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MODIFICATIONS BASED ON COUMARINS. I. SYNTHESIS OF MONOESTERS OF KARATAVIKIC AND GALBANIC ACIDS WITH SUCROSE

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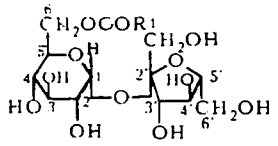
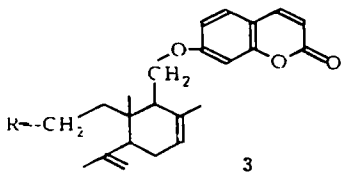
The synthesis has been achieved of water-soluble 6-O-monoesters of sucrose with natural coumarins — karatavikic and galvanic acids — by the transesterification of their methyl esters with sucrose. The structures of the compounds obtained have been confirmed by IR, UV, PMR, and ^{13}C NMR spectroscopies.

In plants of the *Ferula* genus, acids — karatakivic and galvanic — and also methyl galbanate have been detected among coumarins with monocyclic sesquiterpene substituents [1-3]. These acids possess a considerable bacteriostatic activity in relation to Gram-positive and Gram-negative bacteria [4, 5], but are insoluble in water, which restricts their practical use. It was therefore of interest to obtain water-soluble surface-active derivatives of these plant acids with carbohydrates in the aim of studying their properties and biological activity. Modifications of natural acids with carbohydrates in the form of esters will enable their hydrophilicity to be enhanced, their toxicity to be considerably decreased, the active transport of the substances to be ensured, and their physiological activity to be retained, enhanced, or even decreased.

We have obtained monoesters of coumarins (karatavikic and galvanic acids) with sucrose by the transesterification of their methyl esters (**1**, **2**), in dimethylformamide in the presence of an alkaline catalyst (K_2CO_3). From the reaction products, by column chromatography on silica gel, we isolated the monesters (**3**, **4**) acylated in position 6 of the glucose moiety of the molecule.



3 **4**



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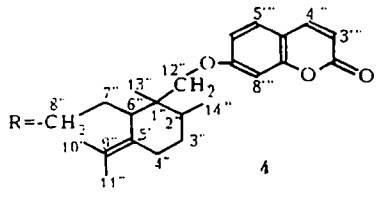

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In the IR spectra of the monoesters of karatavikic and galvanic acids with sucrose (**3**, **4**), just as in the spectra of the initial methyl esters (**1**, **2**), the stretching vibration of the C=C bonds of the aromatic rings appeared in the 1615 and 1510 cm^{-1} regions, and the CO vibrations of the ester group and of α-pyrone in the 1715-1730 cm^{-1} region. The IR spectra of (**3**) and (**4**) also contained absorption bands at 990 and 935 cm^{-1}, which are characteristic for the sugar moiety of the molecule (the −O−C−O−C−O−C− sequence of atoms) and at 3100-3600 cm^{-1} (assoc. OH).

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TABLE 1. Chemical Shifts of the Carbon Atoms of the Carbohydrate Moieties of Compounds (**3**) and (**4**) (δ, ppm, CD_3OH, 0–TMS)

Carbon atom	Sucrose	3	Δδ	4	Δδ
1	91.8	92.3	+0.5	92.1	+0.3
2	71.2	71.4	+0.2	71.5	+0.3
3	72.3	72.6	+0.3	72.4	+0.1
4	69.8	70.3	+0.5	70.2	+0.4
5	72.7	70.2	–2.5	70.4	–2.3
6	60.3	63.8	+3.5	63.6	+3.3
1′	62.0	62.4	+0.4	62.2	+0.2
2′	103.7	104.0	+0.3	104.2	+0.5
3′	77.0	77.4	+0.4	77.5	+0.5
4′	74.0	74.3	+0.3	74.4	+0.4
5′	81.3	81.7	+0.4	81.8	+0.5
6′	61.8	62.2	+0.4	62.0	+0.2

The PMR spectra of the monoesters (**3**, **4**) each contained a group of signals of the protons of the CH and CH_2 groups of the sucrose part of the molecule at 3.8-5.1 ppm, the signal of the anomeric proton of glucose in the 6.0 ppm region, and the signals of the protons of the aromatic ring (6.7-7.3 ppm). The UV spectra of the monoesters were determined by the chromophores of the initial acids and were characteristic for 7-alkylcoumarins [3].

