# ADVANCES IN THE CHEMISTRY OF TETRAZOLES (REVIEW)

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The review is devoted to the newest advances in the chemistry of tetrazoles. New data on the electronic structures, crystal structures, and dipole moments are presented successively. The electronic, vibrational, NMR, and mass spectra are discussed. Data on the acid-base properties and tautomerism of tetrazoles are presented. Numerous methods for the preparation of tetrazole and mono- and disubstituted tetrazoles are reported. The chemical properties of tetrazoles, viz., electrophilic substitution at the ring carbon atom, nucleophilic substitution, alkylation, electrophilic and nucleophilic substitution in the side chain, and the effect of oxidizing and reducing agents, are discussed. Reactions that lead to cleavage of the tetrazole ring, viz., acylation and thermolysis, are examined separately. New data on the use of tetrazoles in medicine, biology, agriculture, the manufacture of polymeric materials, etc. are presented.

Tetrazoles occupy a special place among five-membered nitrogen-containing heterocycles. Tetrazoles contain the maximally possible number of nitrogen atoms in a ring — four — and have partial aromatic character. As compared with other nitrogen-containing heterocycles, higher delocalization energies are characteristic for these compounds. The charge distributions in tetrazoles and their closest heterocyclic analogs, viz., triazoles, also differ substantially. Appreciable differences are observed in the dipole moments, heats of formation, and acid-base properties. These peculiarities have a substantial effect on the chemical and physical properties of tetrazoles. The tetrazole ring is resistant to the action of acids, bases, and oxidizing and reducing agents. Tetrazolate anions have dual reactivity, and this expands the possibilities of the application of these compounds in organic synthesis significantly. Tetrazoles form stable complexes with metals and halogens. Some tetrazoles are stable at 300°C.

The number of publications devoted to the study of tetrazoles increases each year. Significant advances have been made in their use in medicine [1, 2], biology [3], agriculture [4], the manufacture of polymeric materials [5], and in other areas. The physical and chemical properties of tetrazoles, methods for the preparation of these compounds, and their application in the national economy are examined in the present review. The literature data obtained primarily in the last 5 years, including the first half of 1980, are discussed.

## Physicochemical Properties of Tetrazoles

Electronic Structure. The electronic structure of tetrazole has been calculated by various quantum-chemical methods, viz., by means of the $\pi$-electron approximation and modern semiempirical and nonempirical methods that take into account all of the valence electrons (Table 1). It follows from the available data that the electron density in the tetrazole molecule is maximal on the nitrogen atoms in the 1 and 4 positions. Removal of a proton leads to an increase in the electron density on all of the atoms of the tetrazole ring; the nitrogen atoms in the 1 and 4 positions and in the 2 and 3 positions in the tetrazolate anion are equivalent [9, 13]. At the same time, a significant decrease in the electron density on all of the ring atoms occurs in the case of protonation of tetrazole, in which the proton adds to the nitrogen atom in the 4 position [9]. It follows from a comparison of the bond multiplicity indexes $W_{AB}$ of tetrazole and the tetrazolate anion that in the case of the anion the difference between the $W_{AB}$ values for the various ring bonds decreases substantially. Protonation of tetrazole has little effect on the multiplicity of the bonds, particularly the $N_{(1)}$-$N_{(2)}$ bond

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TABLE 1. Charges on the Atoms of Tetrazole

| Charges of the atoms | | | | | Method of calculation | Literature |
|---|---|---|---|---|---|---|
| $N_1$ | $N_2$ | $N_3$ | $N_4$ | C | | |
| −0,13 | −0,09 | −0,08 | −0,16 | +0,08 | LCAO * | 6 |
| −0,41 | −0,02 | −0,06 | −0,19 | 0,00 | *ab initio* | 7 |
| −0,24 | −0,03 | +0,06 | −0,18 | +0,13 | *ab initio* (STO-3G) | 8 |
| −0,29 | −0,01 | +0,001 | −0,28 | +0,30 | CNDO | 9 |
| −0,46 | −0,15 | −0,14 | −0,22 | −0,04 | HMO† | 10 |
| −0,46 | −0,22 | −0,12 | −0,22 | — | PPP† | 11 |
| −0,88 | +0,04 | −0,12 | −0,16 | +0,13 | G-FEMO† | 12 |

*The authors do not give a more specific identification of the method of calculation. †The π charges are presented.

The electronic structures of a series of mono- and disubstituted tetrazoles have been studied by means of the Huckel MO [14, 15] and CNDO [9] methods. In 1- and 2-phenyltetrazoles, as well as 5-R-tetrazoles, the distribution of the electron density depends only slightly on the electronic properties of the substituents. For all of the 5-substituted tetrazoles, as well as the 1- and 2-methyl-substituted tetrazoles, the electron densities on the nitrogen atoms in the 1 and 4 positions are appreciably higher than on the nitrogen atoms in the 2 and 3 positions. Changes that make it possible to explain the dual reactivity of the tetrazolate anion in alkylation and addition reactions are observed on passing from 5-substituted tetrazoles to their anions [9].

Quantum-chemical methods have been successfully used in a number of cases to estimate the structures and reactivities of tetrazoles. Thus on the basis of a comparison of the charges of the atoms and the bond multiplicity indexes calculated by the CNDO/2 method it has been concluded that different degrees of resonance interaction of the tetrazole ring and the amino group exist in 5-aminotetrazole and 2-methyl-5-aminotetrazole [13]. Interesting information regarding the structure of the guanidinium salt of 5-aminotetrazole has been obtained by means of the same method [16]. Quantum-chemical calculations of the stabilities of the conformers and the energy barriers of 2-acetyltetrazole have been made by the Hoffman method and the Dewar $\sigma + \pi$ method [17]. The use of the Pariser-Parr-Pople (PPP) method in the conformational analysis of 1-(5-tetrazolyl)-3,5-diphenylformazan makes it possible to suppose that this compound exists in the syn-s-cis-trans form [18].

The results of quantum-chemical calculations of tetrazoles are in good agreement with the results of experimental investigations. For example, the calculated energy levels of tetrazole are in agreement with the values found from photoelectronic spectroscopic data [19]. The calculated and experimental values of the dipole moments of tetrazole are also in good agreement [6, 7, 12, 20, 21]. Linear relationships between the π-electron densities and the $^{14}N$ chemical shifts have been observed [11]. Similar relationships have been found between the electron density on the carbon atom and the $^{13}C$ and $^{1}H$ shifts [14, 22]. The parameters of the expression $\sigma_\rho = aq_{\sigma+\pi}^{N(1)} + b$, where $\sigma_\rho$ is the electronic constant, and $q_{\sigma+\pi}^{N(1)}$ is the electron density on the nitrogen atom in the 1 position of the ring, were determined in [23] for a series of five-membered nitrogen-containing heterocycles, including tetrazole. A correlation between the $\sigma_\rho$ substituent constants and the charges on the nitrogen atoms in the 1 and 4 positions of the ring is observed for 1- and 2-methyl-5-substituted tetrazoles [9].

Finally, it must be noted that quantum-chemical data have been used in the study of protropic and azidoazomethine-tetrazole tautomerism [8, 24], acid-base properties [25], isotopic exchange of hydrogen [26], and the thermal stabilities of tetrazoles [10], as well as the deprotonation of tetrazolium ions to give zwitter ions [27].

Crystal Structure. A number of papers devoted to the study of the crystal structure of tetrazoles with various structures by x-ray diffraction analysis have been published in recent years. An examination of the available data makes it possible to establish certain general principles in the crystal structure of tetrazoles. In the opinion of Ansell [28] and Alcalde and co-workers [29], the bond lengths in tetrazoles constitute evidence for the aromatic character of the tetrazole ring. At the same time, the tetrazole ring in 1,6-dimethyl-7-ethoxycarbonylpyrazolo[1,5-d]tetrazole is less aromatic than the pyrazole ring [29]. This

TABLE 2. UV Spectra of Substituted 5-(R-phenyl)Tetrazoles and Their Anions in Acetonitrile at 25°C

| R | Tetrazole | | Tetrazolate anion | |
|---|---|---|---|---|
| | λ, nm | $\varepsilon_{max}$ | λ, nm | $\varepsilon_{max}$ |
| *p*-$CH_3$ | 242 | 15 000 | 252 | 17 000 |
| *m*-$CH_3$ | 235 | 9 800 | 252 | 14 400 |
| H | 240 | 13 500 | 252 | 14 000 |
| *p*-Cl | 250 | 21 300 | 257 | 19 300 |
| *p*-Br | 247 | 19 800 | 258 | 17 600 |
| *m*-Cl | 241 | 13 600 | 253 | 13 800 |
| *m*-$NO_2$ | 231 | 21 500 | 254 | 18 000 |

conclusion was drawn on the basis of a comparison of the bond lengths in the tetrazole and pyrazole rings: the $N_{(2)}$-$N_{(3)}$ bond in tetrazoles is shorter than the $N_{(1)}$-$N_{(2)}$ and $N_{(3)}$-$N_{(4)}$ bonds [28], while the bonds between the atoms of the pyrazole fragment have approximately identical lengths [29].

