resulting solution was extracted with chloroform, the extract was evaporated, and the residue was chromatographed on a column of Al_2O_3 (elution with acetone). The fraction with R_f 0.75 was collected; 0.75 g (86%) of (IXa).

D. Following procedure C, but using 0.77 g (6 mmoles) of dimethyl sulfate instead of CH_3I, 0.63 g (73%) of (IXa) was obtained.

LITERATURE CITED

1. V. D. Orlov, S. M. Desenko, K. A. Potekhin, and Yu. T. Struchkov, *Khim. Geterotsikl. Soedin.*, No. 2, 229 (1988).
2. A. A. Krauze, É. É. Liepin'sh, Yu. É. Pelcher, Z. A. Kalme, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 1, 75 (1987).
3. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, *NMR Spectroscopy in Orgnaic Chemistry* [in Russian], Khimiya, Leningrad (1983).
4. V. K. Lusis, D. Kh. Mutsenietse, A. Z. Zandersons, I. B. Macheika, and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, No. 3, 393 (1984).
5. A. A. Potekhim (ed.), *Properties of Organic Compounds. Handbook* [in Russian], Khimiya, Leningrad (1984).

SELECTIVE $N_{(2)}$ ALKYLATION OF TETRAZOLE AND 5-SUBSTITUTED TETRAZOLES BY ALCOHOLS

A. O. Koren' and P. N. Gaponik

UDC 547.796.1

Alkylation of tetrazole and its 5-substituted derivatives by 5-tert-butyl, isopropyl, and cyclohexyl alcohols in concentrated H_2SO_4 results in high yields of the corresponding 2-alkyltetrazoles alone, irrespective of electronic properties and size of the substituent at the 5-position of the tetrazole ring. The tert-butylation of tetrazole in phosphoric acid results in the formation of a mixture of isomeric 1- and 2-substituted derivatives, the concentration of the 1-isomer increasing with decrease in the concentration of the acid in the mixture.

Alkylation is one of the main methods of the synthesis of N-substituted tetrazoles. Up to the present time the alkylation of salts of tetrazoles by alkyl halides and alkyl sulfates, which generally results in a mixture of isomeric 1- and 2-substituted tetrazoles has been most extensively studied [1]. Practically all the described cases of selective alkylation of tetrazoles at the $N_{(2)}$ atom involve steric hindrances to the approach to the reaction center at $N_{(1)}$ and/or the presence of a strong electron-acceptor group at the 5-position of the tetrazole ring [1, 2]. The reactions of tetrazoles with other alkylating agents and in other media (neutral, acidic) have been studied to a considerably lesser extent.

In [3-5] was described the alkylation of a series of tetrazoles with α-ferrocenyl alcohols in acetic and trifluoroacetic acids, also leading to the formation of a mixture of isomeric 1- and 2-substituted derivatives in the absence of a bulky aryl substituent, or a strong electron-acceptor (NO_2) at the 5-position of the tetrazole ring. Using the α-ferrocenylalkylation of tetrazole as an example, it was shown that on transition from acetic to trifluoroacetic acid, i.e., when the acidity of the medium is increased, the proportion of the 1-isomer in the mixture substantially increases [4].

Scientific-Research Institute of Physicochemical Problems, V. I. Lenin Belorussian State University, Minsk 220080.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1643-1647, December, 1990. Original article submitted May 15, 1989.