The position of the acyl residues in the kakativikic and galvanic acid monesters were determined from the ^{13}C NMR results. For comparison we obtained the spectrum of unsubstituted sucrose. The assignment obtained corresponded to that given by Mathlouthi et al. [6].

Table 1 gives the ^{13}C chemical shifts for the carbohydrate parts of compounds (**3**) and (**4**) and their differences for the corresponding carbon atoms of the monoesters relative to sucrose.

Acylation at the primary hydroxy group of glucose was confirmed by the fact that the signals of the carbon atoms in the α-position with respect to the ester group (the C-6 atoms) had shifted downfield by 3.3-3.5 ppm, while those in the β-position (C-5 of glucose) had undergone a diamagnetic shift by 2.3-2.5 ppm in comparison with the chemical shifts of the corresponding carbon atoms of unsubstituted sucrose. The chemical shifts the carbon atoms of the other primary hydroxy groups in the fructose part of the sucrose molecule had changed insignificantly ($\Delta\delta$ $\pm$0.5 ppm).

EXPERIMENTAL

UV spectra were recorded on a Specord UV-VIS spectrophotometer, IR spectra on a UR-20 instrument (tablets with KBr), and PMR spectra on a Tesla 487 instrument (80 MHz) with HMDS as internal standard, in deuterated solvents ($CDCl_3$, C_5D_5N). ^{13}C NMR spectra were taken on a Bruker WP-80 instrument with a working frequency of 20.15 MHz. The course of the reactions was monitored by TLC on Silufol UV-254 plates. The substances were purified and separated by column chromatography on silica gel L (0.04-0.1 mm) (Czechoslovakia).

Methyl Esters of Karatavikic and Galvanic Acids (1) and (2). The air-dry roots of *Ferula karatavica* Rgl. and *F. gummosa* Boiss. (1.5 kg) were steeped at room temperature for 24 h three times in 6-, 4- and 4-liter portions of chloroform. The extracts were combined, and the solvent was distilled off in vacuum. By a threefold treatment of the ethereal solution with 5% Na_2CO_3, followed by acidification with 10% H_2SO_4, the residue was separated into acidic and neutral fractions (by the usual procedure). The acidic fractions were methylated with methyl alcohol in the presence of sulfuric acid. Methyl karatavikate was isolated by recrystallization from alcohol and 80% alcohol. Yield 2.5%, mp 107°C. Found, %: C 73.50; H 7.12; $C_{25}H_{30}O_5$. Calculation, %: C 73.01; H 7.30; M^+ 410. UV Spectrum (EtOH, λ_{max}, nm): 326 (lgε 4.18), IR spectrum (KBr, ν, cm^{-1}): 1720-1740 (α-pyrone CO_3, ester CO), 1615, 1510(Ar). PMR Spectrum (δ, ppm, $CDCl_3$): 0.83 (3H, s), 1.55 (6H, d), 3.55 (3H, s, $-OCH_3$), 4.0 (2H, d, J = 6.5 Hz, $-CH_2-O-Ar$), 4.7 (2H, d, $=CH_2$), 5.31 (1H, d, CH=), 6.07 (1H, d, J = 10 Hz, H‴-3), 6.7-6.85 (2H, Ar), 7.28 (1H, d, Ar), 7.5 (1H, d, J = 10 Hz, H‴-4). Methyl galbanate was isolated by column adsorption chromatography on silica gel L (0.04-0.1 mm) using hexane–ethyl acetate (4:1) as eluent. Yield 2.8%, bp 95°C/5 mm Hg. Found, %: C 72.54; H 7.69; $C_{25}H_{32}O_5$. Calculation, %: C 72.82; H 7.77; M^+ 412. UV spectrum (EtOH, λ_{max}, nm): 326 (lgε 4.24). IR Spectrum (KBr, ν, cm^{-1}): 1715 (α-pyrone CO), 1730 (ester CO), 1615, 1510 (Ar). PMR Spectrum (δ, ppm, $CDCl_3$): 0.88 (3H, d, J = 7 Hz, CH_3, C-14″), 1.08 (3H, 5, CH_3, C-13″), 1.32 (3H, s,

