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SYNTHESIS OF N-TETRAHYDROPYRANYL-S-METHYLMETHIONINESULFONIUM SALTS

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D,L-Methionine reacts in alkaline medium with 4-methyl-3,4-epoxytetrahydropyran via the amino group to form, in accordance with the Krasusskii rule, an oxirane ring opening product, namely N-(4-hydroxy-4-methyl-3-tetrahydropyranyl)-D,L-methionine. N-(4-Hydroxy-4-methyl-3-tetrahydropyranyl)-S-methylmethioninesulfonium salts are synthesized in high yields by methylating the latter then treating it with organic or inorganic acids.

Methylmethioninesulfonium chloride (vitamin U) has found wide application in clinical practice as an effective antiulcerative preparation [1], Work is currently in progress in several countries to find new pharmaceutical preparations based on methylmethionine-sulfonium, this being directed primarily towards replacing the Cl^- anion by the anions of different organic and inorganic acids.

In the current work we have undertaken the purposive synthesis of previously unknown salts of N-(tetrahydropyranyl)-S-methylmethionine-sulfonium (N-THPMMS) having organic and inorganic acid anions, using as the starting compound 4-methyl-5,6-dihydro-2H-pyran (I), a side-product from the dioxane process manufacture of isoprene [2] (see scheme).

By oxidizing the starting compound (I) we obtained 4-methyl-3,4-epoxytetrahydropyran (II). The reaction of the latter with D,L-methionine in the sodium salt form proceeded smoothly when an excess of alkali was used. This prompted an increase in pH and helped transform the amino acid, existing in solution as a zwitterion, into a conjugate base [3]. Thus, when epoxide II was treated with D,L-methionine sodium salt in aqueous solution for 3 h at 80°C, N-(4-hydroxy-4-methyl-3-tetrahydropyranyl)-D,L-methionine (III) was produced in 65% yield. In the IR spectrum of product III the intense absorption band observed at 1589 cm^{-1} was typical of the NH_2 group vibrations, while the 1610 cm^{-1} band correspond to the CO_2^- anion vibrations [4]. In a previous work [5] the researchers have used IR, PMR and mass-spectral methods to demonstrate, taking the reaction of piperidine with 2-aryl-4-methyl-4,5-epoxytetrahydropyrans as an example, the preferred formation of one of the stereoisomers, namely the trans-diaxial epoxide ring opening product. This configuration of amino and hydroxyl groups is also typical of other epoxides of the pyran series [2, 6]. On this basis it should be expected that the opening of the epoxide ring would also proceed trans-diaxially in accordance with the Krasusskii rule (i.e., at the least substituted carbon atom) when the amino acid was used. When product III was methylated for 1.5 h at 115°C in a mixture of 18 N H_2SO_4 and methanol, N-(4-hydroxy-4-methyl-3-tetrahydropyranyl)-S-methylmethioninesulfonium bisulfate (IV) was formed. This product was not isolated as it did not crystallize. Anionite EDE-10P in the OH-form was used to remove excess sulfuric acid from the reaction mixture and convert (N-THPMMS)-bisulphate IV into base V. It was seen from the ion-exchange process as the water-diluted reaction mass was passed through this anionite and from the selection and analysis of the individual fractions of the solution exiting from the column that the pH gradually changed from 9 to 6-7.

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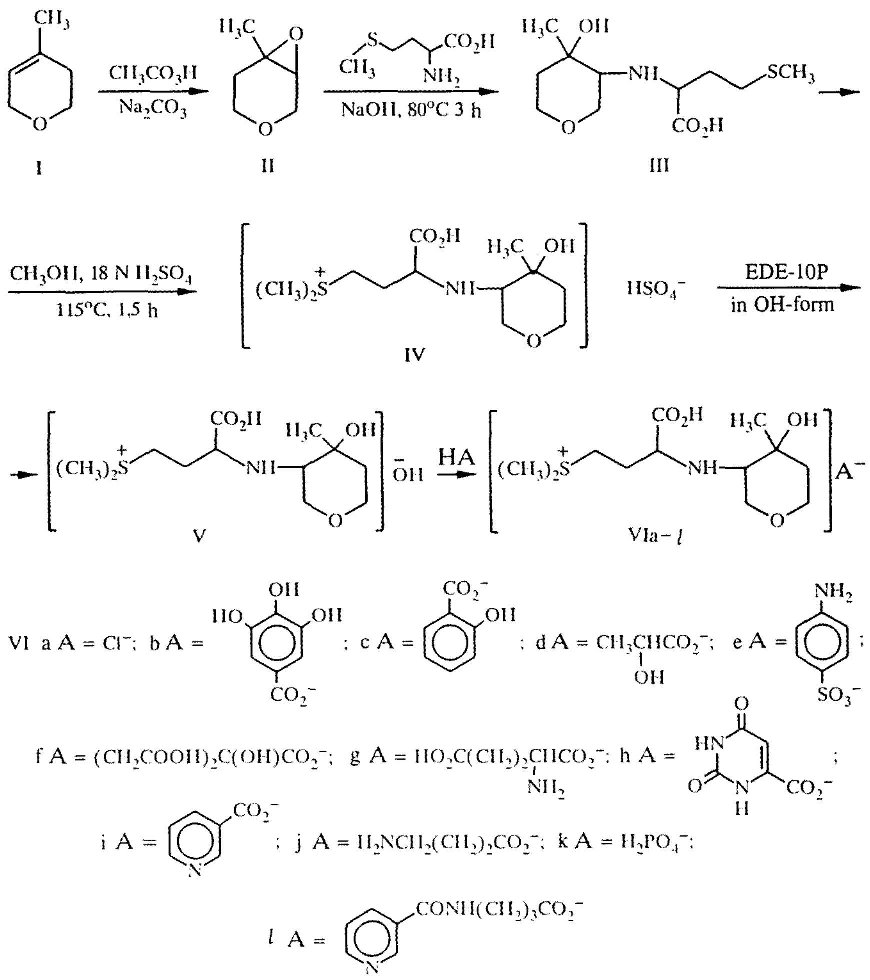
TABLE 1. Physical Properties and Spectral Characteristics of Synthesized Compounds VIa-*l*

