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REACTION OF TETRAHYDROPYRANYL AZIDES WITH 5-R-BICYCLO[2.2.1]-2-HEPTENES

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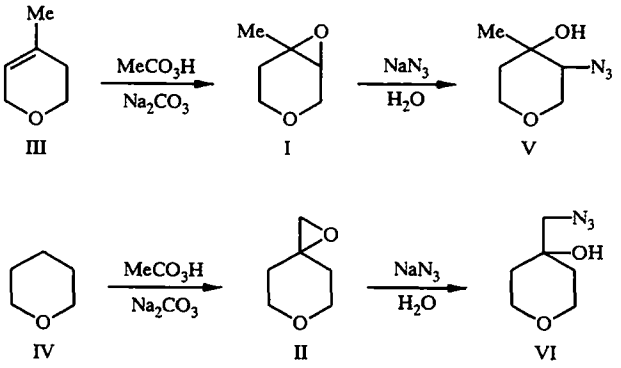
The reaction of 5-R-bicyclo[2.2.1]-2-heptenes with 3-azido-4-hydroxy-4-methyltetrahydropyran and 4-azidomethyl-4-hydroxytetrahydropyran, obtained by opening the oxirane ring in epoxytetrahydropyrans with sodium azide, leads to the formation of N-tetrahydropyranylaziridines with 100% stereoselectivity.

The reaction of nucleophilic agents with epoxides of the tetrahydropyran series is a convenient method for the stereoselective synthesis of various functional derivatives of this type, which are of interest as potential biologically active compounds or synthons for their preparation [1-3].

In a continuation of research into the reaction of nucleophiles with epoxides of the [1.2.4] pyran series we investigated the reaction of the latter with sodium azide. 4-Methyl-3,4-epoxytetrahydropyran (I) and 1,6-dioxaspiro[2.5]octane (II) were synthesized by the oxidation of 4-methyl-5,6-dihydro-2H-pyran (III) and 4-methylenetetrahydropyran (waste products in the production of isoprene by the dioxane method) by peracetic acid. During the treatment of the epoxides (I) and (II) with an aqueous solution of sodium azide after 3-5 days at 20°C 3-azido-4-hydroxy-4-methyltetrahydropyran (V) and 4-azidomethyl-4-hydroxytetrahydropyran (VI) are formed with yields of 89 and 80% respectively.



Earlier [4] in the case of the reaction of piperidine with 2-aryl-4-methyl-4,5-epoxytetrahydropyrans it was shown by spectroscopic methods (chromato-mass, IR, and PMR spectra) that one of the stereoisomers, i.e., the product of *trans*-diaxial opening of the epoxide ring, was formed preferentially. On this basis it could be expected that, as in the case of amines and amino acids [4, 5], *trans*-diaxial opening of the α-oxide ring will occur with attack by the highly nucleophilic azide ion on the least substituted carbon atom according to the Krasusskii rule. As established by TLC and PMR spectra, the reaction leads exclusively to one tetrahydropyranyl azide. The structure of the tetrahydropyranyl azides (V, VI) was proved by means of the IR and PMR spectra and also by chemical transformations.

There are no published data on the 1,3-dipolar cycloaddition of heterocyclic azides at the double bond of olefins. At the same time, study of this question is undoubtedly both of theoretical interest in connection with determination of the relationships relating the structure of the reacting olefins to the *exo* or *endo* direction of the reaction and of practical interest in connection with the aim of synthesizing new biologically active products.

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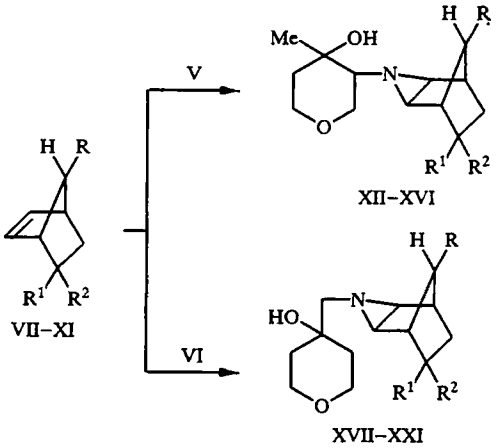
TABLE 1. Characteristics of the Synthesized Compounds (XII-XXI)