An interesting peculiarity of tetrazoles is the relatively low sensitivity of the geometrical parameters to the effect of the nature of the substituents, to isomerism, and to complexing [28]. On the other hand, the ionization of tetrazoles leads to appreciable changes in their structures. The $N_{(1)}$-$N_{(2)}$ and $N_{(3)}$-$N_{(4)}$ bond lengths, as well as the $N_{(1)}$-C and $N_{(4)}$-C bond lengths, respectively, are equal in tetrazolate anions [28, 30]. A similar principle is also observed in the case of mesoionic tetrazoles [31]. It is interesting that conjugation between the phenyl groups and the positively charged tetrazole ring is absent in the 2,3-diphenyl-5-mercaptotetrazolium cation [31]. Unfortunately, one cannot form an unambiguous judgment regarding the mutual orientation of the structural fragments in phenyltetrazoles on the basis of the available information. The conclusion that conjugation between the phenyl ring and the tetrazole ring is absent in tetrazolo[1,5]benzothiazole [32] evidently cannot be extended to substituted 5-phenyltetrazoles. From the data in [33] it can be concluded that the tetrazole and phenyl fragments in some 1-(p-methylphenyl)-5-R-tetrazoles are oriented at an angle of ∿90 deg. However, no quantitative data apropos of this conclusion are available.

Dipole Moments. Tetrazole has the highest dipole moment among five-membered nitrogen-containing heterocycles. The experimental values of the dipole moment of tetrazole found in dioxane are 5.11 [34], 5.15 [20], 5.10 [35], and 4.96 D [36]. These results are in good agreement with the values calculated for 1H-tetrazole by means of vector additive schemes, viz., 5.16 [34] and 5.26 D [37], as well as with the values obtained by quantum-chemical methods, viz., 4.85 [12] and 5.17 D [7]. The dipole moments of 2H-tetrazole found by means of vector schemes and calculated by quantum-chemical methods, respectively, are 2.38 [34], 2.04 [37], and 2.04 D [20]. It follows from a comparison of the experimental dipole moments of tetrazole with the values calculated for the 1-H and 2-H tautomers that tetrazole exists primarily in the form of the 1-H tautomer [24]. In the gaseous phase the dipole moments of tetrazole and C-deutero- and N-deuterotetrazoles determined from data from the microwave spectra of these compounds are, respectively, 2.19, 5.30, and 2.14 D [38]. It follows from this that tetrazole and N-deuterotetrazole in the gaseous phase exist primarily in the form of the 2-H tautomer, while the 1-H form predominates in the case of C-deuterotetrazole.

Higher dipole moments are characteristic for 1- and 5-monosubstituted tetrazoles, as well as 1,5-disubstituted tetrazoles, as compared with 2-substituted tetrazoles. For example, the dipole moments of 1- and 2-ethyltetrazoles are, respectively, 5.46 and 2.65 D [35, 39]. This makes it possible to establish the individuality of 1,5- and 2,5-disubstituted tetrazoles by comparison of the experimental values of the dipole moments with the values calculated by a vector scheme for structural models that contain substituents in the 1 or 2 position of the ring [39]. The state of the azidoazomethine-tetrazole tautomeric equilibrium can be estimated from the dipole moments [40].

Electronic and Vibrational Spectra. Tetrazole has weak absorption in the UV region of the spectrum: $\lambda_{max}$ 203 nm (ε 178) in water at pH 1.5. The character of the UV spectra of tetrazole derivatives is determined by the nature and position of the substituents in the

TABLE 3. Vibrational Spectra of 1-R'-5-R-Tetrazoles

| R | R' | Stretching vibrations, $cm^{-1}$ | | | Stretching-deformation vibrations, $cm^{-1}$ |
|---|---|---|---|---|---|
| | | I | II | III | |
| H | H | 1251, 1259 | 1440, 1450 | 1518 | 1012, 1048, 1082 |
| H | $CH_3$ | 1220, 1275 | 1440, 1467 | 1489 | 968, 1040, 1100 |
| $CH_3$ | H | 1260, 1270 | 1409, 1440 | 1560, 1580 | 1000, 1050, 1089 |
| $NH_2$ | H | 1298 | 1445, 1460 | 1605 | 995, 1060, 1160 |
| $CF_3$ | H | 1235, 1310 | 1370, 1410 | 1500, 1528 | 1020, 1045, 1160 |

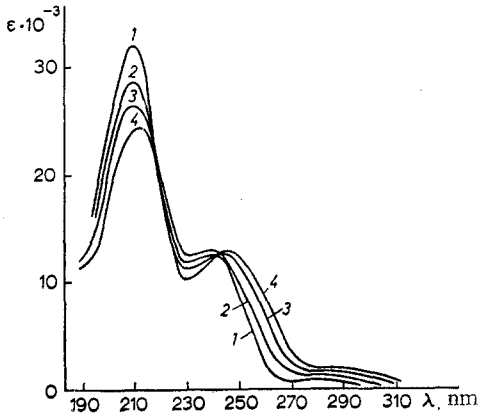



Fig. 1. UV spectra of 2-methyl-5-(m-bromophenyl)tetrazole in aqueous solutions of sulfuric acid with various concentrations (%): 1) 18.1; 2) 52.4; 3) 61.6; 4) 80.7.

tetrazole ring. The highest absorption intensity is characteristic for phenyltetrazoles: 210-300 nm [$\varepsilon \approx (1\text{-}3)\cdot 10^4$]. The molar extinction coefficient increases on passing from 1-phenyltetrazoles to the isomeric 2-phenyl- and 5-phenyltetrazoles; this is associated with a change in the $\pi$-electron interaction between the phenyl and tetrazole rings [41, 42]. The character of the $\pi$-electron interaction between the phenyl ring and the tetrazole ring can be judged from the UV spectra of isomeric 1- and 2-alkyl-5-phenyltetrazoles. Thus disruption of the coplanarity of the system occurs as a result of steric interaction between the phenyl ring and the alkyl substituent in the 1 position of the heteroring. This leads to a hypsochromic shift of the $\lambda_{max}$ bands of these compounds and to a decrease in the molar extinction coefficients [41, 42].

As compared with substituted 5-phenyltetrazoles, a change in the position and intensities of the absorption bands is observed in the UV spectra of their anions [43] (Table 2). The change in the electronic structure of the tetrazole ring in the case of protonation is also reflected in the character of the UV spectra of these compounds. A decrease in the molar extinction coefficient of the short-wave band ($\lambda_{max}$ 210 nm) and a 5-7 nm bathochromic shift of the absorption maximum at 240 nm occur in the case of protonation of 2-methyl-5-(m-bromophenyl)tetrazole in sulfuric acid [44] (Fig. 1).

The effect of the nature of the solvent on the electronic spectra of tetrazoles was studied in the case of a number of mesoionic compounds. It was established that a correlation relationship is observed between $\lambda_{max}$ of mesoionic tetrazoles and the polarity parameters ($E_T$) of the solvents [45]. Despite the fact that there have apparently been no systematic studies of the UV spectra of tetrazoles, electronic spectroscopic methods are finding wide application in the study of prototropic tautomerism and acid-base equilibria [24, 46], the ion-molecular composition of salts of tetrazoles in organic solvents [47], the nature of the color of tetrazolium salts [48], and in the determination of the conformation of tetrazolylformazans [18].

A rather large number of publications have been devoted to the study of the vibrational spectra of tetrazoles [49]. Early studies devoted to the experimental assignment of the bands of the vibrational spectra of tetrazoles were limited to only the region of the stretching-deformation vibrations of the ring, viz., 1000 to 1100 $cm^{-1}$. The remaining bands usually were not identified because of difficulties of a theoretical nature. A detailed analysis of the IR spectra of a number of substituted tetrazoles by means of a comparison of the experimental spectra with the results of a theoretical calculation of the frequencies and forms of the normal vibrations of the tetrazole ring was recently conducted [39, 50, 51]. It was

shown that the stretching and stretching-deformation vibrations of the ring in substituted tetrazoles retain their specific character with respect to frequency (Table 3). The absence of specific character with respect to form is explained by the fact that the ring vibrations are mixed with one another and with the deformation vibrations of the groups of the substituents. However, in all cases it may be assumed that the group I vibrations are primarily stretching vibrations of C-N and N-N bonds, the group II vibrations are primarily stretching vibrations of the N=N bond, and the group III vibrations are primarily stretching vibrations of the C=N bond (Table 3). Thus these results can be used in the identification of all of the bands of the vibrational spectra of tetrazole and its derivatives. In recent years IR and laser Raman spectroscopy have become widely used in the study of prototropic [24], azido-azomethine-tetrazole [52, 53], and amino-imino tautomerism [53], the acid-base properties of tetrazoles [24], and the crystal structures of these compounds [54].

NMR Spectra. Nuclear magnetic resonance spectroscopy is widely used in the study of the structures and reactivities of tetrazoles. The literature data through 1974 have been examined in a previous review [49]. Studies published in the last 5 years are discussed below.

More study has been devoted to the NMR spectra of phenyltetrazoles than to the spectra of other tetrazoles. The effect of the nature of the substituents in the phenyl ring, solvents, annular isomerism, and some other factors on the parameters of the NMR spectra of these compounds has been investigated. The existence of correlations of the chemical shifts ($\delta$) of the 5-H protons attached to the ring carbon atom in substituted 1- and 2-phenyltetrazoles with the $\pi$-electron densities, substituent constants, and parameters of the PMR spectra of monosubstituted benzenes has been demonstrated [14]. The character of the solvent and isomerism also affect the $\delta$(5-H) chemical shift. The difference in the chemical shifts due to the nature of the solvent is higher for 1-phenyltetrazoles than in the case of the isomeric 2-substituted compounds, and this makes it possible to use this parameter as a useful criterion in the evaluation of the individuality of the isomers [14].