Compound	Empirical Formula	mp, °C	PMR Spectrum (in CF_3COOD), ppm								Yield, %
			3-tetrahydropyranyl			$(CH_3)_2S^+$ (6H), s	$=S^+CH_2$ (2H), t	CH_2 (2H), t	CH (1H), d	NH_2 (2H), s	
			$4-CH_3$ (3H), s	5-H (2H), t	2-H, 3-H, 6-H (5H) m						
VIa	$C_{12}H_{24}ClNO_4S$	>300	1,32	1,75	3,40...3,95	1,90	3,65	2,65	4,10	7,06	87
VIb	$C_{19}H_{29}NO_9S$	>300	1,35	1,70	3,35...3,85	1,85	3,60	2,60	4,15	6,92	90
VIc	$C_{19}H_{29}NO_7S$	>300	1,30	1,65	3,34...3,92	1,90	3,55	2,62	4,10	7,15	94
VId	$C_{15}H_{29}NO_7S$	252...253	1,25	1,75	3,35...3,85	1,86	3,65	2,55	4,10	6,85	96
VIe	$C_{18}H_{34}N_2O_9S_2$	290...291	1,30	1,70	3,40...3,95	1,85	3,60	2,60	4,15	7,65	98
VIf	$C_{18}H_{31}NO_{11}S$	260...261	1,25	1,70	3,30...3,95	1,80	3,60	2,60	4,10	7,54	97
VIg	$C_{17}H_{34}N_2O_9S$	178...179	1,30	1,75	3,35...3,84	1,90	3,60	2,55	4,10	7,82	96
VIh	$C_{17}H_{27}N_3O_8S$	190...191	1,30	1,70	3,40...3,98	1,95	3,55	2,60	4,15	7,95	87
VIi	$C_{18}H_{18}N_2O_6S$	230...231	1,30	1,75	3,25...3,80	1,80	3,50	2,60	4,10	7,52	72
VIj	$C_{16}H_{32}N_2O_6S$	210...211	1,20	1,75	3,20...3,70	1,80	3,60	2,60	4,10	7,25	75
VIk	$C_{12}H_{26}NO_8PS$	212...213	1,25	1,70	3,40....3,95	1,80	3,60	2,65	4,15	7,15	80
VI*l*	$C_{22}H_{35}N_3O_7S$	190...191	1,20	1,75	3,25...3,75	1,80	3,65	2,60	4,10	7,05	85



A measured amount of the appropriate acid was added to the eluate, then the solution was concentrated in vacuum and the resultant N-THPMS salts (VIa-1) were crystallized at room temperature. The yields of salts IV were close to the quantitative amounts; structures were corroborated by means of PMR spectroscopy (see Table 1). It was found that N-THPMMS salts form new coordination compounds with copper chloride [7]. These complexes proved to be biologically active substances with a variety of beneficial properties.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (in thin films or in Vaseline oil), and PMR spectra were taken using a Tesla BS-487 C (80 MHz) in CF_3CO_2D and $CDCl_3$, internal standard HMDS.

Elemental analysis data from compounds VIa-1 with respect to C, H and N were in line with calculated values.

4-Methyl-3,4-epoxytetrahydropyran II was obtained using the technique described in a previous work [2].

N-(4-Hydroxy-4-methyl-3-tetrahydropyranyl)-D,L-methionine (III, $C_{11}H_{21}NO_4S$). A 2.6 g (18 mmoles) sample of D,L-methionine was added to a solution of 0.8 g (20 mmoles) of NaOH in 20 ml water and 2 ml (18 mmoles) of epoxide II was added to the resulting salt solution. The mixture was stirred for 3-4 h at 80°C, then neutralized with 4 N HCl to pH 7. The resultant precipitate was recrystallized from aqueous alcohol; mp 212-213°C. PMR spectrum (CF_3COOD, δ ppm): 1.12 (3H, s, 4-CH_3); 1.84 (2H, t, 5-H); 2.35-3.70 (5H, m, 2-H, 3-H, 6-H); 6.92 (1H, s, NH_2). Yield 2.4 g (65%).

N-(4-Hydroxy-4-methyl-3-tetrahydropyranyl)-S-methylmethionine-sulfonium Salts (VIa-*l*). A mixture of 3 g (0.011 moles) of N-(4-hydroxy-4-methyl-3-tetrahydropyranyl)-D,L-methionine III, 0.8 ml (0.01 moles) of methanol and 3.5 ml (0.03 moles) of 18N sulfuric acid was kept for 1.5 h at 115°C. After cooling to 20°C the solution was diluted in 1:6 ratio with water and eluted through a layer of EDE-10P anionite in the OH-form. The eluate was collected until the pH reached 6-7, then 0.01 moles of organic or inorganic acid was added to it. The resultant aqueous salt solution was concentrated in vacuum and crystallized from aqueous ethanol. Physical properties and spectral characteristics of synthesized compounds VI are shown in Table 1.

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