4-(p-Methoxyphenyl)-7-methyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (IIIc). A 1.64 g (5 mmole) sample of VIII was hydrogenated at room temperature and normal pressure in the presence of Raney nickel. The precipitate was removed by filtration and washed on the filter with chloroform. The solvent was removed, and the residual benzodiazepinone IIIc was chromatographed on aluminum oxide (elution with chloroform) to give a product with mp 222°C (from alcohol). The yield was 0.8 g (57%). Found: C 72.6; H 5.4%. $C_{17}H_{19}N_2O_2$. Calculated: C 72.8; H 5.7%.

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ISOTOPIC HYDROGEN EXCHANGE IN 1- AND 2-ARYL-5-METHYLTETRAZOLES

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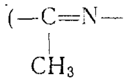
The rate constants for basic deuterium exchange of the methyl group (k_D) in 2-phenyl-5-methyltetrazole (I) and 1-aryl-5-methyltetrazole (II) and its derivatives with a polar substituent (R) in the phenyl ring were measured. The increased CH acidity of II as compared with I [k_D(II)/k_D(I) ~20] is in agreement with the calculated and experimental values regarding the character of the electron-density distribution in the molecules. The effect of R on the rate of deuterium exchange of the methyl group correlates with the σ° constants ($\rho = 3.0$, $r = 0.997$). The results of measurement of the kinetic isotope effect during deuterium (tritium) exchange in II (k_D/k_T ~1.8) are discussed in connection with the peculiarities of the stepwise reaction mechanism.

Up until recently little was known regarding the reactivities of methyl derivatives of tetrazole. The methyl group in 1-phenyl-5-methyltetrazole does not undergo the condensation with benzaldehyde that is characteristic for compounds with a methyl group attached to a ring azomethine group  $(-\underset{CH_3}{\underset{|}{C}}=N-)$, even under rather severe conditions in the presence of zinc chloride [1]. In our experiments we were unable to obtain a product of condensation of 1-(4-nitrophenyl)-5-methyltetrazole with p-nitrobenzaldehyde either in alcohol in the presence of sodium alkoxide or in acetic anhydride. However, 1-phenyl-5-methyltetrazole reacts with diethyl oxalate to give pyruvic acid derivatives [1]. Quantitative data on the lability of the hydrogen atoms of the methyl group are limited to the results of measurements of the rate of deuterium exchange of 1-phenyl-5-methyltetrazole in an alcohol solution of potassium ethoxide [2]. In the present research we made a comparative study of the effect of structural factors on deuterium exchange in a number of 5-methyltetrazole derivatives (I-VII):

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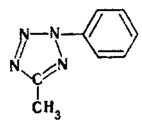

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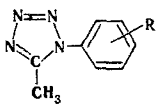

II–VII

II R=H; III R=4-OCH$_3$; IV R=4-Cl; V R=3-Cl; VI R=4-NO$_2$; VII R=3-NO$_2$

The kinetics of deuterium exchange in an alcohol solution of potassium alkoxide were studied. The conditions under which the reaction was carried out and the results of the kinetic measurements are presented in Table 1.

The results make it possible to draw the conclusions listed below.

1. The rate of exchange of the hydrogen atoms of the methyl group in II is higher by a factor of ~20 than in the case of tetrazole I. This is in agreement with the data on the electron-density distribution in the methyl derivative of tetrazole. The electron charges on the ring α-carbon atom and on the hydrogen atoms of the methyl group calculated by the CNDO/2 (complete neglect of differential overlap) method are higher for II ($\Delta q_{\alpha\text{-C}} = 0.1629$, $\Delta q_H = 0.0271$) than for I ($\Delta q_{\alpha\text{-C}} = 0.1570$, $\Delta q_H = 0.0225$). The q_H values for 5-methyltetrazoles satisfy the general relationship between the logarithms of the relative rate constants for deuterium exchange and the electron charges (q_H) that was previously established for a series of five-membered aromatic heterocycles [3].

The results of a study of the IR spectroscopic parameters of the methyl groups in tetrazoles confirm the above conclusion: Higher intensity of the band of the C–H symmetrical stretching vibration is observed for the methyl group in I [$(A_{CH}{}^{S})^{1/2} = 20.4$] than for tetrazole II [$A_{CH}{}^{S})^{1/2} = 15.8$].