Linear relationships between the chemical shifts of the aromatic protons and the F, R, and Q empirical structural parameters have been found in series of substituted 5-phenyltetrazoles [55]. The experimentally measured parameters of the PMR spectra of a number of substituted 5-phenyltetrazoles [55] and 1-phenyl-5-methyltetrazole [56] are in good agreement with the values calculated by additive schemes. A characteristic multiplet or singlet, respectively, is observed in the PMR spectra of phenyltetrazoles, depending on the presence or absence of interannular conjugation [57, 58]. Electronic interaction between the phenyl and tetrazole rings is also reflected in the $^{13}C$ NMR spectra. The difference in the $^{13}C$ chemical shifts of the phenyl ring [$\Delta\delta = \delta C_{(3)} - \delta C_{(2)}$] when conjugation is present usually exceeds 2.9 ppm, whereas $\Delta\delta < 0.7$ ppm when coplanarity is disrupted [58]. Strong interannular conjugation in 2-phenyl-, 5-phenyl-, and 2-methyl-5-phenyltetrazoles has been observed by means of such tests, whereas conjugation is disrupted or is completely absent in 1-phenyl-, 5-(o-nitrophenyl)-, and 1-methyl-5-phenyltetrazoles [57, 58].

The applicability of this approach for the study of interannular conjugation in condensed systems has been demonstrated in the case of isomeric phenyl-substituted pyrazolo[1,5-d]tetrazoles [29] and triazolo[2,3-d]tetrazoles [52]. Ciarkowski and co-workers [55] on the basis of PMR spectral data arrived at the conclusion that the electronic interaction between the phenyl and tetrazole rings in substituted 5-phenyltetrazoles is determined by the negative inductive effect of the heteroring. However, considering the fact that this conclusion was drawn only on the basis of an analysis of empirical relationships, the nature of the interannular conjugation in 5-phenyltetrazoles cannot be definitively established.

A substantial change in the $^{13}C$ chemical shifts of both the ring carbon atom [$\Delta\delta C_{(5)}$ = 4.75 ppm] and the carbon atom of the phenyl ring bonded to it [$\Delta\delta C_{(1)}$ = 6.25 ppm] is observed on passing from 5-phenyltetrazole to the corresponding tetrazolate anion. This constitutes evidence for significant charge delocalization in the 5-phenyltetrazole anion [59]. The protonation of tetrazole, as well as 1- and 2-substituted tetrazoles, in aqueous solutions of sulfuric acid leads to an increase in the chemical shifts of the 5-H protons [25, 60, 61]. It has been shown that the shift of the signals of these protons in 37.0-61.1% $H_2SO_4$ is due to a change in the component of the diamagnetic shielding constant due to protonation [60].

Of the numercus examples of the application of NMR spectroscopy for the solution of structural problems and the investigation of the reactivities of tetrazoles, one should primarily note prototropic [57-59, 62], azidoazomethine-tetrazole [40, 52, 63-68], thione-thiol [70], and keto-enol [69, 70] tautomerism, as well as exhaustive alkylation [42]. In the lat-

ter case during a study of the alkylation of 1- and 2-methyl-5-phenyltetrazoles from the PMR spectral data it was demonstrated unambiguously that the reaction center is the nitrogen atom in the 4 position. Data on the application of $^{14}N$ NMR spectroscopy for these purposes are available [71]. An attempt was recently made to evaluate the biological activity of tetrazolyl-containing antibiotics from the parameters of the $^{13}$ and $^{15}N$ NMR spectra [72]. The range of application of NMR spectroscopy for the study of the chemical transformations of tetrazoles is expanding each year; the most valuable information has been obtained as a result of the combined use of PMR and $^{13}C$ NMR spectroscopy [25, 29, 52, 58, 59, 64, 73].

Mass Spectra.* One of the effective methods for the investigation of the structure of tetrazoles is mass spectrometry. The successful use of this method is primarily associated with the development in recent years of the characteristic schemes of the fragmentation of tetrazole and its derivatives. The mass spectrum of tetrazole is characterized by an intense (10% of the maximum peak) molecular-ion peak ($M^+$). The maximum peak in the spectrum of tetrazole corresponds to the formation of the $[M - N_2]^+$ cation radical. Competitive elimination of HCN is another extremely specific pathway in the fragmentation of the molecular ion of tetrazole.

The fragmentation of the molecular ions of mono- and disubstituted tetrazoles depends on the nature and position of the substituents in the ring. The mechanism of the dissociative ionization of substituted 1- and 2-phenyltetrazoles has a number of features in common with the pathway of fragmentation of isomeric 5-phenyltetrazoles. The most intense peaks in the mass spectra of 5-phenyltetrazoles correspond to the $[M - \dot{N}_2]^+$ and $[M - N_2 - HCN]^+$ ions. The formation of a number of $[M-HN_3]^+$, $[M-HN_4]^+$, and $[M-CHN_4]^+$ fragment ions also occurs as a result of competitive processes of fragmentation of the molecular ions of these compounds [74, 75]. In some cases the fragmentation of molecular ions of substituted 5-phenyltetrazoles is anomalous in character. Thus, for example, an ion with m/z 134, the formation of which is assumed to occur as a result of fragmentation of the molecular ion with the simultaneous transfer of an oxygen atom of the nitro group to the ring carbon atom, is observed in the mass spectrum of 5-(o-nitrophenyl)tetrazole [76]. This mechanism makes it possible to explain the nature of the ortho effect in the mass spectra of condensed tetrazoles that contain on o-nitrophenyl fragment [76, 77]. Fundamental differences in the character of the dissociative ionization of 5-phenyl- and 5-hetaryltetrazoles are not generally observed [76]. 5-Pyridyl-, 5-pyrazinyl-, and 5-(2-phenyl)-4-quinazolinyltetrazoles, in the mass spectra of which metastable $[M - 2N_2]^+$ ions are observed [78], constitute exceptions.

In the general case the mass spectra of 1,5-disubstituted tetrazoles present a more complex pattern as compared with the spectra of the isomeric 2,5-disubstituted compounds. A characteristic of 2-methyl-5-R-tetrazoles is the formation under the influence of electron impact of an $[M+1]^+$ ion, the intensity of the peak of which depends on the magnitude of the ejection potential. It is assumed that the $[M + 1]^+$ ion is a product of the interaction of the molecular ion with neutral 2-methyl-5-R-tetrazole [49, 79].

The general pathway of fragmentation of substituted 1- and 2-phenyl-5-R-tetrazoles is the successive elimination of $N_2$ and RCN from the corresponding molecular ions with the formation of ions with equal masses. In the case of 1-phenyltetrazoles the intensity of the peak corresponding to the $[M - \dot{N}_2]^+$ ion is higher than in the case of the 2-phenyl derivatives, and this makes it possible to unambiguously identify the isomers [41, 80]. Deviations from the general fragmentation scheme are observed for some 1- and 2-phenyl-5-R-tetrazoles; this is associated with the specific structures of these compounds. Thus the first step in the fragmentation of the molecular ions of substituted 1-phenyl-5-methyltetrazoles is rearrangement, which leads to the formation of $[M - \dot{N}_2]^+$ pseudomolecular ions of 5-substituted 2-methylbenzimidazole and 1-substituted 3-methylazirine [81]. The fragmentation of the molecular ions of substituted 1-phenyl-5-styryltetrazoles is accompanied by the ejection of an $(N_2H)^{\cdot}$ radical. In addition, $[M - H]^+$ ion peaks are observed in the mass spectra of these compounds, and this indicates the high lability of the hydrogen in the molecular ions [82]. The fragmentation of the molecular ions of 1-phenyl-5-mercaptotetrazoles is characterized primarily by the simultaneous ejection of N and S, which is usually accompanied by the

*The authors thank N. A. Klyuev for his participation in the selection of the literature on the mass spectra of tetrazoles.

appearance of the maximum peak in the spectrum. The pattern of the dissociative ionization of 5-mercaptotetrazoles is supplemented by the elimination of a tetrazole fragment, as well as by the ejection of $HN_3$ [83, 84]. As expected, 1-phenyl- and 1-phenyl-4-methyltetrazolines have specific mass spectra. Depending on whether the heteroatom (N, O, or S) is bonded to the ring carbon atom, the primary fragment ion has a phenylcarbodiimide, phenyl isocyanate, or phenyl isothiocyanate structure, respectively [85].

The application of mass spectrometry gives good results not only in the solution of complex structural problems associated with the elucidation of the structures of condensed [85, 86] and mesoionic [87] tetrazoles but also in the case of tetrazolium salts [88]. Mass-spectrometric data have frequently been invoked for the interpretation of the mechanism of the thermal decomposition of tetrazoles [41, 78, 89, 90], in the study of the selectivity of the nitration of 1-phenyl5-styryltetrazole [82], and in some other cases [91].

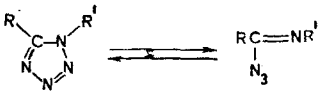
Acid–Base Properties. Tetrazole and 5-substituted tetrazoles are heterocyclic N–H acids with $pK_a$ values from −0.8 $H_0$ unit to 7 pH units. When they are dissolved in mineral acids, these compounds behave as weak organic bases. A large amount of literature has been devoted to the study of the acid-base properties of tetrazoles. Experimental data through 1979 have been examined in a previous review [24]. The results obtained in the last two years are presented below.

In a study of the acidities of substituted 5-phenyltetrazoles in aqueous alcohol solutions and in the dimethyl sulfoxide (DMSO)–water system it was shown that the $pK_a$ values of these compounds correlate with the substituent constants ($\rho$ 1.52 and 1.67, respectively) [92]. According to Kaczmarek and co-workers [92], the thermodynamic parameters for the dissociation of tetrazole, 5-methyltetrazole, and 5-trideuteromethyltetrazole calculated from the dependence of the $pK_a$ values on the reciprocal temperatures are, respectively, $\Delta H^\circ$ 53, 53, and 50 kJ/mole; $\Delta S^\circ$ 0.09, 0.07, and 0.06 J/mole-°K. It was also shown that an inverse secondary isotope effect ($K_H/K_D$ = 0.9) is observed when a hydrogen atom in the methyl group of 5-methyltetrazole is replaced by deuterium.

