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SYNTHESIS AND REACTION OF 4-METHYL-3,4-EPITHIOTETRA-HYDROPYRAN WITH α-AMINO ACIDS

S. A. Vasil'eva, L. Kh. Kalimullina, and M. G. Safarov

4-Methyl-3,4-epithiotetrahydropyran was synthesized by the recyclization of 4-methyl-3,4-epoxytetrahydropyran by the action of thiourea. The product reacts with α-amino acids in an alkaline medium with regioselective opening of the thiirane ring at the least substituted carbon atom.

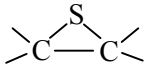
Keywords: tetrahydropyran amino acids, thiourea, epithiotetrahydropyran, epoxytetrahydropyran.

Among the large number of reactions leading to the formation of compounds with a thiirane ring the substitution of the oxygen atom in oxiranes by a sulfur atom occupies a special position on account of its high selectivity, the mild reaction conditions, and in a number of cases the high yields of the final reaction products [1]. This is why we investigated the reaction of the previously synthesized 4-methyl-3,4-epoxytetrahydropyran (**1**) with thiourea [2].

We separated the transformation of the oxirane ring into a thiirane ring into two stages. Initially, S-(4-hydroxy-4-methyl-3-tetrahydropyranyl)isothiuronium sulfate (**2**) is formed with a 70% yield in the reaction of the epoxide **1** with thiourea in water at 0°C for 5 h in the presence of an equimolar amount of sulfuric acid. By careful treatment with an equimolar amount of sodium carbonate in water at 0-5°C for 6 h it is converted into the thiirane **3** with a yield of 78%.

By realizing the reaction in steps it was possible not only to increase the yield of the thiirane but also to change the nature of the reaction significantly. If the pH of the medium, the temperature, and the polarity of the solvent (hexane, methanol, water) are increased, the formation of the thiirane ring is facilitated, and at the same time the rate of its nucleophilic opening is increased. Thus, a high yield of the thiirane is achieved by maintaining a specific pH value and temperature in the reaction medium (with the use of sodium carbonate in place of sodium hydroxide, 0-5°C).

As in the case of α-oxides [1], the transformation of the oxirane **1** into the thiirane **3** in all probability represents a series of consecutive ionic reactions with the formation and opening of the oxothiolane ring (structures **A**-**C**).

In the IR spectrum of the thiirane **3** there is an absorption band in the region of 810 cm^{-1}, corresponding to the stretching vibrations of the  group. In the ^1H NMR spectrum in the region of 3.1 ppm there is a doublet for the C(3)H proton of the thiirane group.

Bashkirian State University, Ufa, Russia; e-mail: VasilyevaSA@bsu.bashedu.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 202-206, February, 2003. Original article submitted March 31, 2000. Revision submitted November 15, 2000.

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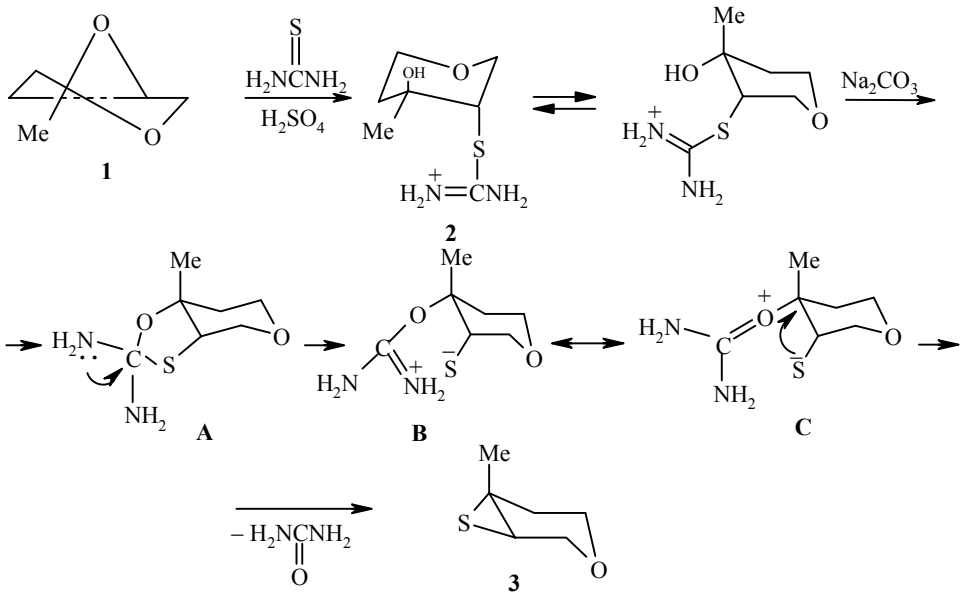
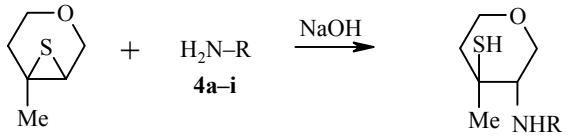
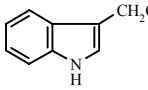
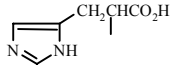


