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MODIFICATIONS BASED ON COUMARINS III. SYNTHESIS OF DIESTERS OF KARATAVIC AND GALBANIC ACIDS AND MIXED DIESTERS OF COUMARIN ACIDS AND SALICYLIC ACID WITH SUCROSE

A. F. Artamonov, M. T. Aldabergenova, F. S. Nigmatullina, and B. Zh. Dzhiembaev

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The synthesis of 6,6'-diesters of sucrose with natural coumarins — karatavic and galbanic acids — has been achieved by the transesterification of methyl esters of these acids with monosucrose esters of the same acids, and so has that of mixed 6,6'-diesters of these coumarin acids and salicylic acid by a reaction between methyl salicylate and a monoester of the corresponding coumarin acid. The structures of the compounds obtained have been confirmed by IR, UV, PMR, and ^{13}C NMR spectroscopies.

Continuing investigations on the modification of coumarin acids with carbohydrates and polyhydric alcohols [1, 2], in the present paper we give the results of the synthesis of diesters of karatavic and galbanic acids with sucrose by the transesterification of their methyl esters with sucrose (molar ratio of methyl ester to sucrose 2:1; method A) or with a monoester of the corresponding acid (molar ratio of methyl ester to monoester 1:1; method B) in DMFA in the presence of an alkaline catalyst. We also consider the synthesis of mixed 6,6'-diesters of coumarin acids and a phenolcarboxylic acid (salicylic) with sucrose by a reaction between a monoester of the corresponding coumarin acid and methyl salicylate in the presence of K_2CO_3.

The isolation of karatavic and galbanic acids from plants of the *Ferula* genus and the synthesis of their methyl esters and that of 6-monoesters of coumarin acids with sucrose (yield 55-56%) is described in [1].

In contrast to the synthesis of monoesters, by the transesterification of methyl esters of the coumarin acids with sucrose (by method A) we succeeded in obtaining the 6,6'-diesters with yields of not more than 10%. It was possible to raise the yield of the 6,6'-diesters of the coumarin acids to 20-23% by the transesterification of their methyl esters with the 6-monosucrose ester of the corresponding coumarin acid (method B).

We isolated the 6,6'-diesters (**1**), (**2**) and the mixed 6,6'-diesters of the coumarin acids and salicylic acid (**3**), (**4**) from the reaction products by column chromatography on silica gel.

In the IR spectra of the diesters (**1**)-(**4**) the stretching vibrations of the C=C bonds of the aromatic ring were present in the 1608-1616 and 1504-1512 cm^{-1} regions, and the CO vibrations of ester groups and those of the α-pyrone CO in the 1714-1736 cm^{-1} region, while in the spectra of compounds (**3**) and (**4**) the CO vibration of the salicylic acid ester group appeared at 1690 cm^{-1}. The IR spectra of compounds (**1**)-(**4**) also contained the absorption bands in the 3100-3600 cm^{-1} region that are characteristic for associated OH groups.

In the PMR spectrum of each of the diesters (**1**)-(**4**) there was a group of signals of the CH and CH_2 groups of the sucrose part of the molecule at 3.5-5.0 ppm, the signals of the anomeric proton of glucose at 5.2-5.34 ppm, and the signals of the protons of the aromatic ring in the 6.75-7.85 ppm region.

The UV spectra of the diesters (**1**) and (**2**) were determined by the chromophores of the initial acids and were characteristic for alkylcoumarins [3].

The positions of the acyl residues in the diesters (**1**)-(**4**) were determined from ^{13}C NMR results. For comparison, we obtained the spectrum of unsubstituted sucrose. The correlation obtained agreed with the literature [4]. Table 1 gives the ^{13}C

A. B. Bektorov Institute of Chemical Sciences, Academy of Sciences, Republic of Kazakhstan, Almaty, fax (3272) 61 57 65. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 461-465, July-August, 1998. Original article submitted April 20, 1998.

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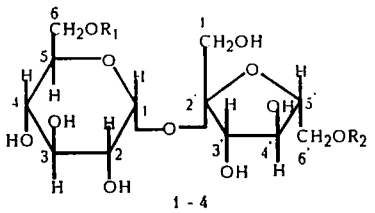
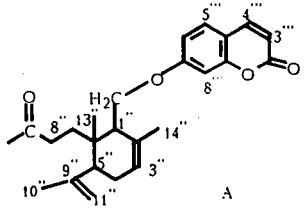
TABLE 1. Chemical Shifts of the Carbon Atoms of the Carbohydrate Moieties of Compounds (**1**)-(**4**) (δ, ppm, CD_3OD, 0 — TMS)