The protonation of tetrazoles in aqueous solutions of sulfuric and perchloric acids is described by the $H^\circ$ acidity function. The $pK_{BH^+}$ values of tetrazoles range from −2 to −9 $H^\circ$ units. A linear relationship between the $pK_{BH^+}$ and $pK_a$ values of 5-R-tetrazoles is observed over a rather wide range of changes in the $pK_{BH^+}$ and $pK_a$ values, and this makes it possible to quantitatively evaluate the acid-base properties of 5-substituted tetrazoles with the most diverse structures [61].

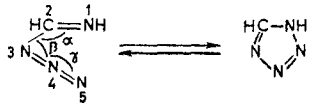
Tautomerism. The following types of tautomerism are known for tetrazoles: prototropic, amino-imine, thione-thiol, keto-enol, and azidoazomethine-tetrazole tautomerism. More study has been devoted to prototropic [24], amino-imine [49], and azidoazomethine-tetrazole [93, 94] tautomeric transformations than to the other types of tautomerism. The problems of prototropic and amino-imine tautomerism have been examined in detail in recent reviews [24, 49]. The most important studies of azidoazomethine-tetrazole tautomerism made in recent years are discussed below.

In general form, azidoazomethine-tetrazole tautomerism can be represented as



The state of the tautomeric equilibrium depends mainly on the nature of the R and R' substituents and the medium. Electron-acceptor substituents generally promote a shift of the equilibrium to favor the azidoazomethine, particularly if such substituents are attached to the $N_1$ atom. In neutral and basic media the equilibrium is usually shifted to favor the tetrazole [52, 95]. At the same time, when certain condensed tetrazoles are dissolved in acids, they are converted to azidoazomethines [66, 67, 96]. It is also known that azidoazomethines undergo condensation to tetrazoles only in neutral form [97].

A theoretical examination of azidoazomethine-tetrazole tautomerism was recently made by means of the *ab initio* [8] and MNDO [98] methods. The cyclization of azidoazomethine to tetrazole is realized in several steps. In the first step angle $\gamma$ of the azide decreases, and this is accompanied by a change in the lengths of the $N_3$–$N_4$ and $N_4$–$N_5$ bonds. This is followed



by a simultaneous change in the α, β, and γ angles until α reaches the value found in tetrazole; only the length of the $N_4$–$N_5$ bond changes in the process. The process is complete when angle γ reaches the limiting value and all of the bond lengths have changed significantly. It was also shown that in the cyclization of azidoazomethine to tetrazole the free electron pair in the transition state migrates from $N_1$ to along a pathway toward the $N_5$ atom, and the transition state has a structure that is close to that of the starting azide. These results are in good agreement with the experimental data obtained in a study of the cyclization of azidoazomethines to tetrazoles [53, 97].

## Methods for the Preparation of Tetrazoles

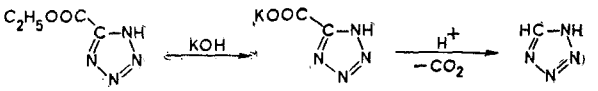
The preparation of tetrazole and its derivatives was first described by Bladin ∿100 years ago [99]. The most important results obtained in recent years with respect to the synthesis of tetrazoles and investigations of the reactions involved in their formation will be examined below.

Tetrazole. Tetrazole can be obtained by the reaction of hydrazoic acid with hydrocyanic acid, by diazotization of 5-aminotetrazole in the presence of reducing agents, and as a result of the oxidative degradation of mono- and disubstituted tetrazoles [49, 100].

Although no information on the mechanism of the formation of tetrazole from hydrazoid and hydrocyanic acids is available, it may be assumed that this reaction is a process that involves 1,3-dipolar cycloaddition.

The diazotization of 5-aminotetrazole is a convenient and well-investigated method for the preparation of tetrazole. If the reaction is carried out in a solution of hypophosphorous acid, the possiblity of the accumulation of the explosive diazotetrazole in the reaction medium is excluded, and tetrazole is formed in high yield.

Tetrazole-5-carboxylic acid, which is readily decarboxylated in an acidic medium to give tetrazole, is formed as an intermediate in the oxidation of mono- and disubstituted tetrazoles. Tetrazole can also be obtained in good yield by the alkaline hydrolysis of ethyl tetrazole-5-carboxylate with subsequent acidification of the reaction solution with perchloric acid and decarboxylation at 90°C [10]. Finally, a simple method for



the preparation of tetrazole, which consists in the reaction of ethyl orthoformate with sodium azide and ammonium chloride, was recently proposed [102]. An imido ester, which under the influence of sodium azide is converted to azidoazomethine, which undergoes cyclization to tetrazole, is evidently formed in the first step in this case.

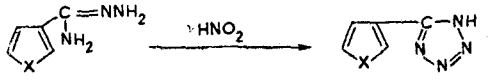
1-Substituted Tetrazoles. Methods for the synthesis of 1-substituted tetrazoles have not been adequately developed. The principal method for the preparation of these compounds is the addition of hydrazoic acid to isonitriles [100, 103]. Isonitriles with various structures undergo the reaction, and tetrazoles are usually formed in high yields. Thus 1-(1-adamantyl)- and 1-(2-adamantyl)-tetrazoles are obtained in 91 and 54% yields, respectively, in the reaction of 1- and 2-adamantyl isonitriles with hydrazoic acid [104]. Another method for the preparation of 1-substituted tetrazoles is the coupling of diazonium salts with diformylhydrazine [100]. 1-Substituted tetrazoles are also formed in the reaction of imido chlorides obtained from monosubstituted formamides with nitrous acid [100]. However, these methods have limited application, mainly because of the low yields of final products. 1-Substituted tetrazoles can be obtained by the alkylation of tetrazole. This reaction will be examined in detail in our discussion of the chemical properties of tetrazoles.

Of the "undiscovered" methods for the preparation of 1-substituted tetrazoles, one should point out the 1,3-dipolar cycloaddition of alkyl (aryl) azides to hydrocyanic acid. It might be expected that this method would be successful, since the addition of organic azides to nitriles is a widely used method for the prepration of 1,5-disubstituted tetrazoles.

2-Substituted Tetrazoles. Although it is a surprising fact, no methods for the preparation of 2-substituted tetrazoles other than the alkylation of tetrazole are evidently known. At the same time, methods such as diazotization of monosubstituted amidrazones of carboxylic acids, the reaction of phenylhydrazones of α-nitrobenzaldehyde with hydrazine, and the coupling of phenylsulfonylhydrazones with aromatic and heterocyclic diazo compounds, which have been used usccessfully for the preparation of 2,5-disubstituted tetrazoles [100, 105], with appropriate modification can be used for the synthesis of 2-substituted tetrazoles.

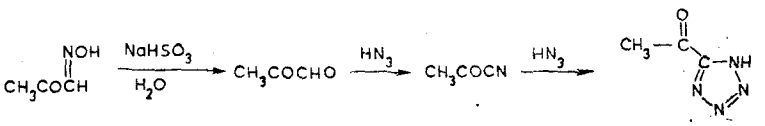
5-Substituted Tetrazoles. As compared with the methods for the preparation of 1- and 2-substituted tetrazoles, the methods for the synthesis of 5-substituted compounds have been studied rather thoroughly [49, 101]. The most widely used method is the reaction of nitriles with nitrous acid or inorganic azides. Sodium azide [106] or ammonium azide [107, 108] obtained in situ is normally used. The use of inorganic azides makes it possible to avoid contact with the explosive and poisonous hydrazoic acid, and the yields of final products are not decreased. Lewis acids such as aluminum chloride serve as catalysts for the reaction [109]. The structure of the nitrile has an appreciable effect on the reaction rate. Tetrazoles are formed with greater ease from nitriles that contain electron-acceptor substituents. The presence of a heteroatom (N, O, S, Se) in the nitrile molecule [106-108, 110] does not interfere with the normal course of the reaction. Dimethylformamide (DMF) is most often used as the solvent [108].

Of the other methods used in recent years for the preparation of 5-substituted tetrazoles, the diazotization of amidrazones of heterocyclic acids should be cited [107]. Thus, for example, the corresponding tetrazoles are obtained in high yields by the action of nitrous acid on amidrazones of thiophenecarboxylic and selenophenecarboxylic acids:




Included among original methods that have not been previously used for the synthesis of 5-substituted tetrazoles are the reactions of N-(α-chlorobenzylidene)carbamoyl chloride [111] with sodium azide and N-4-dimethylaminophenyl nitriles [112] with hydrazoic acid. However, in the latter case 5-substituted tetrazoles are formed in low yields.

An interesting instance of the conversion of isonitrosoacetone to 5-acetyltetrazole was described in [113]. Zhurkevich and Gerasimenko proposed that the reaction of isonitrosoacetone reacts with excess sodium bisulfite to give an adduct, the subsequent transformations of which under the influence of sodium azide in acetic acid lead to 5-acetyltetrazole. However, it is more likely that the formation of 5-acetyltetrazole proceeds via a different pathway. It is known [114] that oximes are cleaved to give the corresponding carbonyl compounds by the action of sodium bisulfite under mild conditions. In this case the formation of 5-acetyltetrazole can be represented as

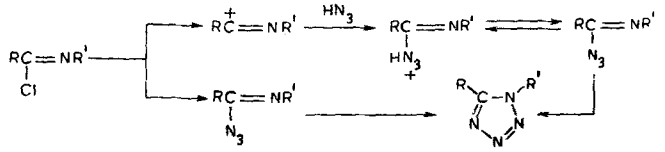



Still another example of the formation of 5-substituted tetrazoles, in which α-diazoacetophenone is converted to 5-benzoyltetrazole under the influence of sodium methoxide as a result of a complex reaction should be cited [115].