Compound	Molecular formula	Found, %			Calculated, %			mp, °C	Yield, %
		C	H	N	C	H	N		
XII	$C_{13}H_{21}NO_2$	69,81	9,36	6,15	69,92	9,47	6,27	138...139	86
XIII	$C_{14}H_{20}N_2O_2$	67,62	8,04	11,12	67,71	8,11	11,28	118...119	88
XIV	$C_{15}H_{23}NO_4$	63,92	8,14	4,82	64,03	8,24	4,97	206...207	68
XV	$C_{15}H_{23}NO_2$	72,13	9,18	5,39	72,25	9,29	5,61	199...200	75
XVI	$C_{14}H_{23}NO_2$	70,72	9,64	5,82	70,84	9,76	5,90	172...173	85
XVII	$C_{13}H_{21}NO_2$	69,78	9,35	6,12	69,92	9,47	6,27	136...137	85
XVIII	$C_{14}H_{20}N_2O_2$	67,56	8,04	11,19	67,71	8,11	11,28	108...109	87
XIX	$C_{15}H_{23}NO_4$	63,85	8,14	4,79	64,03	8,23	4,96	208...209	69
XX	$C_{15}H_{23}NO_2$	72,18	9,16	5,49	72,25	9,27	5,61	127...128	72
XXI	$C_{14}H_{23}NO_2$	70,68	9,62	5,79	70,84	9,76	5,51	167...168	82

In the present work we investigated the reaction of 5-R-bicyclo[2.2.1]-2-heptenes (VII-XI) with the azides (V) and (VI) in acetonitrile at 60°C for 50-70 h and showed that it led with 100% selectivity to the formation of *endo*-6-R-4′-hydroxy-4′-methyl-3′-tetrahydropyranyl-*exo*-3-azatricyclo[3.2.1.$0^{2,4}$]octanes (XII-XVI) and *endo*-6-R-4′-hydroxy-4′-methyltetrahydropyranyl-*exo*-3-azatricyclo[3.2.1.$0^{2,4}$]octanes (XVII-XXI) with yields of 72-87% (Table 1).



VII-IX, XI-XIV, XVI-XIX, XXI R = H, X, XV, XXR = cyclopropyl;
VII, XII, XVIIR^1 = R^2 = H; VIII, XIII, XVIII R^1 = H, R^2 = CN;
IX, XIV, XIX R^1 = CH_3, R^2 = COOH; X, XV, XXR^1 = R^2 = H; XI, XVI, XXI R^1 = H, R^2 = CH_3

The exclusive exo selectivity in the cycloaddition of diazomethane to norbornene and its derivatives is explained in [6, 7] by the favorable transition state (the torsion effect and steric hindrances to *endo* attack). In this connection it seems most likely that the addition of the azines (V, VI) to cyclic olefins of the norbornene series begins with *exo*-attack of the reagents at the C=C bond and leads to the unstable Δ^2-triazoline (A). The dissociation of the triazoline (A) includes the intermediate formation of the diazonium betaine (B), which can be transformed as a result of a Wagner–Meerwein rearrangement into the imine (XXII) or aziridine (XII) [8].

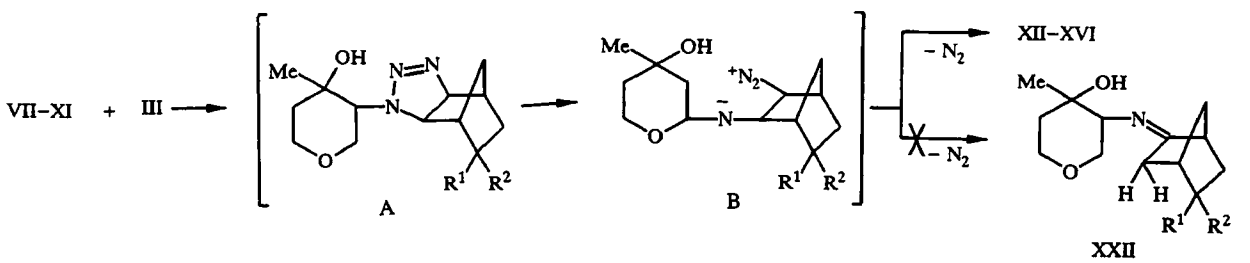


TABLE 2. PMR Spectra of the Synthesized Compounds (XII-XXI) (deuterochloroform, δ, ppm)