Earlier it was shown that epoxides of the pyran series are suitable synthons for the introduction of a tetrahydropyranyl group into various organic compounds by nucleophilic addition [3, 4]. Thus, the introduction of a tetrahydropyranyl radical into the structures of mono- and dicarboxylic neuroactive amino acids leads to the appearance of psychotropic activity [5]. In this connection it seemed interesting to use previously unknown thiiranes of the tetrahydropyran series in this reaction.

Amino acids are bifunctional compounds and can react both at the amino and at the carboxyl group. In aqueous solutions they exist in the form of zwitterions [6, 7], which in the presence of a small excess of alkali change into the conjugate base.



4, 5 **a** R = CH_2CO_2H; **b** R = $Me_2CHCH_2CHCO_2H$; **c** R = $HO_2CCHCH_2CO_2H$;
d R = $MeS(CH_2)_2CHCO_2H$; **e** R = $Me_2CHCHCO_2H$; **f** R = $CH_2CH_2SO_3H$;

g R = $PhCH_2CHCO_2H$; **h** R =  ; **i** R = 

It was found during treatment of the thiirane **3** with the sodium salts of *D,L*-amino acids **4a-i** in water at 70°C for 3 h the N-(4-mercapto-4-methyltetrahydropyran-3-yl)-*D,L*-amino acids **5a-i** are formed with yields of 83-89% (Table 1). The IR spectra of the products **5a-i** contain a strong absorption band in the region of 1580-1590 cm^{-1}, characteristic of the stretching vibrations of the N^+H_2 group, and also a band at 1610-1630 cm^{-1}, which corresponds to the stretching vibrations of the CO_2^- group [8].

For the case of the reaction of piperidine with 2-aryl-4-methyl-4,5-epoxytetrahydropyrans it was shown that one of the stereoisomers is formed preferentially, i.e., the product from *trans*-diaxial opening of the epoxide ring [9]. A similar arrangement of the amino and hydroxyl groups is typical of other epoxides of the pyran series [2, 10]. By TLC and IR and ^1H NMR spectroscopy (Table 1) we established that, as in the unsymmetrical

TABLE 1. The Characteristics of the Synthesized Compounds **5a-i**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	^{1}H NMR spectrum (CF_3COOD), δ, ppm					Yield, %
		C	H	N		$C(4)H_3$ (3H, s)	CH_3R (3H, s)	$C(5)H_2$ (2H, t)	$C(2)H_2$, C(3)H, $C(6)H_2$, (5H, m)	$^+NH_2$, (2H, s)	
5a	$C_8H_{15}NO_3S$	46.96 / 46.88	7.25 / 7.36	6.74 / 6.82	117-118	1.30	—	1.75	3.30-3.70	7.10	84
5b	$C_{12}H_{23}NO_3S$	55.25 / 55.14	8.69 / 8.86	5.26 / 5.35	125-126	1.15	1.40	1.85	3.35-3.78	7.15	88
5c	$C_{10}H_{17}NO_5S$	45.59 / 45.45	6.52 / 6.48	5.19 / 5.30	135-136	1.20	—	1.68	3.32-3.98	7.12	83
5d	$C_{11}H_{21}NO_3S_2$	47.16 / 47.28	7.41 / 7.57	4.92 / 5.01	122-123	1.30	1.52	1.84	3.55-4.10	6.95	85
5e	$C_{11}H_{21}NO_3S$	53.32 / 53.41	8.41 / 8.55	5.49 / 5.66	113-114	1.15	1.55	1.76	3.24-3.96	7.80	83
5f	$C_8H_{17}NO_4S_2$	37.51 / 37.63	6.49 / 6.71	5.62 / 5.48	175-176	1.25	—	1.86	3.32-3.98	7.84	87
5g	$C_{15}H_{21}NO_3S$	60.83 / 60.99	7.29 / 7.16	4.61 / 4.74	118-119	1.30	—	1.75	3.56-4.15	7.82	86
5h	$C_{17}H_{22}N_2O_3S$	59.92 / 61.05	6.49 / 6.63	8.26 / 8.37	120-121	1.35	—	1.65	3.30-4.05	7.52	83
5i	$C_{12}H_{19}N_3O_3S$	50.34 / 50.51	6.56 / 6.71	14.48 / 14.72	161-162	1.45	—	1.86	3.62-4.24	7.95	89

