THE AMINOETHANOLYSIS REACTION OF KHELLACTONE DERIVATIVES

A. M. Aminov and G. K. Nikonov

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As is well known, the acid residues in diesters of dihydropyranocoumarins possess different stabilities to alkali according to their positions [1, 2]. Thus, on saponification with alkali under mild conditions the acid attached to the benzyl carbon atom is split off, and under more severe conditions than present at $C_{3'}$. On methanolysis (or ethanolysis), as a result of nucleophilic substitution a 3'-acyloxy-4'methoxy- or a 3'-hydroxy-4'methoxy-3'-, 4'-dihydroseselin is formed [3].

This reaction is accompanied by epimerization at the $C_{4'}$ asymmetric center as a consequence of which the diesters of cis-khellactone give a mixture of (±)-trans-khellactones (or methylkhellactones) [4]. In view of this, it appeared of interest to follow the behavior in this reaction of aminoethanol which, playing the roles of both nucleophilic reagent and alkali, may lead to the formation of water-soluble nitrogen-containing coumarin derivatives.

We have studied diester of khellacetone — visnadin, pteryxin, and anomalin. The reaction was performed in dioxane. At room temperature and with brief heating, all three coumarins reacted with aminoethanol forming a mixture of two nitrogen-containing substances with the compositions $C_{21}H_{27}O_6N$ (I) and $C_{16}H_{19}O_5N$ (II). These were readily soluble in water and gave positive reactions with alkaloid reagents. The only difference in the behaviour of the initial substances with aminoethanol was found in the rate of the reaction — for pteryxin it took place faster than for anomalin, which is apparently due to the length of the carbon chain of the acid residue. It is characteristic that the final reaction product on heating was the same substance, regardless of the initial diester.

Esters of linear and angular dihydrofurocoumarins with acyloxy groups on the benzyl carbon atoms also react with aminoethanol to form amines. However, we have not investigated the structures of the compounds obtained in this way.

We then studied the products formed in the aminoethanolysis of visnadin. On reacting with aminoethanol at room temperature it gave three compounds which were obtained chromatographically in the individual states.

Substance (I) (M^+ 389) — a water-soluble amorphous powder — gave the reaction for alkaloids. This substance is extremely unstable and even on standing in aqueous solution it is transformed into compound (II). The IR spectrum of (I) had a maximum at 334 nm (log ε 4.30) showing that the chromophoric group of 7-hydroxy coumarin undergoes no change during the reaction. In the IR spectrum, the absorption bands due to the coumarin nucleus remained. The NMR spectrum (Table 1) showed that the molecule of the substance contained the pyranocoumarin skeleton and an α-methylbutyric acid residue at $C_{3'}$, while the signals of the protons of the acetyl group at $C_{4'}$ had disappeared and the signal of an aminoethoxy group had arisen. The appearance of the latter was accompanied by a diamagnetic shift of the H-4' signal by 1.9 ppm because of the electron-donating influence of the substituent present in the $C_{4'}$ position. This permitted the conclusion that in the first stage of aminoethanolysis the acyloxy group $C_{4'}$ is replaced by an aminoethoxy group with the retention of the acyl residue at $C_{3'}$ and, consequently, compound (I) has the structure of 4'-aminoethxoy-3'-(α-methylbutyryloxy) dihydroseselin.

Substance (II), with the composition $C_{16}H_{19}O_5N$, formed colorless crystals with mp 86-88°C (ethyl acetate), $[\alpha]_D^{20}$ −62,5° (c 1,0; ethanol), M^+ 305, R_f 0.3. The compound fluoresces

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Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR.
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TABLE 1. Parameters and Assignment of the Signals of the NMR Spectra of the Products of the Aminoethanolysis of Visnadin