1,5-Disubstituted Tetrazoles. The reaction of imido chlorides with hydrazoic acid or inorganic azides, the addition of alkyl (aryl) azides to nitriles, the Schmidt reaction with ketones, the diazotization of heterocyclic derivatives of hydrazine, and several other reactions are among the most widely used methods for the preparation of 1,5-disubstituted tetrazoles.

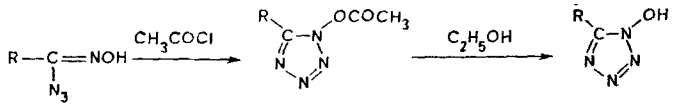
Despite the fact that the addition of hydrazoic acid to imido chlorides is widely used as an effective method for the synthesis of disubstituted tetrazoles, very little study has been devoted to the mechanism of this reaction. It is assumed that the formation of tetrazoles proceeds in one of two directions [116-118]. In the first case 2,5-disubstituted tetrazoles are obtained as a result of cyclication of the azidoazomethine that is formed as a

consequence of monomolecular solvolysis of the imido chloride to give an imino carbonium and subsequent addition to it of hydrazoic acid or by bimolecular nucleophilic replacement of the chlorine in the imido chloride by an azide group:



It is also possible that the reaction of imido chlorides with hydrazoic acid is a process involving 1,3-dipolar cycloaddition. On the basis of new data [116, 119, 120] obtained in a study of the reaction of imido chlorides with various structures with inorganic azides in dimethylformamide (DMF) it may be assumed that the formation of the azidoazomethine proceeds via a mechanism involving bimolecular nucleophilic substitution.

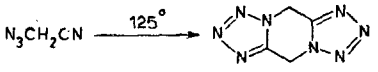
Of the two conformers — syn and anti — in which forms azidoazomethines can exist, tetrazoles are formed via cyclization of the anti form [117, 121]. The nature of the substituent attached to the imido nitrogen atom affects the ability of the azidoazomethines to undergo cyclization. Thus it was previously assumed [122] that azidoximes can exist only in the azide form. However, in recent years it was shown [123-127] that when azidoximes are treated with acetyl chloride, they undergo cyclization to give 1-hydroxy-5-substituted tetrazoles:



In a study of the kinetics of the cyclization of aromatic azidoazomethines it was shown [117] that the cyclization rate constants correlate with the σ substituent constants ($\rho = 1.45$). The reaction of imido chlorides with hydrazoic acid or inorganic azides makes it possible to obtain 1,5-disubstituted tetrazoles with various structures — from the simplest dialkyl and diaryl derivatives [68, 128] to condensed complex systems [66, 119, 121, 129, 130]; the yields of tetrazoles are high in most cases.

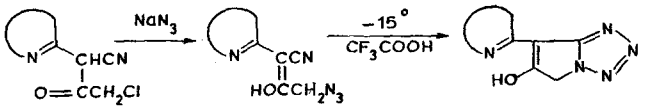
The formation of 1,5-disubstituted tetrazoles from nitriles and alkyl or aryl azides is an example of 1,3-dipolar cycloaddition. In a study of the kinetics of the reaction of alkyl azides with chloro and fluoro derivatives of acetonitrile [39] it was shown that electron-acceptor substituents in the azide molecule slow down the formation of tetrazoles. The rate constants for the reaction of substituted alkyl azides with trifluoroacetonitrile correlate with the σ* substituent constants ($\rho = 0.99$). The activation parameters of the reaction are characteristic for processes that take place via a mechanism involving 1,3-dipolar cycloaddition.

New data on the synthetic possibilities of the reaction of nitriles with organic azides have been published in recent years and have significantly expanded the scope of this method for the preparation of 1,5-disubstituted tetrazoles. An example of this is provided by the preparation of 5H,10H-di-tetrazolo[1,5-a;1,5-d]pyrazine by prolonged heating of azidoacetonitrile in an autoclave [131]:

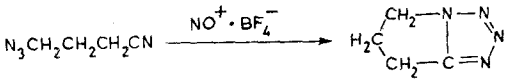


The preparation of 1-trimethylsilyl-5-substituted tetrazoles from trimethylsilyl azide and aliphatic or aromatic nitriles has been described [132, 133].

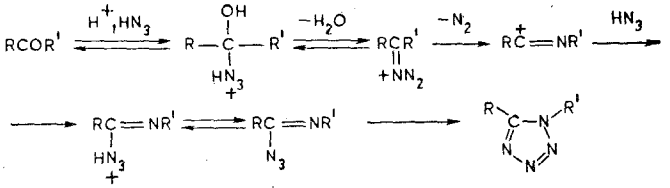
It has been recently demonstrated [134] that the reaction of 2-(2-hetaryl)-3-keto-4-chlorobutyronitriles with sodium azide in DMF gives enols of 2-(2-hetaryl)-3-keto-4-azidobutyronitriles, which are converted to the corresponding tetrazoles in high yields under surprisingly mild conditions:



An interesting case of intramolecular cyclization of 4-azidobutyronitrile by the action of nitrosonium tetrafluoroborate was observed by Singh and Biani [137]:

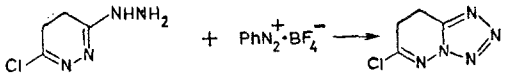


One of the widely used methods for the preparation of 1,5-disubstituted tetrazoles is the Schmidt reaction with ketones [121]. The mechanism of this reaction has been studied thoroughly and can be represented by the scheme



Substituted amides are formed along with tetrazoles in the reaction of ketones with hydrazoic acid. The use of a threefold to fivefold excess of hydrazoic acid and aprotic acids as the catalysts usually promotes the formation of tetrazoles. This method had been previously used chiefly for the synthesis of the simplest 1,5-disubstituted tetrazoles. In recent years, particularly in connection with the extensive study of the chemistry of steroidal ketones [136-142], the Schmidt reaction has been used successfully for the preparation of tetrazoles from progesterone, testosterone [143], and other complex ketones [144]; it has been demonstrated that the most effective catalyst for promoting the formation of tetrazoles is boron trifluoride etherate. Although the use of sulfuric acid as the catalyst in the Schmidt reaction with ketones is less convenient, since it leads to a mixture of substituted amides and tetrazoles, the preparation of tetrazoles in good yields by the method from 1,5,6,7-tetrahydroindol-4-ones [145] and methyl cyclopropyl ketone [146] was recently reported.

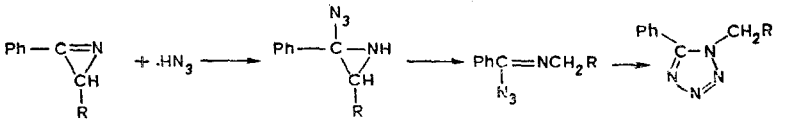
Such methods of synthesis of 1,5-disubstituted tetrazoles as diazotization of heterocyclic derivatives of hydrazine and the addition of hydrazoic acid to imido chlorides differ essentially only with respect to the method of generation of the azido group in the azidoazomethine, which is formed in each of these reactions. Nevertheless, in a number of cases, particularly when the preparation of the imido chloride is difficult, diazotization of hydrazine derivatives is the preferred method. Hydrazino derivatives of pyridine [147], pyridazine [148], quinoxaline [149], triazine [150, 151], and some other nitrogen heterocycles [152-154] are normally used for these ends. Nitrous acid [149-152] or diazonium salts [147, 148] are used as the diazotizing agents. For example, good results were obtained in the diazotization of 3-hydrazino-6-chloropyridazine with benzenediazonium tetrafluoroborate [148]:



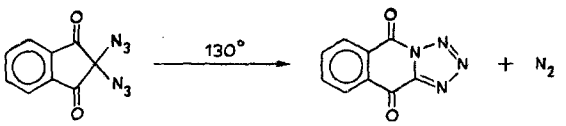
These two methods complement one another well and make it possible to obtain 1,5-disubstituted tetrazoles with the most diverse structures.

Of the previous unknown methods for the preparation of 1,5-disubstituted tetrazoles, one should note the reaction of azirines with hydrazoic acid or iodous azide, the thermolysis of geminal diazides, the addition of iodous azide to unsaturated rings, the condensation of aldehydo ketones with 5-aminotetrazole, and several others.

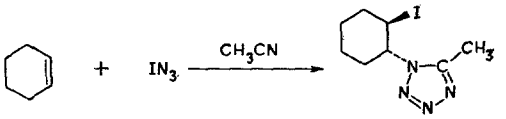
The formation of 1,5-disubstituted tetrazoles from azirines and hydrazoic acid or iodous azide takes place in several steps [155-157]. In the first step the addition of hydrazoid acid to the azirine gives an azidoazirine, the subsequent transformations of which lead to an azidomethine and a tetrazole:



When geminal diazides are heated to 130-150°C, they undergo rearrangement with the formation of 1,5-disubstituted tetrazoles [158, 159]. Thus the corresponding tetrazole is obtained in good yield from 2,2-diazido-1,3-indandione:



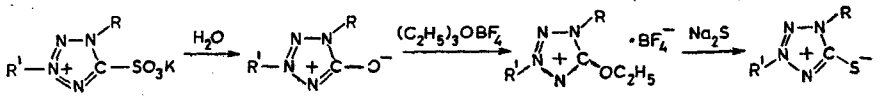
The addition of iodous azide to cyclohexene [160], cyclooctene [162], and other unsaturated rings [163] in solution in acetonitrile proceeds via a trans scheme and leads to the corresponding 1,5-disubstituted tetrazoles:



The condensation of aldehydo ketones with 5-aminotetrazole [163], the reaction of hydrazoic acid with nitrones [112], and the addition of azido chelate cobalt complexes to isonitriles [163] and of phosphimines to α-azidoalkyl isocyanates [165] are also included among the new methods for the synthesis of 1,5-disubstituted tetrazoles. Finally, one must note the reaction of diazonium salts with diacylhydrazines, which is a well-known method for the preparation of 1,5-disubstituted tetrazoles that was recently perfected by I. Ya. Postovskii and V. A. Zyryanov [15].

