and pyrimidin-4-yl-nitrenes. Subsequently pyrimidin-2-ylnitrene and its derivatives are converted via ring contraction into 1-cyano-3-R-5-R'-pyrazoles and 2-amino-4-R-6-R'-pyrimidines[119]. The 1-cyanopyrazoles formed can split off HCN with formation of pyrazoles (at 500°C), while under more severe conditions (at 700°C) nitrogen is split off with formation of cyanopenta-2,4-dienes[120]. Under still more severe conditions, the unsubstituted 3*H*-pyrazole gives rise to cyanoallene and tetrolonitrile in proportions of 1 : 3.

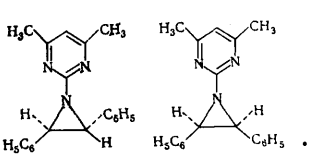
On gas-phase pyrolysis, tetrazolo[1,5-*c*]pyrimidine gives rise to cyanoimidazoles only[119]. The pyrolysis of tetrazolo[1,5-*a*]pyrimidines in solvents (cyclohexane, isobutane, naphthalene, anthracene, phenanthrene, mesitylene, and anisole[118,122]) involves the formation of 2-aminopyrimidine, secondary 2-aminopyrimidines, or a mixture of both. Furthermore, pyrimidin-2-ylnitrene can take part in cycloaddition reactions with aromatic hydrocarbons via the following mechanism involving the formation of compounds (**XCIII**)[118]:



(XCIII)

7-Methyl-5-methylthiotetrazolo[1,5-*c*]pyrimidine gives rise to 1-cyano-4-methyl-5-methylthioimidazole on pyrolysis in organic solvents, i.e. ring contraction can occur also in solvents; in addition, amino-derivatives are produced[122].

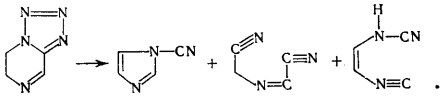
The pyrolysis of tetrazolo[1,5-*a*]pyrimidines in the presence of *trans*-stilbene without a catalyst (160°C) or in the presence of a catalyst (copper acetylacetonate, 120°C), leading to the formation of derivatives of *trans*- and *cis*-aziridines (**XCIV**) and (**XCV**) (40% and 3% respectively) has also been described[113]:



(XCIV) (XCV)

The pyrolysis of 8-phenyltetrazolo[1,5-*c*]pyrimidine in dichlorobenzene [123] proceeds with formation of indole in 50% yield. When the above tetrazole was refluxed in trifluoroacetic acid, mainly the initial product, which failed to react, was isolated. On gas-phase pyrolysis, tetrazolo[1,5-*a*]quinoxaline and tetrazolo[5,1-*c*]quinazoline form identical products. Ring contraction results in the formation of 2-cyanobenzimidazole and ring opening gives rise to *N*-cyanoanthranilonitrile [60].

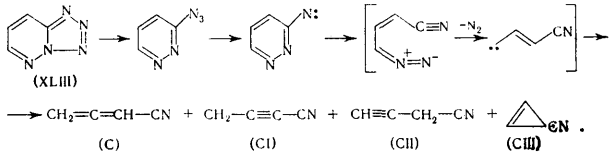
The pyrolysis of tetrazolo[1,5-*a*]pyrazine (XCVI) in the gas phase [19,122] involves ring contraction and the formation of compound (XCVII) and the ring cleavage products (XCVIII) and (XCIX):



(XCVI) (XCVII) (XCVIII) (XCIX)

In organic solvents (cyclohexane) the thermolysis proceeds with formation of 2-aminopyrazine [122], which confirms the formation of a nitrene and 1-cyanoimidazole as a result of ring contraction. On heating in acetic acid, the 5,6-diphenyl derivative of compound (XCVI) [8] gives rise to a mixture of 2,5-diphenylimidazole (56%) and 1-acetyl-5-diphenylimidazole (3%). Wentrup's studies [122] have shown that the formation of these products can be readily accounted for by the primary contraction of the nitrene ring.