Carbon atom	Sucrose	1	Δ	2	Δ	3	Δ	4	Δ
1	91.82	92.26	+0.44	92.15	+0.33	92.22	+0.40	92.18	+0.36
2	71.28	71.54	+0.26	71.44	+0.16	71.50	+0.22	71.42	+0.14
3	72.32	72.71	+0.39	72.58	+0.26	72.46	+0.14	72.43	+0.11
4	69.88	70.33	+0.45	70.26	+0.38	70.23	+0.35	70.20	+0.32
5	72.76	70.25	-2.51	70.33	-2.43	70.43	-2.33	70.38	-2.38.
6	60.34	63.73	+3.39	63.54	+3.20	63.50	+3.16	63.42	+3.08
1'	62.08	62.54	+0.46	62.43	+0.35	62.50	+0.42	62.38	+0.30
2'	103.73	104.15	+0.42	104.24	+0.51	103.92	+0.19	104.10	+0.37
3'	77.06	77.54	+0.48	77.46	+0.40	77.56	+0.50	77.36	+0.30
4'	74.05	74.26	+0.21	74.35	+0.30	74.25	+0.20	74.36	+0.31
5'	81.34	79.23	-2.11	79.03	-2.31	79.55	-1.79	79.65	-1.69
6'	61.83	65.62	+3.79	65.84	+4.01	65.80	+3.97	65.71	+3.88

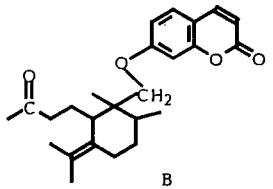


1 - 4

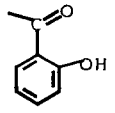
1. $R_1 = R_2 = A$;
2. $R_1 = R_2 = B$;
3. $R_1 = A$; $R_2 = C$;
4. $R_1 = B$; $R_2 = C$



A



B



C

chemical shifts for the carbohydrate moieties of compounds (1)-(4) and the differences for the atoms of the diesters relative to the corresponding atoms of unsubstituted sucrose.

Acylation at the primary hydroxy groups of glucose (C-6) and of fructose (C-6′) confirmed that the signals of the carbon atoms in the α-positions with respect to the ester groups (C6) and (C-6′) were shifted downfield by 3-4 ppm, while those in the β-positions (C-5 and C-5′) had undergone a diamagnetic shift by 1.7-2.5 ppm in comparison with those of the corresponding carbon atoms of unsubstituted sucrose. The chemical shift of the other primary hydroxy group of the fructose part of the sucrose molecule (C-1′) had changed insignificantly ($\Delta\delta$ ±0.5 ppm). The ^{13}C chemical shifts of the acyl groups of the coumarin acids and salicylic acid agreed with the chemical shifts of the carbon atoms of the initial methyl esters of these acids.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument (KBr tablets), and UV spectra on a Mercury-300 instrument with working frequencies of 300 and 75 MHz, respectively, using TMS as internal standard in deuterated methanol (CD_3OD).

The course of the reactions was monitored by TLC on Silufol UV-254 plates. The separation and purification of the substances was achieved by column chromatography on silica gel L (0.04-0.1 mm).

6,6′-Diester of Karatavic Acid and Sucrose (1). Method A. A solution of 1.8 g (0.005 mole) of sucrose in 30 ml of redistilled dimethylformamide (DMFA) was treated with 3.4 g (0.01 mole) of methyl karatavate, and 0.15 g (0.001 mole) of K_2CO_3 was added as catalyst. The reaction was conducted at 90-100°C in argon under reduced pressure (100-120 mm Hg) for 11-13 h. The solvent was distilled off in vacuum and the reaction product was dried at 65-70°C/5-10 mm Hg. The 6,6′-diester (1) was isolated from the product by column chromatography on silica gel L (0.04-0.1 mm) with elution by chloroform–methanol (9:1).

This gave 0.58 g of substance (1), mp 116-118°C, R_f 0.56 [chloroform–methanol (4:1)]. Found, % C 65.73; H 6.67; $C_{60}H_{74}O_{19}$. Experimental, %: C 65.57; H 6.74.

IR spectrum (KBr, ν, cm^{-1}): 1714 (α-pyrone CO), 1728 (ester CO); 1616, 1512 (Ar); 3100-3600 (OH).

UV spectrum (EtOH, λ_{max}, nm); 326 (log ε 4.18).

PMR spectrum (δ, ppm, CD_3OD): 0.89 (6H, d); 1.69 (12H, d); 3.5-3.8 (4H, Ar–O–CH_2–); 3.8-5.0 (13H of sucrose); 5.32 (1H, anom.); 5.45 (2H, CH=, H-3″); 6.18 (2H, dd, J = 10 Hz, H-3‴); 6.38-6.86 (4H, Ar); 7.42-7.47 (2H, Ar); 7.78 (2H, dd, J = 10 Hz, H-4‴).

6,6′-O-Diester of galbanic acid and sucrose (2) was obtained and isolated by column chromatography by method A, as for (1).

This gave 0.52 g (9%) of substance (2), mp 123-125°C, R_f 0.62 (chloroform–methanol, 4:1). Found, %: 65.44; H 7.12, $C_{60}H_{78}O_{19}$. Experimental, %: C 65.33; H 7.08.