Compound	2-H, 4-H (aziridine ring) (d)	1-H, 5-H (bridgehead) (d)	*anti*-8-H (methane bridge) (*d*)	6-H, 7-H, 8-H (*syn*) (m)	6-CH_3 (s), Δc_8	4'-CH_3 (s)	5'-H (t)	2'-H, 6'-H (m)	3'-H, 5'-H (m)	2'-H	OH
XII	2,35	2,60	0,80	1,0...1,65		1,85	1,75	3,45...4,00			3,20
XIII	2,20	2,40	0,80	1,10...1,70		1,30	1,75	3,45...4,10			2,95
XIV	2,35	2,60	0,75	1,15...1,75	0,85	1,35	1,75	3,35...3,95			3,50
XV	2,15	2,40	0,80	1,20...1,60	0,60	1,25	1,65	3,40...4,15			3,20
XVI	2,20	2,50	0,85	1,10...1,65	0,80	1,20	1,70	3,40...4,20			3,50
XVII	2,30	2,60	0,75	1,08...1,60	—			3,65...3,85	1,45...1,80	3,30	3,20
XVIII	2,15	2,60	0,75	1,10...1,70	—			3,50...3,80	1,50...1,75	2,80	3,15
XIX	2,15	2,40	0,80	1,15...1,75	0,90			3,55...3,90	1,45...1,80	2,85	3,40
XX	2,10	2,40	0,80	1,15...1,70	0,60			3,60...3,80	1,50...1,75	2,90	3,10
XXI	2,20	2,50	0,80	1,10...1,70	0,90			3,55...3,85	1,40...1,75	2,85	3,20

In contrast to the activated azides (sulfonyl-, cyano-, and carbonyl-substituted), the addition of tetrahydropyranyl azides to the C=C bond of norbornenes leads, according to TLC and the PMR spectra, to the aziridines (XII-XVI) exclusively. The structure of the adducts (XII-XVI) was confirmed by the data from the PMR spectra, which do not contain signals in the region of the olefinic protons, and the IR spectra (the absence of the azide group). For this type of strained structures the most informative in determination of the *exo* or *endo* orientation of the aziridine fragment of the molecule were the signals of the bridging $C_{(8)}$ atoms and the carbon atoms of the aziridine ring $C_{(2)}$ and $C_{(4)}$. The PMR spectra of the adducts (XII-XXI) (Table 2) are similar to the spectra of the adduct of benzenesulfonyl azide with norbornene [9] and of 3,3-dichlorotricyclo-[3.2.1.$0^{2,4}$]octane [10]. In all cases the protons at the carbon atoms $C_{(2)}$ and $C_{(4)}$, attached to the nitrogen atom in the aziridine ring, are observed in the region of 2.10-2.40 ppm, which agrees with the data in [9, 10]. The bridgehead protons at $C_{(1)}$ and $C_{(5)}$ are downfield in the region of 2.35-2.60 ppm. According to data in [10], it can be stated that the upfield absorption of the *anti*-8-H (0.8 ppm) is due to bending of the methane bridge under the steric pressure of the tetrahydropyranyl group at position 3 of the aziridine ring, so that the *anti*-8-H proton is displaced toward the *exo*-protons at $C_{(6)}$ and $C_{(7)}$, becoming highly eclipsed. The signal of *syn*-8-H lies together with the signals of the protons at $C_{(6)}$ and $C_{(7)}$ in the region of 1.00-1.60 ppm. The five groups of nonequivalent protons of the tetrahydropyran ring in the adducts (XII-XXI) were identified by comparison with the PMR spectra of the tetrahydropyran derivatives [2, 3]. The methyl, nitrile, and carboxyl groups in the *endo* position at $C_{(5)}$ of the bicyclo[2.2.1]-2-heptene molecule do not have an effect on the direction of cycloaddition (Table 1).

It was not possible to realize the cycloaddition of the azides (V, VI) at the C=C bond of simple cyclic olefins (cyclohexane, cyclopentane, and also 4-methyl-5,6-dihydro-2H-pyran and 4-methylenetetrahydropyran). Unlike the activated azides, the tetrahydropyranyl azides do not enter into reaction with olefins even after heating for many hours. The bulky tetrahydropyranyl group evidently creates additional steric hindrances for attack by the azide ion on the unreactive C=C bond of these olefins [10].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument (in thin films in Vaseline oil). The PMR spectra were obtained on a Tesla BS-487 instrument (80 MHz) in deuterochloroform with HMDS as internal standard.