2,5-Disubstituted Tetrazoles. As compared with the methods for the preparation of 1,5-disubstituted tetrazoles, considerably less study has been devoted to methods for the synthesis of 2,5-disubstituted compounds. A collection of the most widely used methods is presented in a recent review [41]. The chief methods among them are the oxidation of formazans, the reactions of arylhydrazones of aromatic aldehydes with aryl azides and of tosylhydrazones of substituted benzaldehydes with benzenediazonium salts, and the isomerization of isoxazoles and triazoles. It is difficult to form a preference for any one of these methods; however, those such as the isomerization of isoxazoles and triazoles are used less often than the others. At the same time, the reactions of phenylsulfonylhydrazones of benzaldehydes with arene- and hetarenediazonium salts [105, 166] and of arylhydrazones of benzaldehydes with aryl azides [15] have been the subject of study by a number of authors. A large number of substituted 2,5-diphenyltetrazoles were recently obtained by means of these methods [105].

Mesoionic Tetrazoles. The literature data on methods for the preparation of mesoionic tetrazoles through 1975 inclusively have been correlated in an exhuastive review by Ollis and Ramsden [167]. The same authors recently published several reports on the preparation of mesoionic 1,2,3,4-tetrazol-5-ones and 1,2,3,4-tetrazole-5-thiones [168, 169]. Mesoionic 1,2,3,4-tetrazol-5-ones are formed in the hydrolysis of the corresponding sulfo derivatives. Treatment of 1,2,3,4-tetrazol-5-ones with triethyloxonium tetrafluoroborate leads to salts that serve as starting compounds for the preparation of 1,2,3,4-tetrazole-5-thiones.



## Chemical Properties

The chemical properties of tetrazoles are examined in the following order: reactions with retention of the tetrazole ring and transformations that lead to degradation of the heteroring. In the first section we initially present data on reactions involving ring substitution, after which we set forth data on reactions in the side chain. In the second section reactions that are of greatest theoretical and practical interest are analyzed.

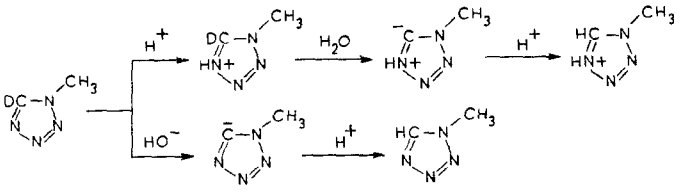
Reactions with Retention of the Tetrazole Ring. Reactions involving substitution in the ring and in the side chain, the alkylation of tetrazoles, and the action of reducing agents are discussed in this section. If the reactivity of the tetrazole ring is evaluated from an index such as the charges on the atoms [9], one should expect that electrophilic reagents should preferably attack the ring $N_1$ and $N_4$ atoms, followed by the $N_2$ and $N_3$ atoms and,

finally, the ring carbon atom. In fact, tetrazoles readily undergo alkylation and acylation at the nitrogen atom and are also protonated when they are dissolved in mineral acids. At the same time, the electrophilic substitution reactions at the carbon atom that are quite common in the aromatic and heterocyclic series (halogenation, nitration, sulfonation, etc.) are completely unknown for tetrazoles or have not been investigated adequately.

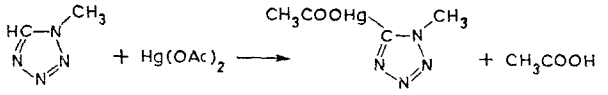
In addition, 5-halotetrazoles and some 1-R-tetrazoles undergo nucleophilic substitution without any special difficulty.

Almost no study has been devoted to the effect of the etrrazole ring on the reactivities of substituents. In most cases reactions in the side chain are not accompanied by anomalous transformations. The specific effect of the tetrazole ring as a substituent has been noted only in the case of nitration of phenyltetrazoles.

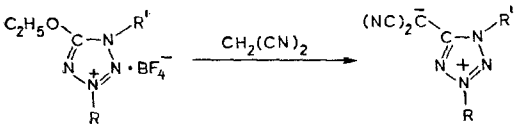
Electrophilic Substitution at the Ring Carbon Atom. The hydrogen atom attached to the ring carbon atom in tetrazole and 1-methyltetrazole is replaced by deuterium when these compounds are refluxed in D20 [38, 170]. Substitution is facilitated by the addition of a base to the reaction medium. A complex dependence of the observed reaction rate constant on the acidity of the medium has been observed in a study of the kinetics of replacement of deuterium by hydrogen in 1-methyl-5-D-tetrazole [170]. When $H_0 = -1.57$, the rate of exchange of deuterium by hydorgen is maximal, after which it decreases markedly as the pH of the medium is increased, reaching a minimum at pH 3-5; it then increases on passing to the alkaline region. These facts can be explained if it is asssumed that substitution occurs via different mechanisms in acidic and alkaline media. The formation of an ylid as an intermediate is postulated in the case of substitution in an acidic medium, whereas a carbanion is the intermediate particle in an alkaline medium:



It might be assumed that the mercuration of 1-R-tetrazoles proceeds via the same mechanism as the replacement of hydrogen by deuterium. It is important to note that a carbanion, which is formed in the rate-determining step of the reaction, is the intermediate in this case. According to the data of the authors of the review, the hydrogen atom attached to the ring carbon atom in 1-methyltetrazole is replaced by an acetoxy group when this compound is refluxed with mercuric acetate in water:

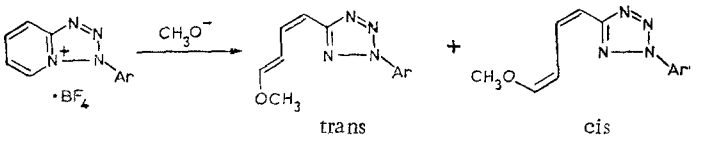


Nucleophilic Substitution. The chlorine atom in 1-phenyl-5-chlorotetrazole is replaced smoothly under the influence of nucleophilic reagents such as alkali metal phenoxides [171-173]. Substitution occurs when the reagents are heated in DMF in the presence of metal hydrides. In recent years this reaction has been used successfully for the identification of alkaloids that contain a phenolic fragment, as, for example, in the establishment of the configuration of gardnerine [171]. In quaternary tetrazolium salts an ethoxy group attached to the ring carbon atom can also be replaced by a nucleophilic reagent such as malonic acid dinitrile [174].



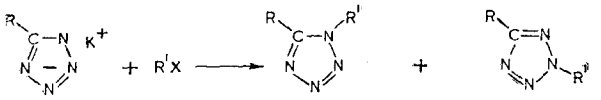
The Smiles rearrangement of 2-(5-tetrazolylthio)-3-aminopyridines is an example of intramolecular nucleophilic substitution at the ring carbon atom [175].

It is interesting that in some 1-aryltetrazoles the tetrazole ring is replaced by an alkoxy group [176]. The possibility of this reaction depends to a considerable extent on the nature of the substituent in the phenyl ring. Thus 5-methyltetrazole is formed in good yield when 1-(p-nitrophenyl)-5-methyl-tetrazole is heated with potassium ethoxide in dimethyl sulfoxide (DMSO). At the same time, 1-phenyl-5-methyltetrazole remains unchanged under these conditions. Sodium methoxide similarly gives rise to the recyclization of 3-aryltetrazolopyridine tetrafluoroborate to give a mixture of stereoisomeric 2,5-disubstituted tetrazoles [177]:



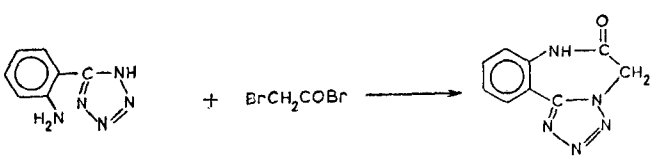

The tetrazole ring in 1-benzoyltetrazole is replaced even more readily; because of this, it is used as an effective benzoylating agent [178].

Alkylation. Isomeric 1- and 2-substituted compounds are formed in the alkylation of salts of tetrazole and 5-substituted tetrazoles with alkyl (aryl) halides and esters of sulfuric and aromatic sulfonic acids [100]:




If the alkylation is carried out at high temperatures and with excess alkylating agent, the reaction products are quaternary tetrazolium salts. Tetrazoles can also be alkylated with diazoalkanes and compounds that contain activated multiple bonds. A peculiarity of the alkylation of tetrazoles is for the formation of two isomers; this is associated with the ambident nature of the tetrazolate anion [9]. The direction and rate of this reaction depend on the nature of the gegenion, the character of the alkylating agent, and the properties of the reaction medium. In addition, the selectivity of the alkylation of 5-substituted tetrazoles is determined to a significant degree by the electronic structure of the substituent attached to the ring carbon atom.