CH_3, C-10″), 1.52 (3H, s, CH_3, C-11″), 3.55 (3H, s, $-OCH_3$), 3.8 (2H, $-CH_2O-Ar$), 6.1 (1H, d, J = 10 Hz, H-3‴), 6.6-6.8 (2H, Ar), 7.2 (1H, d, Ar), 7.5 (1H, d, J = 10 Hz, H-4‴).

6-O-Monoester of Karatavikic Acid and Sucrose (3). With heating (90-95°C) and vigorous stirring, 34.2 g (0.1 mole) sucrose was dissolved in 120 ml of dimethylformamide. Then 13.5 g (0.033 mole) of (**1**) and 0.48 g (0.0035 mole) of K_2CO_3 (calcined at 250-300°C) as catalyst were added. The reaction was performed at 95-100°C and a residual pressure of 100–140 mm Hg in an inert gas (argon) atmosphere for 12-14 h. The sucrose that had not reacted was precipitated with toluene. The solvent was distilled off in vacuum and the reaction product was dried at 65-70°C/5-10 mm Hg and was purified by column chromatography with elution by chloroform–methanol (2:1). This gave 13.5 g (55%) of substance (**3**), soluble in water and alcohol, mp 112-114°C, R_f 0.43 (chloroform–methanol (2:1)). Found, %: C 59.60; H 6.61; $C_{36}H_{48}O_{15}$. Calculation, %: C 60.0; H 6.67. UV Spectrum (EtOH, λ_{max}, nm): 326 (lgε 4.20). IR Spectrum (KBr, cm^{-1}): 1715 (α-pyrone CO), 1730 (ester CO), 1615 (Ar), 3200-3600 (OH). PMR Spectrum (δ, ppm, C_5D_5N): 0.83 (3H, s), 1.55 (6H, d), 3.6-3.8 (2H, $Ar-O-CH_2-$), 3.8-5.1 (13H of sucrose), 5.31 (1H, CH=), 5.91 (H arom.), 6.07 (1H, d, J = 10 Hz, H-3‴), 6.7-6.85 (2H, Ar), 7.2 (1H, Ar), 7.5 (1H, d, J = 10 Hz, H-4‴).

6-O-Monomethyl Ester of Galvanic Acid and Sucrose (4). This was obtained and purified by column chromatography in a similar way to (**3**). The product was 13.4 g (56%) of substance (**4**) soluble in water and in alcohol, mp 110–112°C, R_f 0.30 (chloroform–methanol (4:1)). Found, %: C 60.65; H 6.94; $C_{36}H_{50}O_{12}$. Calculation, %: C 59.83; H 6.92; UV Spectrum (EtOH, λ_{max}, nm): 326 (lgε 4.24). IR Spectrum (KBr, ν, cm^{-1}): 1715 (α-pyrone CO), 1730 (ester CO), 1615, 1515 (Ar), 3200-3600 (OH). PMR Spectrum (δ, ppm, C_5D_5N): 0.71 (3H, d), 0.95 (3H, s), 1.42 (6H, s), 3.6-3.8 (2H, $Ar-O-CH_2-$), 7.2-7.35 (1H, Ar), 7.5 (1H, d, J = 10 Hz, H-4‴).

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