Assignment	Visnadin		Substance (I)		Substance (II)		Khellactone	
	CS, ppm	J,Hz	CS, ppm	J,Hz	CS, ppm	JHz	CS, ppm	JHz
H—3	6,25 d	10,0	6,22 d	10,5	6,22 d	10,0	6,09 d	10,0
H—4	7,64 d	10,0	7,65 d	10,5	7,65 d	10,0	7,49 d	10,0
H—5	7,39 d	9,0	7,45 d	9.0	7,30 d	9,0	7,26 d	8,6
H—6	6,82 d	9,0	6,80 d	9,0	6,78 d	9,0	6,65 d	8,6
$(CH_3)_2C$	1,43 s 1,48 s		1,50 s		1,26 s 1,52 s		1,41 1,44	
H′—3	5,34 d	5,6	5,10 d	6 9	3,8 d	6,9	3,91 d	6,0
H′—4	6,57 d	5,6	4,72 d	6,9	4,12 d	6,9	4,60 d	6,0
CH_3 CH_3 $CH_2-C-COO-$	0,95 tr		0,95 tr					
H	1,19 d	7,0	1,16 d	7,0	—	—	—	—
$-O-CH_2-CH_2-$ $-NH_2$	—		3,5—3,8 m 2,55m		3,6—3,8 m 2,55			
CH_3-COO-	2,15 s 3 (H)							
—OH					2,05 s			

violet in UV light, reacts with alkaloid reagents, and is readily soluble in water and ethanol, poorly soluble in ethyl acetate and benzene, and insoluble in petroleum ether.

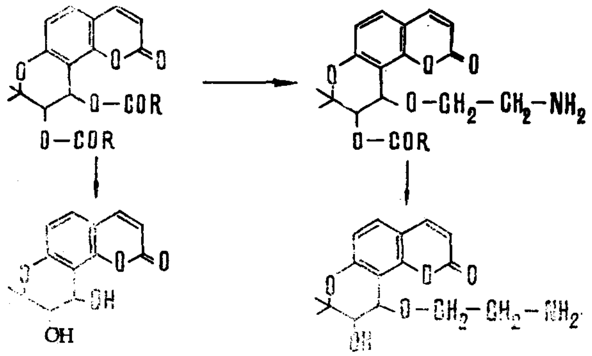
The features of the UV and IR spectra show that it also contains a coumarin skeleton, but the absorption band in the 1740-cm^{-1} region has a lower intensity than that in the spectrum of visnadin, and in the 3450-cm^{-1} region the strong absorption of a hydroxy group is observed.

It can be seen from the NMR spectrum (Table 1) that its molecule is also based on a dihydropyran ring, but there are no acyl residues. As the chemical shifts of the H-3' and H-4' methine protons show, electron-donating substituents — aminoethoxy and hydroxy groups — are present in the $C_{3'}$ and $C_{4'}$ positions.

On analyzing what has been stated above, it may be concluded that in the second stage of aminoethanolysis the ester group at $C_{3'}$ is saponified. Consequently, substance (II) has the structure of 4'-aminoethoxy-3'-hydroxydihydroseselin (II).

We obtained products of similar structure in the aminoethanolysis of the other khellactone diesters mentioned. It is characteristic that regardless of the starting materials, the end product of the reaction was always the same 4'-aminoethylkhellactone even though the intermediate substances differed from one another. It must also be noted that on aminoethanolysis inversion of the configuration at $C_{4'}$ takes place. Thus, the ethanolysis of visnadin [4'(R)-acetoxy-3'(R)-(α-methylbutyryloxy)dihydroseselin] gave 4'(S)-aminoethoxy-3'(R)-hydroxydihydroseselin.

In addition to the substances mentioned, we isolated from the reaction mixture a substance $C_{14}H_{14}O_5$ with mp 184-186°C (ethanol), R_f 0.03 which was identified on the basis of its IR spectrum and a mixed melting point as 3',4'-dihydroxydihydroseselin [trans-khellactone (III)]. Thus, we have established that the aminoethanolysis of diesters of khellactone takes place in the following way:



In view of the facts given, we performed experiments on the aminoethanolysis of the combined coumarins isolated from the roots of *Libanotis lehamannae* Bunge; the coumarins not consisting of khellactone derivatives did not take part in this reaction and the amino derivative formed could easily be isolated from the reaction mixture as an organic base. As a result, we obtained 4'-aminoethyl-khellactone, identical with that obtained from visnadin.