It has been established [2, 4] that the electronic effect of several heteroatoms on the spectral and kinetic characteristics of the methyl groups in azoles with diverse structures is determined, as a rule, by the sum of additive contributions made by the individual heteroatoms or substituents; the possibility of examination of methyl derivatives of five-membered heteroaromatic compounds in a single reaction series with substituted toluenes and six-membered nitrogen heterocycles was also demonstrated. According to [2], the data on the exchange capacities of the methyl groups in five- and six-membered aromatic heterocycles satisfy the correlation expression*

$$\log k_{25^\circ} = -15.9 + 7.6\Sigma\sigma^-(\sigma^\circ). \qquad (1)$$

With allowance for the peculiarities of the mechanism of transmission of the electronic effects that are specific for five-membered heterocycles [2], the effect of the four nitrogen heteroatoms on the CH-acid center in methyltetrazoles I and II can be characterized by the sum of the corresponding σ^- and σ° constants ($\sigma^-_{2\text{-N}} = 1.0$, $\sigma^\circ_{2\text{-N}} = 0.8$, $\sigma^\circ_{3\text{-N}} = 0.5$, $\sigma^\circ_{4\text{-N}} = 0.7$, $\sigma^-_{2\text{-N(R)}} = -0.1$, and $\sigma^-_{3\text{-N(R)}} = -0.6$) [2, 5]. The application of expression (1) to the methyl derivatives of tetrazole shows that the deuterium-exchange rate constants calculated from an additive scheme for I [$\Sigma\sigma^-(\sigma^\circ) = 1.7$] and for II [$\Sigma\sigma^-(\sigma^\circ) = 2.1$] are three to five orders of magnitude higher than the experimental values. The reasons for this are not completely clear. The steric effect of the phenyl ring on the adjacent methyl group in tetrazole II is not of decisive significance, since no appreciable changes in the exchange capacities of the methyl group in the 2 position were observed in control experiments that we carried out in the case of deuterium exchange of 1,2-dimethylimidazole (VIII) and 1-phenyl-2-methylimidazole (IX) (the deuterium-exchange rate constants for VIII and IX at 105°C in a 0.57 N solution of potassium ethoxide in d$_1$-ethanol are, respectively $1.3 \cdot 10^{-5}$ sec^{-1} and $1.5 \cdot 10^{-5}$ sec^{-1}). One cannot exclude the possibility that the σ constants used, which were estimated from data on the reactivities of six-membered nitrogen heterocycles, i.e., compounds with distinctly expressed basic properties ($pK_a \sim 5$), are not always suitable for the quantitative description of the electronic effects of several nitrogen heteroatoms in tetrazoles and related compounds in which the basic properties are manifested extremely weakly ($pK_a < -2$) [6]. In fact, the constants determined in the indicated way may at least in part contain contributions due to specific solvation of the nitrogen heteroatom by the solvent molecules. It is known that the role of this effect in the changes in the relative reactivities of nitrogen-containing compounds is extremely large [5, 7]. In particular, the ability of the nitrogen heteroatom in pyridine and its derivatives to manifest a resonance effect is determined to a considerable extent by specific solvation [7].

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* The rate constants for deuterium exchange pertain to a 0.57 N solution of potassium ethoxide in d$_1$-ethanol.

TABLE 1. Kinetics of Deuterium Exchange in the Methyl Groups of 5-Methyltetrazoles

Compound	R	Medium[a]	Temp., °C	$k \cdot 10^5$, sec^{-1}	$-\lg k$ 25°[b]	δ_{CH_3}, ppm
I	H	A (0,6 N)	50	1,7	6,5	2,64
II	H	A (0,1 N)	50	6,0	5,0	2,62
		B (0,1 N)	25	0,93[c, d]		
			35	3,9		
			50	22,0		
III	4-OCH_3	B (0,1 N)	30	0,62[d]	5,7	2,57
			40	2,0		
			55	11,0		
IV	4-Cl	B (0,1 N)	15	0,76[d]	4,6	2,59
			25	2,7		
			35	8,1		
V	3-Cl	B (0,1 N)	25	2,3	4,6	2,62
VI	4-NO_2	B (0,005 N)	25	5,3	3,0	2,72
VII	3-NO_2	B (0,005 N)	25	4,3	3,1	2,69

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[a] The following symbols were adopted: A = $CD_3OK + CD_3OD$, and B = $C_2H_5OK + C_2H_5OD$ (the concentration of the base is indicated in parentheses). [b] In a solution of 0.1 N $C_2H_5OK + C_2H_5OD$. [c] From the data in [2]. [d] Activation parameters [E (kcal/mole), log A]: II 25.0, 13.2; III 22.6, 11.4; IV 20.9, 10.8.