0009-3122/90/2612-1366$12.50

TABLE 1. Characteristics and Preparation Conditions of 2-Substituted Tetrazoles

Compound	Empirical formula	R	R'	Bp, °C (mm, Hg)	n_D^{20}	PMR spectrum, δ, ppm		Conc. H_2SO_4, %	Duration of reaction, min	Yield, %
						R	R'			
I	$C_5H_{10}N_4$	*t*-Bu	H	67 (20)	1,4404	1,73 (9H, s)	8,66 (1H, s)	96	40	85
								85	40	80
								75	40	82
								65	40	79
II	$C_4H_8N_4$	*i*-Pr	H	59 (17)	1,4388	1,62 (6H, d, J=6,6 Hz CH_3); 5,13 (1H, sept. J=6,6 Hz., CH)	8,64 (1H, s)	96	70	80
III	$C_7H_{12}N_4$	*cyclo*-C_6H_{11}	H	79 (2)	1,4860	1,35...2,20 (10H, m, $(CH_2)_5$); 4,81 (1H, m, CH)	8,67 (1H, s)	96	50	94
IV	$C_6H_{12}N_4$	*t*-Bu	Me	74 (17)	1,4447	1,70 (9H, s)	2,44 (3H, s)	96	30	97
								85	30	96
V	$C_{11}H_{14}N_4$	*t*-Bu	Ph	90 (0,1)	1,5337	1,78 (9H, s.)	7,46...7,56 (3H, m, *m*-, *p*-H); 8,08...8,18 (2H, m, *o*-H)	96	30	100
VI		*t*-Bu	NH_2	—*		1,62 (9H, s)	5,28 (2H, s)	96	40	90
VII	$C_9H_{19}N_5$	*t*-Bu	$CH_2CH_2NMe_2$	68 (0,1)	1,4592	1,68 (9H, s)	2,20 (6H, s, Me) 2,63 (2H, t, J=7,8 Hz NCH_2); 2,95 (2H, t, J=7,8 Hz., CH_2)	96	30	98
VIII	$C_8H_{17}N_5$	*i*-Pr	$CH_2CH_2NMe_2$	65 (0,1)	1,4596	1,57 (6H, d, J=6,6 Hz, CH_3); 5,03 (1H, sept. J=6,6 Hz CH)	2,20 (6H, s, Me) 2,63 (2H, t, J=7,8 Hz, NCH_2); 2,95 (2H, t, J=7,8 Hz, CH_2)	96	70	96
IX	$C_6H_9F_3N_4$	*t*-Bu	CF_3	56 (13)	1,3855	1,79 (9H, s)**	—	96	40	92

*Mp 115-116°C; according to the data in [8], mp 116-117°C.

**^{13}C NMR spectrum: 156.6 (q, $^2J_{CF}$ = 40.2 Hz, C_{ring}), 118.8 (q, $^1J_{CF}$ = 269.7 Hz, CF_3), 66.1 (s, NC), 29.4 (q, J_{CH} = 124.8 Hz, CH_3).

Taking into account the weak basic properties of the tetrazole ring and its high stability to the action of mineral acids [1], we undertook in the present work the study of the alkylation of tetrazole and 5-substituted derivatives by alcohols in a highly acid medium, ensuring the practically complete protonation of the tetrazole ring, and thus eliminating the possibility of the presence of tetrazoles both in the form of tetrazolate anions and in a nonprotonated form. As such a medium we selected H_2SO_4, which in this reaction plays the additional role of a universal solvent and water binding agent.

It was found that the reaction of tetrazoles with alcohols having a structure promoting to a certain extent the stabilization of carbenium ions formed from them (tert-butyl, isopropyl, cyclohexyl) proceeds successfully at room temperature in concentrated H_2SO_4. In all cases, irrespective of the character and size of the substituent at the 5-position of the tetrazole ring, only one of the two possible isomers was obtained (see Table 1), as indicated by the TLC and PMR spectroscopic data. All the N-alkyltetrazoles obtained were assigned to 2-isomers.

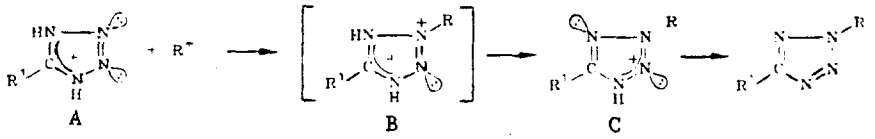
From the characteristic proton signals of the substituents at the 5-position in the PMR spectra, tetrazoles I-VI (see Table 1) were assigned to 2-substituted compounds. Thus, the chemical shifts of protons at the ring carbon atom (5-H) of monosubstituted tetrazoles I-III lie within 8.64-8.67 ppm; under identical conditions, the corresponding signals of 1-alkyltetrazoles are located in a weaker field (9.1-9.3 ppm) [3, 6]. Similar patterns, characteristic for 1- and 2-methyl derivatives of 5-methyl- and 5-aminotetrazoles [7], made it possible to identify the compounds IV and VI structurally similar to them. In the PMR spectrum of tetrazole V, the signals of the phenyl protons are represented in the form of two isolated multiplets, which is particularly characteristic of the 2-isomer and indicates its interannular conjugation [1, 7]. The coincidence of the physical constants of tetrazole VI with those given in [8] also confirms the correctness of the assignments made. Moreover, the corresponding 1-isomers for tetrazoles III-VI are already known [8-10], while 1-tert-butyltetrazole, isomeric to compound I, was synthesized by us according to the method given in [11]. Comparison of the physicochemical and spectral characteristics of these compounds and compounds I, III-VI with taking into account the known regularities [1, 2, 7, 8] also shows that the latter are in fact 2-substituted tetrazoles.