EXPERIMENTAL METHOD

The UV spectra were taken on an SF-4A spectrophotometer, the IR spectra on a UR-10 instrument (KBr), and the NMR spectra on a JNM-100/100-4H MHz instrument (solution of the substance in deuterochloroform, chemical shifts given on the δ scale from the signal of HMDS taken as 0) and the mass spectra on an MKh-1303 instrument. The purity of the substances was checked by chromatography in a thin, fixed layer of KSK silica gel in the toluene–ethyl acetate–methanol (2:1:1) system. Nitrogen was determined by the Dumas method.

The elementary analyses of the compounds corresponded to the calculated figures.

4'-Aminoethoxy-3'-(α-methylbutyryloxy)dihydroseselin. A solution of 1 g of visnadin (mp 86-88°C, $[\alpha]_D^{21}+39°$) in 20 ml of dioxane was treated with an excess (1.5 ml) of monoaminoethanol and the mixture was left at room temperature for 4 h. Then it was acidified with 10% H_2SO_4, diluted with water (1:2), and treated with ether. The aqueous solution (A) was made alkaline with a concentrated solutions of ammonia, and the bases were extracted with chloroform. This gave a mixture of substances with R_f 0.6 and 0.3. These were separated by chromatography in a column filled with KSK silica gel (20 ×3 cm), the substances being eluted with chloroform with the collection of 50-ml fractions. On evaporation of the solvent, fractions 1-9 yielded 0.16 g (16%) of an amorphous substance $C_{21}H_{27}O_6N$, R_f 0.6, M^+ 389, readily soluble in ethanol, chloroform, and water, sparingly soluble in benzene, and insoluble in diethyl ether and petroleum ether.

4'-Aminoethoxy-3'-hydroxydihydroseselin. Fraction 10-18 from the elution of the same chromatographic column yielded 0.380 g (40%) of a substance with mp 86-88°C (from ethyl acetate), $[\alpha]_D^{20}$ –62.5° (c 1.0; ethanol), R_f 0.3, readily soluble in water, ethanol, and chloroform, sparingly in benzene and ethyl acetate, and insoluble in petroleum ether.

UV spectrum: λ_{max} 332 nm (log ε 4.29). IR spectrum, cm^{-1}: 1740 (carbonyl of an α-pyrone), 1610, 1570 (aromatic nucleus), 3450 (OH group) [3', 4'-dihydroxydihydroseselin (trans-khellactone)],

3'4'-Dihydroxydihydroseselin (trans-Khellactone). The aqueous solution A was acidified with 10% H_2SO_4 and treated with chloroform. The solvent was distilled off. This gave a substance with the composition $C_{14}H_{14}O_5$, mp 184-186°C (MeOH), R_f 0.03, yield 20%.

Preparation of 4'-Aminoethoxy-3'-hydroxydihydroseselin from the Combined Coumarins of the Roots of *Libanotis lehmannae*. A solution of 40 g of the combined coumarins in 150 ml of dioxane was treated with 60 ml of monoaminoethanol, and the mixture was heated on the water bath for 3 h. Then it was acidified with 10% H_2SO_4 and diluted with water (1:2), and the unchanged coumarins were extracted with ether. The acid fraction was made alkaline with a concentrated solution of ammonia, and the bases were extracted with chloroform; the extract was dried with anhydrous sodium sulface and filtered, the solvent was evaporated off, and the residue was dissolved with heating in ethyl acetate. On standing, the solution deposited 8 g (20%) of a crystalline substance with mp 86-88°C, R_f 0.3, identical with that obtained from visnadin.

SUMMARY

1. The aminoethanolysis of diesters of khellactone has been investigated and the methods of obtaining water-soluble amino derivatives of khellactone has been developed.

2. The sequence of occurrence of the reactions has been studied, and three substances have been obtained and characterized.

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