In most cases the alkylation of substituted 5-phenyltetrazoles with alkyl or aryl halides give primarily the 2-substituted compounds, regardless of the properties of the medium. In the alkylation of 5-phenyltetrazoles with bromoolefins [179] and N-(chloromethyl)carbamides [180] the yields of the 2-substituted isomers range from 65 to 76%. Replacement of the alkyl halide by 2,4-dinitrofluorobenzene [181] leads to the formation of the 2-substituted derivatives in quantitative yields. At the same time, on passing from 5-phenyltetrazole to tetrazole [182] the amount of the 1-substituted isomer in the reaction products increases to 87%. The lakylation of the sodium salts of some 5-substituted tetrazoles with the chloro derivatives of ferrocene [183] leads to a mixture of isomers, the composition of which is determined by the nature of the substituent attached to the ring carbon atom. In the case of 5-methyltetrazole the ratio of the 1- and 2-substituted isomers is 3:1, as compared with 1:1 in the case of tetrazole; only the 2-substituted isomer is formed in the alkylation of 5-nitrotetrazole. The alkylation of 5-(o-aminophenyl)tetrazole with bromoacetyl bromide [184] and the electrophilic amination of 5-phenyltetrazole [185] should be noted separately. In the first case 5H-benzo[f]tetrazolo[1,5-d][1,4]diazepin-6(7H)-one is formed as a result of acylation of the amino group in the phenyl ring and subsequent intramolecular alkylation:




The reaction products in the amination of 5-phenyltetrazole with hydroxylamine-O-sulfonic acid are 1- and 2-aminotetrazoles in a ratio of ∿ 1:2.

A great deal of data from investigations of the alkylation of tetrazole and 5-substituted tetrazoles are available. However, only qualitative data on the ratios of the isomers formed as a result of alkylation are presented in most of the papers [184, 186, 187]. The interpretation of such results is also complicated by the fact that the salts of tetrazoles in solvents such as acetone, acetonitrile, and DMF, which are used more often than other solvents in alkylation procedures, can exist in various ionic forms, viz., free ions, solvate-separated and intimate ion pairs, and more complex agglomerates. Thus one cannot predict beforehand which form is the principal participant in the reaction. At the same time, the rate of alkylation and the ratio of the isomeric reaction products depend on these factors.

Important advances in this direction have been made in studies of the kinetics of alkylation of salts of substituted 5-phenyltetrazoles with dimethyl sulfate in acetonitrile [43, 47, 188-190]. The principal results of these studies reduce to the following. When the salts of substituted 5-phenyltetrazoles in solution exist in the form of free ions, the reactive particle is the tetrazolate anion. Despite this, the ratio of the isomeric reaction products depends on the nature of the cation. This is associated with the fact that alkylation proceeds in two steps. In the first rate-determining step an unstable intermediate with a structure of the ion-pair type is formed as a result of the addition of dimethyl sulfate to the tetrazolate anion. Subsequent rapid conversion of the intermediate via two pathways leads to isomeric reaction products. The assumption of the existence of an unstable intermediate is very important, since in this case the role of the cation as a factor that affects the ratio of the isomeric tetrazoles becomes understandable. The fact that the alkylation of 5-substituted tetrazoles takes place in two steps is evidently explained by the peculiarities of the structure of the tetrazolate anion. In contrast to other heterocyclic ambident anions, both reaction centers in the tetrazolate anion, viz., the $N_1$ and $N_2$ atoms, have identical natures. In addition, it follows from quantum-chemical calculations [9] that the aromatic character of the system increases markedly on passing from tetrazole to its anion. The latter fact undoubtedly promotes the formation of an intermediate in the reaction of the tetrazolate anion with an electrophilic reagent.

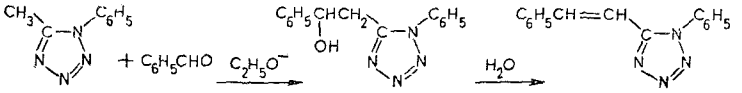
As we have already noted, 1,5- and 3,5-disubstituted tetrazoles can be alkylated to give quaternary tetrazolium salts. In a study of the kinetics of the alkylation of 1- and 2-methyl-5-phenyltetrazoles with dimethyl sulfate in acetonitrile [42] it was shown that the 1-methyl-substituted compounds is alkylated $\sim$ 10 times faster than the 2-substituted isomer. Up until recently it was assumed that in the case of exhuastive alkylation the reaction in all cases takes place at the $N_4$ atom. However, it was recently established that the use of hard alkylating agents makes it possible to obtain a mixture of 1,4,5- and 1,3,5-trisubstituted cations, as, for example, in the alkylation of 1-phenyl-5-R-tetrazoles with dimethyl sulfate and triethyloxonium tetrafluoroborate [191]. The nature of the substituent attached to the ring carbon atom has only a slight effect on the isomer ratio, and the $N_4$ isomer always prevails in the reaction products. At the same time, only 2,4,5-trisubstituted compounds are formed in the alkylation of 2-phenyl-5-R-tetrazoles.

Electrophilic Substitution in the Side Chain. The nitration of 1- and 2-phenyltetrazoles with concentrated nitric acid leads to 1- and 2-(p-nitrophenyl)tetrazoles, respectively [192]. 2-(p-Nitrophenyl)-5-chloromethyltetrazole is obtained in 87% yield from 2-phenyl-5-chloromethyltetrazole under similar conditions [112]. Two products are formed in the nitration of 1,5-disubstituted tetrazoles with nitric acid; for example, the nitration of 1-phenyl-5-styryltetrazole gives 1-(4-nitrophenyl)-5-(4-nitrostyryl)- and 1-(2,4-dinitrophenyl)-5-(4-nitrostyryl)tetrazoles [15]. All authors note that only p-nitro derivatives are formed in the nitration of phenyltetrazoles. This fact is explained either by the peculiarity of the tetrazole ring as a substituent or by the fact that the unprotonated form of the substrate is reactive in nitration.

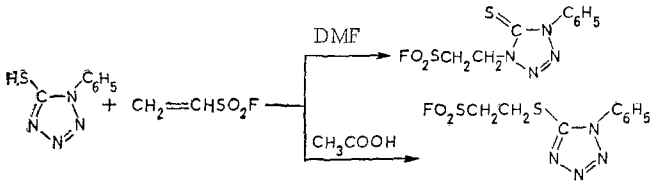
A hydrogen atom of the methyl group in 1-R-phenyl-5-methyltetrazoles is replaced by deuterium when these compounds are dissolved in $CD_3OD$ in the presence of potassium alkoxide [26, 193]; the substitution rate constants correlate with the $\sigma^\circ$ substituent constants ($\rho$ = 3.0). On the basis of an analysis of the kinetic data and the activation parameters it was concluded that the replacement of a hydrogen atom by deuterium proceeds via a carbanion mechanism. Substitution takes place $\sim$ 20 times faster in 1-phenyl-5-methyltetrazole than in the isomeric 2-phenyl-5-methyltetrazole. This once again provides evidence for differences in the reactivities of isomeric 1- and 2-substituted tetrazoles.

The corresponding triazenes are formed by the action of nitrous acids on 5-aminotetrazoles [194, 195], evidently as a result of diazo coupling of the tetrazolediazonium salt with 5-aminotetrazole. Subsequent reduction of the triazenes with, for example, stannous chloride in hydrochloric acid, leads to 5-hydrazinotetrazole.

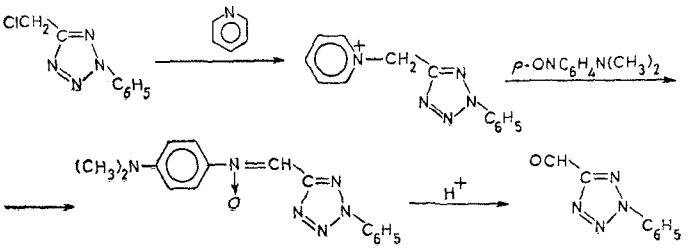
Nucleophilic Addition and Substitution. 5-Hydrazinotetrazoles add smoothly to aliphatic and aromatic aledhydes to give hydrazones [194, 195]. The hydrazones undergo diazo coupling with arenediazonium salts to give tetrazolylformabans, which are valuable in a practical respect [48, 195-197]. In solvents such as DMSO or DMF 1-aryl-5-methyltetrazoles add to aromatic aldehydes in the presence of sodium ethoxide [176]. The resulting unstable hydroxy derivatives are stabilized by splitting out water to give styryltetrazoles:



The reaction of 1-phenyl-5-mercaptotetrazole with epoxides may also serve as an example of nucleophilic addition [198]; stable 5-(β-hydroxyethylthio)tetrazoles are formed in this reaction. At the same time, the addition of ethylenesulfonyl fluoride to 1-phenyl-5-mercaptotetrazole takes place at two centers, and the reaction pathway depends on the nature of the solvent used [199].



The chlorine atom in 2-phenyl-5-chloromethyltetrazole is replaced by nucleophilic reagents such as aliphatic and aromatic amines [200]. The chlorine atom is replaced by iodine (the Finkelstein reaction) and a mercapto group under mild conditions to give the products in good yields [200]. 2-Phenyl-5-chloromethyltetrazole reacts with pyridine to give a pyridinium salt, treatment of which with p-nitroso-N,N-dimethylaniline gives a nitrone. Acid hydrolysis of the latter leads to 5-formyltetrazole (the Krohnke reaction) [201, 202]:



It should be noted that this reaction is still the only method for the preparation of 5-formyltetrazoles.

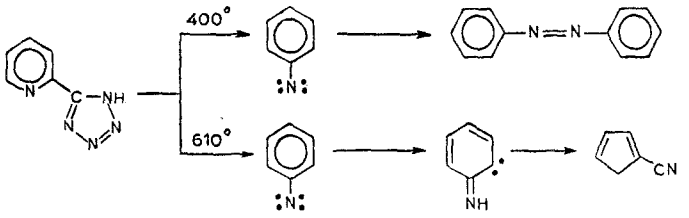
As in the case of ordinary alcohols, the hydroxy group in 2-phenyl-5-hydroxymethyltetrazole is replaced by chlorine when it is treated with thionyl chloride in benzene [201]. 1-Hydroxy-5-R-tetrazoles react smoothly at the hydroxy group with methyl iodide, acyl chlorides, and isocyanates [125, 203]. In reaction with carboxylic acid chlorides 1-R- and 2-R-5-aminotetrazoles behave like ordinary aromatic amines and are converted to the corresponding monosubstituted amides in good yields [204].

