ALKYLATION OF 5-SUBSTITUTED TETRAZOLES WITH MANNICH BASES

V. G. Kitaeva, R. I. Ishmetova,
N. I. Latosh, and N. M. Voronina

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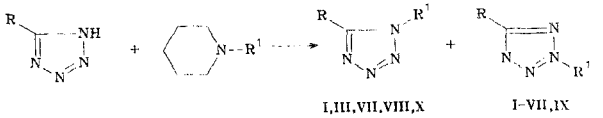
Mixtures of $N_{(1)}$ and $N_{(2)}$ isomers are formed in the alkylation of 1H-5-R-tetrazoles with N-(2-hydroxy-3-methoxy-5-formylbenzyl)piperidine, whereas primarily one of two possible $N_{(1)}$ or $N_{(2)}$ isomers is formed in the case of alkylation with N-(3,5-dimethyl-4-hydroxybenzyl)piperidine, depending on substituent R.

Mannich bases, which have been employed as alkylating agents in the case of aliphatic and aromatic compounds [1-4], are rarely used for the alkylation of heterocyclic compounds. The alkylation of indole with diethyl piperidylmethylformamidomalonate [1, 5] and the alkylation of morpholine, piperidine, and piperazine with β-dimethylaminohydroxypropiophenone [6, 7] have been studied. Data on the alkylation of uracil and alkyluracils with Mannich bases from alkylphenols are available [8].

We have studied the alkylation of 1H-5-R-tetrazoles with Mannich bases obtained from 2,6-dimethylphenol and vanillin; piperidine was used as the amino component.

As a result, we synthesized 1(2)-(3,5-dimethyl-4-hydroxybenzyl)- and 1(2)-(1-hydroxy-2-methoxy-5-formylbenzyl)-5-substituted tetrazoles I-X in 50-77% yields (Table 1).

Alkylation proceeds via the scheme:



I,III,VII,VIII,X I-VII,IX

R^1 = 2,5-dimethyl-4-hydroxybenzyl (A); 2-hydroxy-3-methoxy-5-formylbenzyl (B). I R = benzyl, R^1 = A; II R = phenyl, R^1 = A; III R = phenyl, R^1 = B; IV R = 4-methoxyphenyl, R^1 = A, V R = 4-methoxyphenyl, R^1 = B; VI R = 3,4-dimethoxyphenyl, R^1 = A; VII R = 3,4-dimethoxyphenyl, R^1 = B; VIII R = 4-pyridyl, R^1 = A; IX R = 3-pyridyl, R^1 = A; X R = 4-bromophenyl, R^1 = A

We investigated the effect of the ratio of the starting reagents and the reaction time and temperature on the yields of the alkylation products. We found that the optimum reaction conditions are a Mannich base–tetrazole ratio of 1:2.5 and a temperature of 130°C.

The presence of electron-donor groups in vanillin inhibits alkylation, and this is manifested in an increase in the alkylation time.

The formation of isomers depends on the electron-donor properties of the substituent. The presence at the $C_{(5)}$ atom of a phenyl ring or a phenyl ring with electron-donor properties promotes the primary formation of the $N_{(2)}$ isomer in alkylation with Mannich bases A and B. Substituents with electron-acceptor character in the para position of the phenyl ring lead to the primary formation of the $N_{(1)}$ isomer in alkylation with Mannich base A.

The nature of the alkylating agent is also important: An increase in the number of donor groups in the Mannich base decreases the selectivity of the alkylation.

Mixtures of isomers III and VII (with the exception of V) were isolated as a result of the alkylation of 5-substituted tetrazoles with the Mannich base based on vanillin, whereas individual isomers II, IV, VI, VIII, IX, and X (with the exception of I) were isolated in the alkylation of the Mannich base from 2,6-dimethylphenol.

Absorption at 1000-1100 cm^{-1}, which is characteristic for the skeletal vibrations of the tetrazole ring [9], is observed in the IR spectra of all of the synthesized compounds.

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TABLE 1. Products of Alkylation of 5-Substituted Tetrazoles with Mannich Bases

Compound	mp, °C	R_f[a]	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
I	87—88	0,95	69,3 69,6	5,9 6,3	18,9 18,9	$C_{17}H_{18}N_4O$	69,4	6,2	19,0	50
II	128—129	0,97	68,9	6,1	19,9	$C_{16}H_{16}N_4O$	68,6	5,8	20,0	77
III	163—165	0,93	61,9	4,7	18,2	$C_{16}H_{14}N_4O_3$	61,9	4,6	18,1	61
IV	124—126	0,95	65,6 66,0	6,0 5,9	18,0 18,2	$C_{17}H_{18}N_4O_2$	65,8	5,9	18,1	75
V	167—168	0,95	59,5 59,7	4,9 5,0	16,5 16,8	$C_{17}H_{16}N_4O_4$	60,0	4,7	16,5	48
VI	166—168	0,93	63,7 63,5	5,9 6,0	16,9 16,6	$C_{18}H_{20}N_4O_3$	63,5	5,9	16,5	67
VII	191—193	0,85	58,1 58,2	4,8 5,0	15,3 15,3	$C_{18}H_{18}N_4O_5$	58,4	4,9	15,1	57
VIII	174—175	0,94	64,2 63,9	5,1 5,3	25,2 25,0	$C_{15}H_{15}N_5O$	64,0	5,4	24,9	59
IX	156—157	0,71	64,1 64,0	5,4 5,4	25,0 24,8	$C_{15}H_{15}N_5O$	64,0	5,4	24,9	60
X	146—147	0,63	53,7 53,6	4,6 4,4	15,7 15,5	$C_{16}H_{15}BrN_4O$	53,5	4,2	15,6	65

[a]In an ethyl acetate—acetone—acetic acid—water system (8:2:2:1) for I-IX, and in a hexane—acetone system (2:1) for X.