IR spectrum (KBr, ν, cm^{-1}): 1720 (α-pyrone CO), 1736 (ester CO); 1610, 1510 (Ar); 3200-3600 (–OH).

UV spectrum (EtOH, λ_{max}, nm); 326 (log ε 4.22).

PMR spectrum (δ, ppm, CD_3OD): 0.94 (6H, d); 1.16 (6H, s); 1.54 (6H, s); 1.61 (6H, s); 3.30-3.63 (4H, Ar–O–C_2–); 3.70-4.60 (13H of sucrose); 5.2 (1H, anom.); 6.20 (2H, d, J = 10 Hz, H-3‴); 6.75-7.0 (4H, Ar); 7.42 (2H, Ar); 7.83 (2H, d, J = 10 Hz, H-4‴).

6,6′-Diester of Karatavic Acid and Sucrose (1). Method B. To a solution of 2 g (0.0028 mole) of the 6-monoester of karatavic acid and sucrose in 30 ml of DMFA were added 1.14 g (0.0028 mole) of the methyl ester of the same acid (in 30 ml of DMFA) and 0.04 g (0.00029 mole) of K_2CO_3. The reaction was conducted at 95-105°C in argon under reduced pressure (100-120 mm Hg) for 10-12 h. The solvent was distilled off and the reaction product was dried at 60-70°C/5-10 mm Hg. The 6,6′-diester (1) was isolated as in method A by column chromatography. This gave 0.7 g (23%) of substance (1), mp 116-118°C, R_f 0.56 [chloroform–methanol (4:1)].

Sucrose 6,6′-digalbanate (2) was obtained in a similar way to (1) (by method B) — 0.62 g (yield 20.3%), mp 123-125°C, R_f 0.61 chloroform–methanol (4:1).

6,6′-Diester of Karatavic and Salicylic Acids with Sucrose (3). A solution of 2 g (0.0028 mole) of the monoester of karatavic acid and sucrose in 50 ml of DMFA was treated with 0.42 g (0.0028 mole) of methyl salicylate and 0.04 g (0.00029 mole) of K_2CO_3. The reaction was conducted at 95-100°C/100-120 mm Hg for 8 h. The DMFA was driven off in

vacuum, and the reaction product was dried at 60-65°C/5-10 mm Hg. The mixed 6,6′-diester (**3**) was isolated by column chromatography on silica gel L (0.04-0.1 mm), with elution by chloroform–methanol (9:1).

This gave 0.61 g (26%) of substance (**3**), R_f 0.46 [chloroform–methanol (4:1)], mp 106-107°C. Found, %: C 61.26; H 6.22, $C_{43}H_{52}O_{17}$. Experimental, %: C 61.43; H 6.19.

IR spectrum (KBr, ν, cm^{-1}): 1714 (α-pyrone CO), 1728 (CO, of karatav. ester); 1690 (CO, of salicycl. ester); 1504, 1608 (Ar); 3100-3600 (–OH).

PMR spectrum (δ, ppm, CD_3OD): 0.94 (3H, s); 1.70 (6H, d); 3.29-3.42 (2H, Ar–O–CH_2–); 3.50-4.45 (13H of sucrose); 5.32 (1H, anom.); 5.45 (1H, CH=, H-3″); 6.21 (1H, d, J = 10 Hz, H-3‴); 6.75-6.98 (2H, Ar, karatav.); 7.40-7.58 (1H, Ar, salicyl.); 7.85 (2H, d, J = 10 Hz, 1H, Ar, salicyl., H-4‴); 10.68 (1H, OH, Ph).

6,6′-Diester of galbanic and salicylic acids with sucrose (4) was obtained and isolated by column chromatography in the same way as (**3**). This gave 0.62 g (26%) of substance (**4**), mp 108-110°C, R_f 0.4 [chloroform–methanol (4:1)]. Found, %: C 61.14; H 6.46, $C_{43}H_{54}O_{17}$. Experimental, %: C 61.28, H 6.40.

IR spectrum (KBr, ν, cm^{-1}): 1714 (α-pyrone CO), 1728 (CO, of salicyl.); 1690 (CO, of salicyl. ester); 1608, 1504 (Ar); 3100-3600 (–OH).

PMR spectrum (δ, ppm, CD_3OD): 0.93 (3H, d); 1.17 (3H, s); 1.43 (3H, s); 1.61 (3H, s); 3.30-3.60 (2H, Ar–O–CH_2–); 3.60-4.60 (13H of sucrose); 5.34 (1H, anom.); 6.21 (1H, d, J = 10 Hz, H-3‴); 6.75-7.0 (2H, Ar, galb.; 2H, Ar, salicyl.); 7.46-7.51 (2H, Ar); 7.85 (2H, d, J = 10 Hz, 1H, Ar, salicyl.; H-4‴); 10.51 (1H, OH, Ph).

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