4-Methyl-3,4-epoxytetrahydropyran (I) was obtained by the method in [2].

3-Azido-4-hydroxy-4-methyltetrahydropyran (V). To a solution of 1.0 g (0.01 mole) of sodium azide in 20 ml of water we added 11 ml (0.01 mole) of the epoxide (I). The mixture was stirred on a magnetic stirrer at 20°C for 7 days until the epoxide had completely dissolved. (The reaction was monitored by TLC.) The mixture was then extracted with methylene chloride (3 × 15 ml) and dried, and the solvent was distilled. We obtained 1.4 g (89%) of the azidopyranol (V); bp 84°C (5 mm Hg). IR spectrum (ν, cm^{-1}): 1090, 1125 (CH_2OCH_2); 2125 ($-N_3$); 3420 (N···OH). PMR spectrum: 1.35 (3H, c, CH_3); 1.55 (2H, t, 5-CH_2); 3.20-3.85 (5H, m, 3-CH, 2-CH_2, 6-CH_2); 3.45 ppm (1H, s, OH). Found, %: C 46.11; H 7.26; N 26.57. $C_6H_{11}N_3O_2$. Calculated, %: C 45.85; H 7.05; N 26.73.

4-Azido-4-hydroxy-4-methyltetrahydropyran (VI). The compound was obtained similarly from 1 g (0.01 mole) of sodium azide, 20 ml of water, and 1.1 ml of the epoxide (IV) with a yield of 1.1 g (80%); mp 86-87°C. IR spectrum (ν, cm^{-1}): 1110, 1150 (CH_2OCH_2); 2100 ($-N_3$); 3350 (N···HO). PMR spectrum: 1.65 (4H, t, $2H_3$, $2H_5$); 3.15 (CH_2-N_3); 3.75-3.90 (4H, t, $2CH_2$, 6-CH_2); 2.65 ppm (1H, s, OH). Found %: C 46.29; H 6.94; N 26.49. $C_6H_{11}N_3O_2$. Calculated %: C 45.86; H 7.05; N 26.73.

***exo*-3-Aza-3-(4′-hydroxy-4′-methyl-3′-tetrahydropyranyl)tricyclo[3.2.1.$0^{2,4}$]octane (XII).** In a flask fitted with a reflux condenser we placed 1.78 g (0.01 mole) of 3-azido-4-hydroxy-4-methyltetrahydropyran (V) and 1.05 g (0.01 mole) of bicyclo[2.2.1]-2-heptene (VII) in 5 ml of acetonitrile. The mixture was heated at 60°C with constant stirring on a magnetic stirrer. The end of the reaction was determined by a negative test for azide ion ($FeCl_3$). After heating for 70 h the solvent was distilled, the residue was treated with diethyl ether, and the precipitate was washed with carbon tetrachloride. We obtained 2.1 g (0.009 mole) of (XII) (86%); mp 138-139°C. IR spectrum (ν, cm^{-1}): 1090, 1130 (CH_2OCH_2); 3270 (OH). The other adducts (XIII-XVII) were obtained under analogous conditions. Their characteristics and yields are given in Table 1.

***exo*-3-Aza-3-(4′-hydroxy-4′-tetrahydropyranylmethyl)tricyclo[3.2.1.$0^{2,4}$]octane (XVII).** In a flask fitted with a reflux condenser we placed 1.2 g (0.007 mole) of 4-azidomethyl-4-hydroxytetrahydropyran (VI) and 0.7 g (0.007 mole) of bicyclo[2.2.1]-2-heptane (VII) in 5 ml of acetonitrile. The mixture was heated at 60 °C with constant stirring for 50 h. The

end of the reaction was determined by a negative test for azide ion ($FeCl_3$). The solvent was distilled, the residue was treated with ether, and the crystals that separated were washed with carbon tetrachloride. We obtained 1.4 g (0.006 mole) of the adduct (XVII) (85%); mp 136-137°C. IR spectrum (ν, cm^{-1}): 1090, 1130 (CH_2OCH_2); 3250 (OH). The other adducts (XVIII-XXI) were obtained similarly. Their characteristics and yields are given in Table 1.

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