The Action of Reducing Agents. The tetrazole ring is usually not affected by reducing agents, including those such as sodium borohydride and lithium aluminum hydride. The selectivity of these reducing agents was recently demonstrated in the case of the reduction of tetrazolo[1,5-b]pyridazine to 5,6,7,8-tetrahydrotetrazolo[1,5-b]pyridazine [205] and of methyl tetrazole-5-carboxylate to the corresponding alcohol [206]. The reduction of tetrazolyltriazenes with stannous chloride leads to the formation of 5-hydrazinotetrazoles in good yields [194, 195].

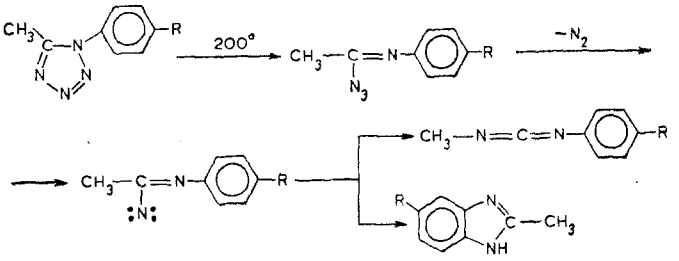
## Reactions Leading to Cleavage of the Tetrazole Ring

The tetrazole ring has rather high thermal and chemical stability. It is cleaved at 250-300°C or when tetrazole or 5-substituted tetrazoles are treated with acylating reagents. In some cases oxidizing agents bring about the degradation of the tetrazole ring. The fragmentation of tetrazoles at high temperatures or under the influence of acylating reagents can be used in a number of cases as a convenient method for the preparation of some nitrogen-containing heterocycles, particularly 1,3,4-oxadiazoles.

Thermolysis. The thermal stability of tetrazoles depends on the nature of the substituents and their position in the ring. In most cases substituted tetrazoles are thermally stable up to 26-.C. Azobenzene is formed in the high-temperature (400°C) pyrolysis of 2-(S-tetrazolyl)pyridine, in which phenylnitrene is the intermediate particle. The transformation is even more complex if thermolysis is carried out at 610°C [207].




When 6-methyltetrazolo[1,5-a]pyridine is heated to 465°C, it also produces phenylnitrene as an intermediate, the subsequent transformations of which lead to a mixture of isomeric methylcyanopyrroles [208]. At the same time, solid tetrazolediazonium chloride undergoes decomposition to carbon and nitrogen even at 110°C [209]. The products of the thermal decomposition of 1,5-disubstituted tetrazoles are carbodiimides and benzimidazoles [210, 211]. The mechanism of this reaction was recently studied by derivatography and mass spectrometry in the case of several substituted 1-phenyl-5-methyltetrazoles [89]. The thermolysis of 2,5-disubstituted tetrazoles takes place in several steps. An imidazide is formed in the first step. The loss of a nitrogen molecule by the imidazide leads to a nitrene, which is converted to a benzimidazole and a carbodiimide:

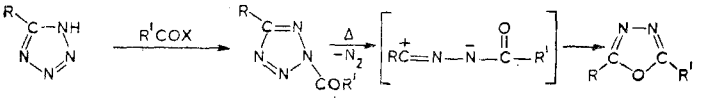



Nitrenes are also formed as intermediates in the photolysis of 1,5-disubstituted tetrazoles [212]. An unusual case of the pyrolysis of 1-phenyl-5-methylsulfonyltetrazole in the presence of phenylhydrazine has been described: 1-arylamino-2-phenyl-3-alkylsulfonylguanidine is formed as a result of a complex reaction [213].

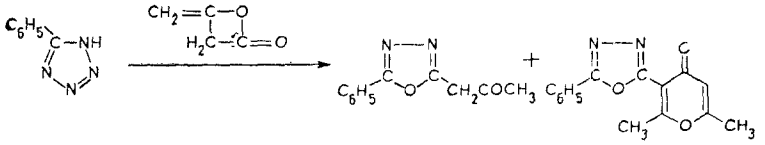
2,5-Disubstituted tetrazoles undergo thermal decomposition at 180-200°C with the evolution of nitrogen. The corresponding nitrilimines are intermediates in the thermolysis. If the reaction is carried out in the presence of compounds that contain multiple bonds, five-membered heterocycles with various structures can be obtained in this case. The composition of the products of the thermolysis of 2,5-disubstituted tetrazoles depends to a considerable extent on the reaction temperature. 3-Arylindazoles are formed in 96-100% yields when 2,5-diaryltetrazoles are heated to 400-500°C. The same products are obtained if the thermolysis is carried out at 200°C in tetralin. However, fluorenes are formed from 2,5-diaryltetrazoles at 800°C [214]. The intramolecular cyclization of the nitrilimines that are formed in the thermolysis of some 2,5-disubstituted tetrazoles leads to the formation of annelated tetrazoles [215].

It is interesting that migration of a phenyl group from the 2 position to the 1 position of the ring rather than degradation of the tetrazole ring occurs when 2,3-diphenyl-5-tetrazolylthiolate or 2,3-diphenyl-5-tetrazolylolate is heated to 150°C [216].

Acylation. Tetrazole and 5;substituted tetrazoles are converted to 1,3,4-oxadiazoles under the influence of acylating agents [100]. The first

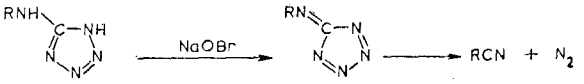


step gives rise to the formation of a 2-acyl derivative of tetrazole, which upon heating is cleaved to give an acylnitrilimine. Cyclization of the latter leads to an oxadiazole. However, the possibility that the formation of oxadiazoles takes place via a synchronous mechanism is not excluded, since direct evidence for the existence of an acylnitrilimine is not available. Anhydrides [217] or chlorides [218] of carboxylic acids are ordinarily used in acylation. In the case of free carboxylic acids the reaction is carried out in the presence of dicyclohexylcarbodiimide [219]. Other acylating agents such as diketene (for the acylation of 5-phenyltetrazole) have also been used [220]. In this case the reaction is a more complex process than is normally the case, and 3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2,6-dimethylpyrone is formed along with 2-acetonyl-5-phenyl-1,3,4-oxadiazole:



Nevertheless, the acylation of tetrazoles can be recommended as a simple method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles, particularly when other methods are ineffective.

Oxidative Cleavage. The tetrazole ring has high stability with respect to oxidizing agents. Oxidative degradation of the substituents without involvement of the tetrazole ring is observed when substituted tetrazoles are treated with potassium permanganate, chromic anhydride, or dilute nitric acid [100]. However, when amino-substituted 5-aminotetrazoles are subjected to oxidation, the tetrazole ring is cleaved. For example, the oxidation of 5-(alkylamino)tetrazoles with sodium hypobromite or lead tetraacetate leads to the formation of isonitriles; the corresponding Schiff base is the intermediate in this reaction [221]:



Finally, one's attention is directed to the interesting case of the photochemical oxidation of 2,5-diphenyltetrazole, which proceeds with cleavage of the tetrazole ring and the formation of 2,4,5-triphenyl-1,2,3-triazole [222].

## Application of Tetrazoles

The most serious advances involve the application of tetrazoles in medicine. One of the first medicinal preparations based on tetrazole, which has been widely used, was cyclopentamethylenetetrazole (Corazole), which is a stimulant with cardiac activity. New semisynthetic antibiotics of the cephalosporin type [2, 223-225], such as the sodium salt of 3-{[(5-mechyl-1,3,4-thiadiazol-2-yl)thio]methyl}-7-[2-(1H-tetrazol-1-yl)acetamido]-3-cepheme-4-carboxylic acid, which are more active than antibiotics of the penicillin series with respect to staphylococcus aureus and other strains of streptococci, have proved to be extremely effective. The semisynthetic antibiotic cephothiam, which is also obtained from tetrazole [225], is even more nearly ideal. In the last decade antibiotics of the cephalosporin series have been tested thoroughly and are widely used in medical practice. Compounds that have antiphlogistic [226, 227], anesthetizing, diuretic [228], and antiallergenic [229, 230] activity and also regulate fat metabolism [] have been found in the tetrazole series.

Tetrazoles have found application in biochemistry and biology [3, 231]. For example, 1-arylsulfonyltetrazoles are used as highly effective condensing agents in the synthesis of polynucleotides [232]. Methods for the practical utilization of tetrazoles in agriculture have been contemplated in recent years [4, 233]. Thus esters of 2-tetrazolylacetic acids, particularly the preparation RR-529, are used as regulators of the growth of fruit plants.

New polymeric materials [5], particularly polymers that have increased thermal stability [234], have been obtained on the basis of tetrazoles.

Many tetrazoles are used as reagents in analytical chemistry. Of these, one should primarily cite 1-(5-tetrazolylazo)-2-naphthol [235] and bis(4-sodio-5-tetrazolylazo)ethyl acetate [236]. Good results have been obtained when tetrazolium salts are used in paper and thin-layer chromatography (TLC) [237]. Salts of 5-nitro- and 5-nitroaminotetrazoles are recommended for use as explosive substances [238-240], and 5-trifluoromethyltetrazole is used in laser technology [241]. Reports concerning the use of complexes of metals with tetrazolylformazans as catalysts for the oxidation of mercaptans [242] and the antioxidant activity of N-tetrazolyl-containing leucoverdazyls [243] have been published recently. It is noted that these compounds are among the strongest inhibitors of the oxidation of hydrocarbons.

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