TABLE 2. PMR Spectra and Dipole Moments of the Alkylation Products

Compound	PMR spectrum, ppm	Dipole moments, D		
		exptl.	calc.	
			$N_{(1)}$ isomer	$N_{(2)}$ isomer
I	2,05; 2,14 (CH_3); 4,19; 4,35 (C—CH_2); 5,41; 5,64 (N—CH_2)[a]; 6,61; 6,93; 7,26 (arom.CH); 8,36 (OH)	5,42	5,3	2,48
II	2,15 (CH_3); 5,79 (CH_2); 7,04; 7,54 (arom. CH); 8,44 (OH)	3,57	5,76	3,32
III	3,95 (OCH_3); 6,01; 5,92 (CH_2) ; 7,57; 8,05 (arom CH); 9,86 (CHO)	4,18	5,76	4,25
IV	2,16 (CH_3); 3,83 (OCH_3); 5,75 (CH_2); 8,43 (OH)	3,77	6,10	3,71
V	3,84 (OCH_3): 5,96; 5,87 (CH_2)[c]; 9,84 (CHO); 7,05; 7,52; 7,98 (arom. CH)	4,32	6,54	4,63
VI	2,16 (CH_3); 3,91 (OCH_3); 5,75 (CH_2); 8,43 (OH); 7,03; 7,13; 7,98 (arom. CH)	4,16	5,30	3,95
VII	3,87 (OCH_3); 5,96; 5,83 (CH_2)[d]; 9,82 (CHO); 7,06; 7,14; 7,54; 7,66 (arom. CH)	4,45	6,79	4,88
VIII	2,18 (CH_3); 5,84 (CH); 8,48 (OH); 7,06; 7,60; 8,76; 9,26 (arom. CH)	4,85	4,54	2,45
IX	2,19 (CH_3); 5,83 (CH_2); 8,48 (OH); 7,06; 7,60; 8,76; 9,26 (arom. CH)	4,15	5,40	3,51
X	2,16 (CH_3); 5,78 (CH_2); 8,45 (OH); 7,04; 7,86 (arom. CH)	4,15	4,81	2,63

[a]A mixture of isomers with $N_{(2)}$:$N_{(1)}$ = 1:1.6. [b]A mixture of isomers with $N_{(2)}$:$N_{(1)}$ = 4:1. [c]Traces of the $N_{(1)}$ isomer. [d]A mixture of isomers with $N_{(2)}$:$N_{(1)}$ = 2.5:1; this is the isomer ratio for the crude products.

We used PMR spectroscopy to confirm the structures and determine the quantitative ratios of the synthesized products. The assignment of the chemical shifts of the $N_{(1)}$ and $N_{(2)}$ isomers was made on the basis of the data in [10, 11], according to which the signal of the protons of the methylene groups in the $N_{(1)}$ position is shifted 0.1-0.3 ppm to stronger field as compared with the $N_{(2)}$ isomers. The $N_{(2)}$:$N_{(1)}$ isomer ratios calculated on the basis of the intensities of the signals of the protons of the 1- and 2-CH_2 groups were 1:1.6 for I, 4:1 for III, and 2.5:1 for VII; only traces of the $N_{(1)}$ isomer were present in V.

The PMR spectra of the compounds with a 2,6-dimethylphenol residue as a substituent (with the exception of I) in the region of methylene group absorption contain only one signal, the assignment of which to an $N_{(1)}$ or $N_{(2)}$ iosmer was made by means of the dipole moments.

A comparison of the measured dipole moments with the values calculated by the method in [13] shows that alkylation products II, IV, VI, and IX were isolated in the form of $N_{(2)}$ isomers, whereas VIII and X were isolated in the form of $N_{(1)}$ isomers (Table 2).

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil and perfluorinated hydrocarbons were recorded with a UR-20 spectrometer. The PMR spectra of solutions in d_6-DMSO were recorded with a Tesla BS 597 A spectrometer (100 MHz). The dipole moments were calculated from the Gugenheim–Smith formula [12]. The dielectric permeabilities of the solutions (dioxane, c = 0.01-0.1 mole/liter) were measured at 25°C with a Tangens-2M dielcometer at 1 MHz. The refractive indexes were measured with an IRF-22 refractometer. The 5-substituted tetrazoles were obtained by the methods in [14].

Products (I-X) of Alkylation of 5-Substituted Tetrazoles. A 0.01-mole sample of the Mannich base and 0.02 g of potassium carbonate were added with stirring to a solution of 0.025 mole of the 5-substituted tetrazole in 30 ml of DMF, and the mixture was heated in a stream of argon or nitrogen at 130°C for 6-15 h. The solution was cooled, 200 ml of water was added, and the mixture was acidified with three drops of concentrated HCl. The precipitate was removed by filtration and dried in air. The crude product was crystallized from aqueous alcohol.

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