Tetrazoles VII and VIII were assigned to the 2-isomers since the corresponding 2-alkyl-5-vinyltetrazoles with characteristic proton signals of the vinyl group (trans, cis, gem) in the PMR spectra: 5.62, 6.28, 6.80 ppm were obtained from them on deamination. For comparison, we cite the same signals of 2-methyl-5-vinyltetrazole at 5.63, 6.33, 6.82 ppm, and of 1-methyl-5-vinyltetrazole – at 5.93, 6.40, 6.69 ppm [12].

Compound IX was identified as the 2-isomer on the basis of a comparison of the chemical shift of the ring carbon atom in the ^{13}C NMR spectrum (156.6 ppm) with the chemical shifts of the corresponding atoms in 2-methyl-5-trifluoromethyltetrazole (157.2 ppm) and 1-methyl-5-trifluoromethyltetrazole (146.3 ppm) synthesized by the method in [7].

The absence of isomerization of 1-substituted derivatives into 2-substituted ones during contact with H_2SO_4, as found by special experiments using 1-tert-butyltetrazole as an example, indicates that, in a strongly acid medium, the tetrazoles are selectively alkylated at the 2-position of the ring. This process can be outlined as follows. It is known that tetrazoles are Hammet bases [13], and under the conditions of this reaction (96% H_2SO_4, $H_0 = -9.9$) are practically completely protonated. The protonation takes place at the $N_{(4)}$ atom [13] with the formation of tetrazolium cations with a symmetrical structure (A), which is confirmed by the presence of not more than two signals in the ^{15}N NMR spectrum of a solution of 1.52 moles/liter of 5-methyltetrazole in 84.4% H_2SO_4 [230.8 ($N_{(1)}$, $N_{(4)}$; 361.6 ppm ($N_{(2)}$, $N_{(3)}$)]. The complete symmetry of the tetrazole ring protonated at the $N_{(4)}$ atom was also shown by quantum chemical calculation of the tetrazolium cation [14], whereby in the latter the multiplicity indices of the $N_{(1)}$–$N_{(2)}$ and $N_{(3)}$–$N_{(4)}$ bonds are practically equal to unity, while the multiplicity index of the $N_{(2)}$–$N_{(4)}$ bond (1.82) is even higher than that of the nonprotonated tetrazole (1.75).

The carbocation R^+, formed during the protonation and dehydration of alcohol ROH molecule, attacks a tetrazolium cation (A) either at the unshared electron pair of the $N_{(2)}$ atom (or, which is in effect the same, $N_{(3)}$) or at the π-bond between them, followed by localization at $N_{(2)}$ or $N_{(3)}$:



A B C

The intermediate (B) obtained is stabilized by the elimination of a proton, possibly from the position neighboring R, forming a 2-substituted tetrazole protonated at $N_{(4)}$ (C), which is deprotonated when the acidity of the medium decreases (dilution of the reaction medium with water).

The fact that the selective alkylation at the $N_{(2)}$ atom is caused by the complete protonation of the tetrazole ring is confirmed by the results of tert-butylation of tetrazole ($pK_{BH} = -2.70$ [13]), carried out by the same method in 87 and 71% phosphoric acid (H_0 –3.7 and –2.3, respectively). In both cases, in the spectra of the reaction products, the 5-H proton signals were recorded not only of the 2-isomer (8.66 ppm), but also of the 1-isomer (9.15 ppm). The ratio of the isomeric 2- and 1-tert-butyltetrazoles, estimated from the integral intensity of these signals, is ~15:1 in the first case and ~5:1 in the second, which corresponds to the decrease in the degree of protonation of the initial tetrazole with decrease in the acidity of the medium. Experiments on the tert-butylation (see Table 1) showed that with decrease in the concentration of H_2SO_4 the isomeric homogeneity of the reaction products is retained as a result of fairly high H_0 values.

