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REACTION OF 4-METHYL-3,4-EPOXYTETRAHYDROPYRAN WITH α -AMINO ACIDS

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Depending on the conditions, α -amino acids react with 4-methyl-3,4-epoxytetrahydropyran at the amin or carboxy group to give products of opening of the oxirane ring in conformity with the Krasusskii rule.

The reaction of epoxide with various nucleophiles is often used in organic synthesis owing to its high selectivity and the mild conditions under which it is carried out. For example, the corresponding amino alcohols were obtained in this way from epoxides of the tetrahydropyran series by the action of aliphatic amines [1, 2]. α -Amino acids can also be regarded as potential nucleophiles, although they exist in the zwitterionic form in aqueous solutions [3, 4]. However, the situation changes when one uses a certain excess of alkali, which promotes an increase in the pH and conversion of the zwitterion to the conjugate base. Using this, we investigated the reaction of 4-methyl-3,4-epoxytetrahydropyran (I), previously synthesized in [2], with a number of amino acids.

It was found that N-(4-hydroxy-4-methyl-3-tetrahydropyranyl)amino acids IIIa-o are formed in the 60-96% yields (Table 1) when epoxide I is treated with sodium salts of amino acids in aqueous solution at 80°C. An intense absorption band at 1580-1590 cm⁻¹, which is characteristic for stretching vibrations of an NH₂ group, and a band at 1610-1620 cm⁻¹, which corresponds to stretching vibrations of the CO_2^- anion [5], are observed in the IR spectra of products IIIa-o. In the case of the reaction of piperidine with 2-aryl-4-methyl-4,5-epoxytetrahydropyrans the primary formation of one of the stereoisomers - the product of trans-diaxial opening of the epoxide ring - was proved by spectral methods (by means of the chromatographic mass, IR, and PMR spectra) in [6]. This sort of orientation of the amino and hydroxy groups is also characteristic for other epoxides of the pyran series [2, 7]. On the basis of this it might be expected that, when amino acids are used, opening of the epoxide ring

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TABLE 1. Characteristics of the Synthesized Compounds (IIIa-o IV-VI)									
		,	PMR spectrum (in CF_3COOD), δ , PPm						
Com- pound	Empirical formula	mp, °C	4-CH₃ (3H),	CH ₃ of acid (3H),	5-H (2H),	2-H, 3-H, 6-H (5H),	OH, S	NH2, S	Yield,

s ; S t C₈H₁₅NO₄ 1.75 3,3 . . . 3,6 7.06 80 1.32 83 IIIa 79 3,3 . . . C₁₁H₂₁NO₄S 212213 1,12 1.84 3,7 _ 6,92 61 IIIb . . . 194 . . . 195 1,21 1,42 1,68 3,35 . . . 3,76 7,06 63 C₉H₁₇NO₄ HIC C10H19NO5 ____ 201... 202 1,52 1,67 3,32 . . . 3,98 7,15 HIM 1.14 61 C11H19NO4 1,84 3.32 . . . 3.96 7,15 75 164 . . . 165 1,24 Ille 1,55 1,76 3.55 . . . 4,28 83 240...241 1,13 6,78 C12H23NO4 HI 7,65 7,54 C9H17NO5 241.. 242 1,35 1,74 3,72 ... 4,06 -----96 IIIg ____ 3,32 . . . 3,98 212 1.251,86 ____ 80 C12H24N2O 211 Шĥ 7,82 7,84 239 1,84 3,24 . . . 3,96 94 238 . . . -----___ $C_{12}H_{24}N_4O_4$ 1.45IIIi 1.75 3,32 . . . 3,98 86 C15H21NO4 205 . . . 2061,36 IIIj 7,80 1.86 3,45 . . . 4,06 90 211 ... 212 1,34 ____ Шk C17H22N2O4 C12H19N3O4 1,84 ----7,75 80 III III m 277 . . . 278 1,32 3,56 . . . 4,15 298 . . . 82 $C_{11}H_{21}NO_4$ 299 1,26 1,75 3,56 . . . 4,34 7,82 7,95 $C_{11}H_{21}NO_4$ 230 . . . 231 1,46 1,76 3,62 . . . 4,24 90 IIIn 128 . . . 129 1,35 ____ 1,82 3,42 . . . 4,05 8,04 88 IIIo C11H19NO6 -----1,64 3,55 ... 3,96 4,52 7,52 721.25 IV* $C_{22}H_{27}NO_6$ V* 3,32 . . . 4,05 4,82 8,08 60 1.28 ____ 1,64 C₁₈H₂₅NO₅ 1,94 3,55...3,96 4,76 7,05 92 VI* 1.45 C17H23NO5

*The PMR spectra were obtained from solutions in CDCl3.



would proceed trans-diaxially in accordance with the Krasusskii rule, i.e., at the least substituted carbon atom. Since mixtures of L- and D-amino acids (with the exception of IIe) were subjected to the reaction, the products formed are also racemates.

The reaction of oxiranes with amino acids at the second nucleophilic center - the carboxy group - is also of definite interest. esters IV-VI are formed in 60-92% yields when Nsubstituted amino acids are heated with epoxide I in $CHCl_3$ in the presence of p-toluenesulfonic acid (p-TSA).



IV $R^1 = Ts$, $R^2 = CH_2Ph$; V $R^1 = COPh$, $R^2 = i \cdot Pr$; VI $R^1 = Ac$, $R^2 = CH_2Ph$

Opening of the oxirane ring under acid-catalysis conditions is not always as unambiguous as in the action of bases [8]. In our case one therefore might have expected the formation of mixtures of products. However, data from TLC, as well as the PMR and IR spectra, provide evidence from the formation of only products of opening of the epoxide ring at the least substituted carbon atom.