In the thermolysis of tetrazolo[1,5-*b*]pyridazine (XLIII) [119], one of the most stable of the condensed tetrazoles, ring opening results in the formation of cyanoallene (C), tetrolonitrile (CI), propargyl cyanide (CII), and 2-cyanocyclopropene (CIII):



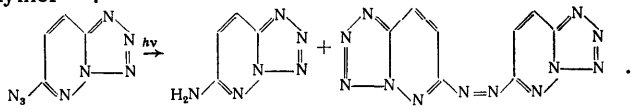
(XLIII)

$\rightarrow CH_2{=}C{=}CH{-}CN + CH_2{-}C{\equiv}C{-}CN + CH{\equiv}C{-}CH_2{-}CN +$

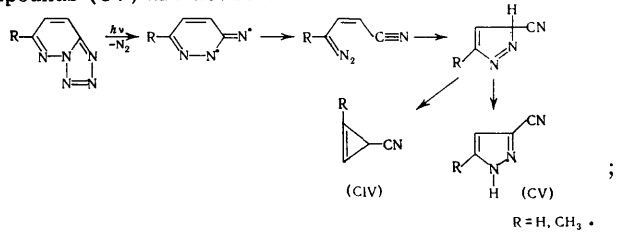
(C) (CI) (CII) (CIII)

When 9,10-tetrazolophenanthridine is heated to 500°C, a nitrene dimer is formed and then 9-cyanocarbazole and 4-cyanocarbazole (possibly as a result of ring opening and recyclisation [60]).

The photolysis of 6-azidotetrazolo[1,5-*b*]pyridazine in alcoholic solution for 20 h leads to the formation of a mixture consisting of 95% of 6-aminotetrazolo[1,5-*b*]pyridazine, 3% of the corresponding azo-compound, and 2% of a polymer [124]:



The photolysis of 8-R-tetrazolo[1,5-*b*]pyridazines [125] in methanol or methylene chloride results mainly in the formation of 3-cyano-R-cyclopropenes (CIV) in 20–25% yield and 3-cyano-5-R-pyrazoles (CV) in 0.1% yield. In acetone the yield of compounds (CIV) decreases to 5%, while compounds (CV) are not formed:

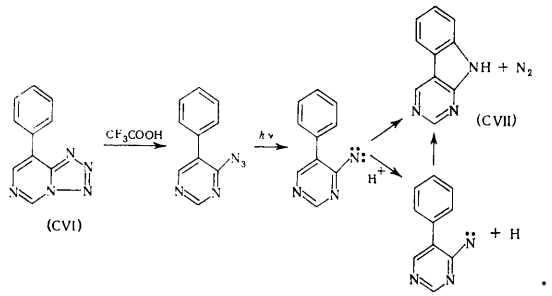


(CIV) (CV)

R = H, CH_3.

7,8-Diphenyltetrazolo[1,5-*a*]pyrazine decomposes photolytically in acetic acid in the course of 32 h with formation of 4,5-diphenylimidazole (10%) and benzoic acid (7%). [26]

The photolysis of 8-phenyl-, 8-*p*-tolyl-, 8-*p*-methoxyphenyl-, and 8-*p*-chlorophenyl-tetrazolo[1,5-*c*]pyrimidines (CVI) in trifluoroacetic acid leads to the corresponding 2*H*-pyrimido[4,5-*b*]indoles (CVII) [123], which are formed in a high yield. This process can be used as a method for the synthesis of indoles. In a non-polar medium, photolysis takes place slowly and with low yields. The quantum yield of the photolysis of the 8-phenyl derivative is 0.5:



(CVI) (CVII)

o0o

The properties of condensed tetrazoles, the mode of various reactions in which they are involved, and the structures of the reaction products are directly related to the distribution of electron density in the molecule. The latter is in turn determined by the electron-accepting properties of the tetrazole ring and of the nitrogen-containing heterocycle and by the electronic nature of the substituents.

The distribution of electron density influences the stability of the condensed tetrazole ring and its capacity for being opened at the $N_{(1)}{-}C_{(5)}$ bond with formation of the isomeric azidoazomethine derivatives of the nitrogen-containing heterocycles. The protonation, alkylation, electrophilic substitution, covalent hydration, and reduction reactions as well as reactions with alkalis depend on the electron-accepting properties of the tetrazole ring.

The stability of the tetrazole ring determines the mode and rates of reactions with nucleophilic agents, cycloaddition reactions, thermolysis, photolysis, and reactions with organometallic, organophophorus, and other compounds.

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