EXPERIMENTAL

The PMR spectra were obtained on a JEOL JNM-PS-100 spectrometer, using solutions in acetone-D_6 and HMDS as internal standard. The ^{13}C and ^{15}N NMR spectra were recorded on a Bruker WM-360 spectrometer with working frequencies of 90.56 and 36.50 MHz, respectively. For the ^{13}C NMR spectroscopy solutions in $CDCl_3$ were used. The chemical shifts of the ^{15}N nuclei were measured as recommended in [15], relative to external standard (nitromethane, $\delta_N = 380.23$ ppm) and are given with reference to anhydrous liquid ammonia at 25°C ($\delta_N = 0$ ppm). Tetrazole and substituted tetrazoles were obtained by known methods; the properties of the compounds corresponded to the data in [16-19].

The results of the elemental analysis for C, H, N correspond to the calculated data.

1-tert-Butyltetrazole ($C_5H_{10}N_4$), mp 37-38°C; bp 105°C (1 mm Hg). PMR spectrum: 9.15 (1H, s, CH); 1.70 ppm (9H, s, t-Bu).

General Method for the Preparation of Tetrazoles I-IX. A 27.5 mmole portion of the alcohol was added dropwise, with stirring over a period of 10 min, to a solution of 25 mmoles of tetrazole or a 5-substituted tetrazole in 17-18 ml of an acid, while maintaining the temperature at 20-25°C. The reaction mixture was stirred for 20-60 min, and then poured into 100 g of ice water and extracted with methylene chloride (4 × 25 ml). The combined extract was washed with 10 ml of water, 10 ml of a 3% Na_2CO_3 solution, 10 ml of water, and dried over anhydrous $MgSO_4$. In the case of aminotetrazoles VI-VIII, the reaction mixture after the dilution was neutralized with 110 g of a 25% NaOH solution with cooling, extracted with benzene (6 × 25 ml), and the combined extract was dried over anhydrous K_2CO_3. The solvent was evaporated and the residue was distilled in vacuo.

LITERATURE CITED

1. G. I. Koldobskii, V. A. Ostrovskii, and V. S. Poplavskii, *Khim. Geterotsikl. Soedin.*, No. 10, 1299 (1981).
2. F. R. Benzon, *Heterocyclic Compounds*, R. Elderfield (ed.) [Russian translation], Vol. 8, Mir, Moscow (1969), p. 7.
3. A. V. Sachivko, V. P. Tverdokhlebov, and I. V. Tselinskii, *Zh. Org. Khim.*, **22**, 206 (1986).
4. A. V. Sachivko, V. P. Tverdokhlebov, and I. V. Tselinskii, *Zh. Org. Khim.*, **22**, 1112 (1986).
5. I. Yu. Shirobokov, A. V. Sachivko, V. P. Tverdokhlebov, V. P. Ostrovskii, I. V. Tselinskii, and G. I. Koldobskii, *Zh. Org. Khim.*, **22**, 1763 (1986).
6. A. O. Koren', V. A. Ostrovskii, P. N. Gaponik, I. E. Titova, V. S. Poplavskii, G. V. Avetikyan, and G. I. Koldobskii, *Zh. Obshch. Khim.*, **58**, 825 (1988).
7. R. J. Spear, *Austral. J. Chem.*, **37**, 2453 (1984).
8. R. A. Henry, *J. Heterocycl. Chem.*, **13**, 391 (1976).
9. D. M. Zimmerman and R. A. Olofson, *Tetrahedron Lett.*, **58**, 5081 (1969).
10. H. Quast, L. Bieber, and G. Meichsner, *Ann.*, No. 5, 469 (1987).
11. P. N. Gaponik, V. P. Karavai, and Yu. V. Grigor'ev, *Khim. Geterotsikl. Soedin.*, No. 11, 1521 (1985).
12. O. A. Ivashkevich and P. N. Gaponik, *Dokl. Akad. Nauk Belorussian SSR*, **30**, 523 (1986).
13. V. A. Ostrovskii, G. I. Koldobskii, N. P. Shirokova, and V. S. Poplavskii, *Khim. Geterosikl. Soedin.*, No. 4, 559 (1981).
14. V. A. Ostrovskii, N. S. Panina, G. I. Koldobskii, B. V. Gidaspov, and I. Yu. Shirobokov, *Zh. Org. Khim.*, **15**, 844 (1979).
15. P. R. Srinivasan and R. L. Lichter, *J. Magn. Reson.*, **28**, 227 (1977).
16. P. N. Gaponik and V. P. Karavai, *Vestn. Beloruss. Gos. Un-ta*, Ser. 2, No. 3, 51 (1980).
17. W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).