The fact that the local spectroscopic parameters of the methyl group (A_{CH} and δ_{CH_3}) measured in an inert solvent (CCl_4) are subject to the additivity rule [4] also provides evidence in favor of the conclusion that the deviations noted are influenced by solvation.

2. The effect of the substituents in the phenyl portion of the molecules on the rate of deuterium exchange of the methyl group in the 1-(R-aryl)-5-methyltetrazole series is satisfactorily conveyed by correlation expression (2), which, despite the incomplete coplanarity of the molecules [8], shows the presence of conjugation between the tetrazole and aryl fragments :

$$\log k = -5.3 + 3.0\sigma^{\circ} \quad (r = 0.9967;\ n = 6) \tag{2}$$

By comparing the sensitivity constants (ρ) in expressions (1) and (2) one can estimate the magnitude of the bridge effect, which is characterized in this case by a transmission coefficient of 0.36.

A comparison of the kinetic data obtained in this research with the results in [6] shows that there is a definite correlation between the trend of the change in the kinetic CH-acidity and the basic dissociation constants. However, in contrast to the deprotonation reaction that we studied, the effect of substituent R on the basic properties of the tetrazole molecules proceeds via an induction mechanism according to [6].

3. The rates of the exchange reactions of I-VII are comparable to the rates of deuterium exchanges in six-membered nitrogen heterocycles with "active" methyl groups (4-methylpyridine, 2- and 4-methylquinoline, etc.) [5]. However, in contrast to the latter, which readily undergo condensation with aldehydes, diazonium salts, etc. [9], the investigated methyltetrazoles I-VII are inert with resepct to electrophilic reagents.

To determine the peculiarities of the stepwise reaction mechanism more precisely we measured the kinetic isotope effect (KIE) in the case of deuterium (tritium) exchange of deuterium- and tritium-substituted 1-phenyl-5-methyltetrazole with a 0.1 N solution of potassium methoxide in methanol. The relatively high KIE ($k_D/k_T \sim 1.8$ at 45°C) provides a basis for the conclusion that as in the case of other methyl derivatives of aromatic heterocycles [5], the exchange reaction of methyltetrazoles proceeds via a carbanion mechanism and that the step involving fragmentation of the C–H bond to give the carbanion is the rate-determining step. The absence of a correlation between the CH-acid properties and the reactivities in electrophilic condensation may be a consequence of both the inadequate comparability of the conditions under which the processes under the comparison were carried out and the fact that the course of the condensation reactions may be determined not only by the rate of cleavage of the C–H bond but also by the conditions that determine the possibility of subsequent reaction of the resulting carbanion with the electrophilic agent.

EXPERIMENTAL

Compound I was obtained by the reaction of acetaldehyde phenylhydrazone with 2,4,6-tribromophenyl azide [10]. The Dimroth method, which is based on the reaction of the corresponding arenediazonium salts with a diacylhydrazine [11], was used for the synthesis of II-VII. The individuality of the compounds was confirmed by elementary analysis, thin-layer chromatography (TLC) [Silufol UV-254, chloroform–alcohol (13:0.5)], and the PMR spectroscopic data (the data are presented in Table 1; the spectra were recorded with a Perkin–Elmer R-12B spectrometer from $CDCl_3$ solutions relative to hexamethyldisiloxane). The method used to study the exchange reaction was described in [12]. In the isotopic exchange of I and II with a solution of potassium methoxide in deuteromethanol (CD_3OD) the percentage of deuterium was determined by PMR spectroscopy from the change in the integral intensity of the signal of the protons of the methyl group. In the case of deuterium exchange in a solution of potassium ethoxide in ethanol (C_2H_5OD) the isotopic analysis of I-VII was accomplished by IR spectroscopy from the change in the extinction coefficients of the bands of the deformation vibration of the methyl group at 1090 and 1415 cm^{-1}. The tritium activity was measured by a scintillation method.

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