The presence of a tetrahydropyranyl fragment in the amino acid molecules does not hinder their subsequent modification with respect to the free functional groups. For example, N-(4-

^{*}All the rest are D,L isomers.



hydroxy-4-methyl-3-tetrahydropyranyl)-N-carboxymethylammonium-S-carboxymethylmethionesulfonium dichloride (VII) and N-(4-hydroxy-4-methyl-3-tetrahydropyranyl)-S-methylmethioninesulfonium iodide (VII) were obtained in 60-63% yields from IIIb by the action of monochloroacetic acid and CH_3I , respectively.

EXPERIMENTAL

The IR spectra of thin films or suspensions in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in CF_3CO_2D and $CDCl_3$ were obtained with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane (HMDS) as the internal standard.

The results of elementary analysis of III-VIII for C, H, and N (Cl, S) were in agreement with the calculated values.

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

<u>N-(4-Hydroxy-4-methyl-3-tetrahydropyranyl)amino Acids IIIa-o</u>. The amino acid (18 mmole) was added to a solution of 0.8 g (20 mmole) of NaOH in 20 ml of water, 2 ml (18 mmole) of epoxide I was added to the resulting solution, and the mixture was stirred for 3-4 h at 80°C. It was then neutralized to pH 7 with 4 N HCl solution, and the resulting precipiate was recrystallized from water. The characteristics and yields of the esters obtained are presented in Table 1.

<u>Amino Acid Esters IV-VI</u>. A 17 mmole sample of the N-substituted amino acid was dissolved in 50 ml of $CHCl_3$, 1.9 ml (17 mmole) of epoxide I and 0.01 g (0.005 mmole) of p-toluene-sulfonic acid were added, and the mixture was stirred for 33-55 h with a magnetic stirrer at 60-65°C. The characteristics and yields of the esters obtained are presented in Table 1.

<u>N-(4-Hydroxy-4-methyl-3-tetrahydropyranyl)-N-carboxymethylammonium-S-carboxymethylmethio-</u> ninesulfonium Dichloride (VIIb, $Cl_5H_{27}Cl_2NO_8S$). Water (10 ml) was added to a mixture of 0.69 g (3 mmole) of IIIb and 1.39 g (8 mmole) of ClCH₂CO₂H, and the mixture was stirred fo4 2 h at 80°C. Evaporation gave 1 g (60%) of salt VII with mp 160-161°C. IR spectrum: 1320 (C-S), 1775 (CO₂H), 2415, 1490, 2565 cm⁻¹ (NH).

 $\frac{N-(4 \text{ Hydroxy-4-methyl-3-tetrahydropyranyl})-\text{S-methylmethioninesulfonium Iodide (VIII, Cl_2H_2, INO, S).}{Mater (10 ml) was added to a mixture of 0.46 g (2 mmole) of IIIb and 0.18 ml (3 mmole) of CH_3I, and the resulting mixture was stirred for 6 h at 40-45°C. Evaporation gave 0.5 g (63%) of salt VIII with mp 169-170°C. IR spectrum: 1585 (NH), 1630 (CO_2H), 3430 cm⁻¹ (OH).$

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REACTION OF HEXAMETHYLDISILOXANE WITH 2-ETHOXY-1, 3-DIOXOLANE

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The reaction of hexamethyldisiloxane with 2-ethoxy-1,3-dioxolane is described. It is shown that cleavage of the endo- and exocyclic carbon-oxygen bonds of the ortho ester occurs under mild conditions (16-20°C) in the presence of acidic catalysts with the formation of 2-(trimethylsiloxy)ethyl formate, the subsequent transformation of which leads to ethyl formate, trimethylethoxysilane, and 1,2-bis(trimethylsiloxy)ethane.

The literature contains data on the reaction of acetals and ortho esters with alkoxysilanes [1-4] and 1,3-dioxa-2-silacycloalkanes [5], which proceeds with cleavage of the carbonoxygen and, correspondingly, silicon-oxygen bonds. Information regarding the reactions of ortho esters with silixanes is not available.

We have studied the acid-catalyzed reaction of hexamethyldisiloxane (HMDS) (I) with 2-ethoxy-1,3-dioxolane (II) for the first time. It was established that the reaction proceeds under mild conditions and leads to the formation of 2-(trimethylsiloxy)ethyl formate (IV), trimethylethoxysilane (III), 1,2-bis(trimethylsiloxy)ethane (V), and ethyl formate (VI).

It is assumed that the initial product is the unstable 2-trimethylsiloxy-1,3-dioxolane, which readily undergoes isomerization to IV. The subsequent reaction of IV and III leads to final products V and VI. According to GLC data, the maximum yield of aldehyde IV is 16-20% and was obtained when phosphorus pentoxide and concentrated nitric acid were used as catalysts (Table 1).

An increase in the temperature from 20°C to 100°C and a change in the molar ratio of the components have virtually no effect on the yield of product IV (Table 1).

Very small amounts (up to 1%) of 2-(trimethylsiloxy)ethanol (VII) and trimethylsilanol (VIII) were detected in the rection mixture by chromatographic mass spectrometry. The formation of the indicated compounds constitutes evidence for partial hydrolysis of the starting compounds and final products:



1,2-Bis(1',3'-dioxolan-2'-yloxy)ethane (IX), which may be formed by isomerization of dioxolane II under the experimental conditions [6], is present in trace amounts in the reaction mixture.

It is known that cyclic ortho esters readily undergo isomerization to acyclic compounds under the conditions of solvolysis reactions. Reverse reactions are realized in exceptional bases [6].

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