18. W. P. Norris, *J. Org. Chem.*, **27**, 3248 (1962).
19. J. H. Nelson, N. E. Takach, R. A. Henry, D. W. Moore, W. M. Tolles, and G. A. Gray, *Magn. Reson. Chem.*, **24**, 984 (1986).

^1H AND ^{13}C NMR STUDY OF AZIDO-TETRAZOLE TAUTOMERISM OF 2-AZIDO-4-METHYLPYRIMIDINE

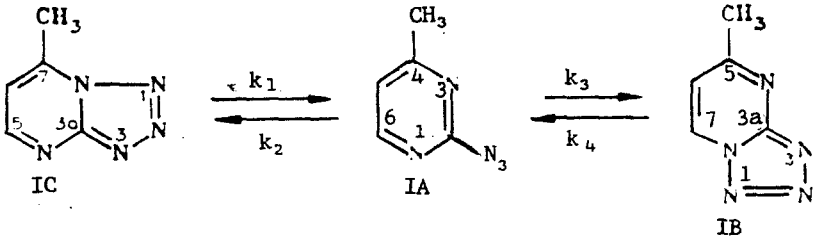
V. P. Krivopoalov, V. O. Mamatyuk, and V. P. Mamaev*

UDC 543.422.25:541.623:547.855.7

Using ^1H and ^{13}C NMR and IR spectroscopic methods, it was found that 2-azido-4-methylpyrimidine exists in solutions in tautomeric equilibrium with two tetrazole forms, the ratio between which is determined by the polarity of the solvent, while in a crystalline state, according to the ^{13}C NMR CP MAS data it has the structure of the 7-methyltetrazolo[1,5-a]pyrimidine isomer.

It was previously reported [1] that the condensation of 5-aminotetrazole with 4,4-dimethoxybutan-2-one or nitrosation of 2-hydrazino-4-methylpyrimidine produces one and the same product which, according to the authors, has the structure of 5-methyltetrazolo[1,5-*a*]pyrimidine (IB). However, it was found in [2] by ^1H and ^{13}C NMR methods that by the first method instead of compound IB, the isomeric 7-methyltetrazolo[1,5-*a*]pyrimidine (IC) is formed, existing in a $CDCl_3$ solution in equilibrium with 2-azido-4-methylpyrimidine (IA):

Scheme 1



In discussing the scheme of formation of compound I, the authors of [1] did not take into account the ability of the substituted 5-aminotetrazoles to undergo the thermally reversible Dimroth rearrangement, proceeding via the intermediate formation of substituted C-azidoformamidine ("guanylazide") [3, 4], and also the possibility of reversible recyclization of the IC ⇌ IB isomers, which possibly is the cause for the inconsistency with [2].

On analyzing the data for the tautomeric equilibrium of compound I [2] and 2-azido-4,6-dimethylpyrimidine (II) in a $CDCl_3$ solution [5], it was pointed out that the amounts of the azide forms are comparable in both cases, although a decrease in the relative stability of the azide tautomer, symbatical to the number of the electron-donor methyl group: 2-azi...pyrimidine (IIIA) > (IA) > (IIA), should have been expected.

In view of the above contradictory data, we undertook a detailed investigation of the tautomeric equilibrium IC ⇌ IA ⇌ IB in solvents of various polarities, and also determined the structure of compound I in the crystalline state.

*Deceased.

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1648-1654, December, 1990. Original article submitted April 24, 1989.

0009-3122/90/2612-1370$12.50