oxiranes, the addition of α-amino acids to the thiirane **3** is accompanied by opening of the ring at the least substituted carbon atom and takes place more readily than in the oxiranes. The difference in the energies of the C–S and C–O bonds clearly affects the reactivity of these carbon atoms to a greater degree than the difference in the strain energies of the ring.

EXPERIMENTAL

The IR spectra were recorded on UR-20 instruments (in thin films or in Vaseline oil). The ^{1}H NMR spectra were recorded on a Tesla BS-487 C instrument at 80 MHz with HMDS as internal standard.

The purity of the obtained compounds was monitored by TLC (Silufol UV-254, 2:1 methylene chloride–ethyl acetate).

4-Methyl-3,4-epoxytetrahydropyran (**1**) was obtained by the method in [2].

S-(4-Hydroxy-4-methyltetrahydropyran-3-yl)isothiuronium Sulfate (2). A solution of thiourea (8 g, 100 mmol) in concentrated sulfuric acid (3 ml) and water (35 ml) was added dropwise to the epoxide **1** (11.4 g, 100 mmol). The mixture was stirred at 0-5°C for 5 h and was then carefully evaporated. The residue was crystallized from ethanol, and 20 g (70%) of compound **2** was obtained; mp 164°C (decomp.). IR spectrum, cm^{-1}: 675 (C–S); 1675 (C=N$^+$H$_2$); 3300 (OH); 3420 (NH$_2$); 1110 (CH$_2$–O–CH$_2$). ^{1}H NMR spectrum (D$_2$O), δ, ppm: 1.15 (3H, s, C(4)H$_3$); 1.75 (2H, t, C(5)H$_2$); 3.30 (1H, s, OH); 3.45-3.75 (5H, m, C(2)H$_2$, C(3)H, C(6)H$_2$); 7.15 (2H, s, NH$_2$); 7.35 (2H, s, =N$^+$H$_2$). Found, %: C 29.32; H 5.84; N 9.55; S 29.49. $C_7H_{16}N_2O_6S_2$. Calculated, %: C 29.15; H 5.59; N 9.71; S 22.24.

4-Methyl-3,4-epithiotetrahydropyran (3). To a solution of the isothiuronium salt **2** (5 g, 19 mmol) in water (50 ml) we added dropwise a solution of sodium carbonate (1.8 g, 19 mmol) in water (20 ml). The mixture was stirred at 0-5°C for 6 h. The organic layer was separated, washed with water, dried over magnesium sulfate, and distilled under vacuum. We obtained 1.96 g (78%) of compound **3**; bp 60°C (40 mm Hg), n_D^{20} 1.4460, d_4^{20} 1.0295 g/cm^3. ^{1}H NMR spectrum (CDCl$_3$), δ, ppm: 1.35 (3H, s, C(4)H$_3$); 1.75 (2H, t, C(5)H$_2$); 3.10 (1H, s, C(3)H); 3.35 (2H, t, C(2)H$_2$); 4.10 (2H, t, C(6)H$_2$). Found, %: C 55.22; H 7.65; S 24.51. $C_6H_{10}OS$. Calculated, %: C 55.34; H 7.74; S 24.62.

N-(4-Mercapto-4-methyltetrahydropyran-3-yl)amino Acids (5a-i). To a solution of sodium hydroxide (0.8 g, 20 mmol) in water (20 ml) we added the amino acid (18 mmol). To the solution of the obtained salt we added the epoxide **1** (2 ml, 18 mmol). The mixture was stirred at 70°C for 2-3 h, after which it was neutralized to pH 7 with 4 N hydrochloric acid. The precipitate was recrystallized from aqueous ethanol (1:1).

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