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MODIFICATIONS BASED ON COUMARINS. II. SYNTHESIS OF α-MONOGLYCERIDES OF KARATAVIC AND GALBANIC ACIDS AND THEIR PHOSPHATES

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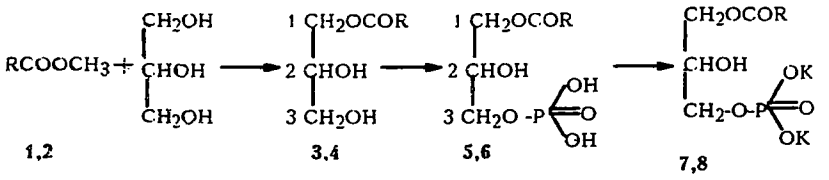
The synthesis has been performed of α-monoglyceride derivatives of coumarins – karatavic and galbanic acids and their modified derivatives – phosphates. The structures of the compounds have been confirmed by IR, UV, PMR, and ^{13}C and ^{31}P NMR spectroscopies.

In plants of the *Ferula* genus, among coumarins with monocyclic sesquiterpene substituents there are also found acids – karatavic and galbanic – which possess a considerable bacteriostatic activity [1-3]. Galbanic acid has also been found to have hepatoprotective properties [4].

Continuing investigations on the synthesis of esters of coumarins with polyols, it appeared of interest to obtain glycerol derivatives and α-monoglyceride phosphates and their water-soluble potassium salts.

The modification of natural acids in the form of esters and their derivatives – phosphates – will permit an increase in solubility and a decrease in toxicity, ensure the active transport of substances, and preserve, enhance, or even change physiological activity.

In the present paper we describe the preparation of monoglycerides of coumarinic acids (karatavic and galbanic) by the transesterification of their methyl esters (**1** and **2**) with glycerol in the presence of an alkaline catalyst (KOH). The α-monoglycerides (**3** and **4**) were isolated from the reaction products by column chromatography on silica gel. The α-monoglycerides were phosphorylated with phosphoric anhydride at an equimolecular ratio of the reagents. The monophosphates (**5** and **6**) were isolated from the reaction products by column chromatography on silica gel. The potassium salts of the phosphates (**7** and **8**) were obtained by neutralizing the acid phosphates with an alcoholic solution of alkali.



In the IR spectra of the α-monoglycerides of karatavic and galbanic acids (**3** and **4**), just as in the spectra of the initial methyl esters (**1** and **2**), the stretching vibrations of the C=C bonds of the aromatic ring were present in the 1590 and 1500 cm^{-1} regions, and the vibrations of the α-pyrone CO and of the ester group in the 1715 and 1735 cm^{-1} regions, respectively. Vibrations of associated OH groups were also present, in the 3200-3600 cm^{-1} region.

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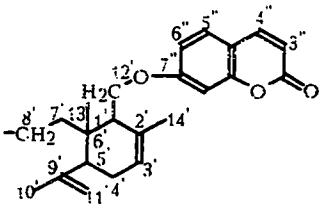
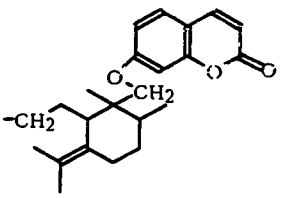


R(1,3,5,7)



R(2,4,6,8)

The IR spectra of the α-monoglyceride monophosphates (**5** and **6**) contained absorption bands corresponding to the vibrations of the P=O group (1240 cm^{-1}) and the P−O−C bond (1060, 930—940 cm^{-1}).

The UV spectra of the α-monoglycerides and their phosphates were determined by the chromophores of the initial acids and were characteristic for 7-alkylcoumarins [5].

In the PMR spectra of the α-monoglycerides (**3** and **4**), in addition to the signals of aromatic protons in the 6.6-7.4 ppm region, there were signals of the protons of the glycerol residue: a two-proton doublet in the 4.6 ppm region, corresponding to the methylene protons of an acylated primary alcohol group, and a two-proton doublet in the 4.0 ppm region, due to methylene protons in the geminal position to a hydroxyl. The methine proton of the secondary hydroxy group of glycerol was represented by a multiplet in the 4.2-4.5 ppm region.

The positions of the acyl residues in the α-monoglycerides of karatavic and galbanic acids (**3** and **4**) were determined by ^{13}C NMR spectroscopy. For comparison we took the spectrum of unsubstituted glycerol. Acylation at one of the primary hydroxy groups of glycerol was confirmed by the fact that the signals of the carbon atom (C-1) present in the α-position with respect to the ester group were shifted downfield by 2.8-3.2 ppm, while the C-2 signal had undergone a diamagnetic shift of 2.1-2.2 ppm in comparison with the chemical shifts of unsubstituted glycerol. The chemical shift of the carbon atom of the other primary hydroxy group of glycerol (C-3) changed insignificantly ($\Delta\delta = \pm 0.5$ ppm).

In the ^{31}P NMR spectra of the monophosphates there were solitary signals in the 2.3-2.6 ppm region, confirming the presence of a P−O−C bond.

EXPERIMENTAL

UV spectra were recorded on a Specord UV-VIS spectrophotometer, IR spectra on a UR-20 instrument (KBr tablets), and PMR spectra on a Tesla 487 (80 MHz) instrument with HMDS as internal standard in deuterated solvents ($CDCl_3$ and C_5D_5N). ^{13}C NMR spectra were taken on a Bruker WP-80 instrument with a working frequency of 32.44 MHz, using 80% orthophosphoric acid as external standard. The course of the reactions was monitored by TLC on Silufol UV-254 plates. Individual substances were isolated by column chromatography on silica gel L (0.04-0.1 mm).

Methyl Esters of Karatavic and Galbanic Acids (1 and 2). Air-dry roots of *Ferula karatavica* Rgl. and *Ferula gummosa* Boiss. (1 kg each) were steeped three times with 4-liter portions of chloroform for 24 h at room temperature. The extracts were combined, the solvent was distilled off in vacuum and the residue was separated into acid and neutral fractions by the usual method of the threefold treatment of an ethereal solution with 5% Na_2CO_3 followed by acidification with 10% H_2SO_4 solution. The acid fractions were methylated with methyl alcohol in the presence of sulfuric acid. Methyl karatavate (**1**) was isolated by crystallization from alcohol and 80% alcohol. Yield 2.7%, mp 107°C. Found, %: C 73.22; H 7.20; $C_{25}H_{30}O_5$. Calculated, %: C 73.01; H 7.30; M^+ 410. UV spectrum (EtOH, λ_{max}, nm): 326 (log ε 4.20). IR spectrum (KBr, ν, cm^{-1}): 1720-1740 (CO, α-pyrone; CO, ester) 1615, 1510 (Ar).

PMR (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, $=CH_2$, C-11′), 5.31 (1H, d, =CH, H-3′), 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 (**2**) was isolated by column chromatography on silica gel (0.04-0.1 mm) using hexane−ethyl acetate (4:1) as eluent. Yield 3.0%, bp 95°C (5 mm). Found, %: C 72.60; H 7.68, $C_{25}H_{30}O_5$. Calculated, %: C 72.82; H 7.77; M^+412. UV spectrum (EtOH, λ_{max}, nm): 326 (log ε 4.22). IR spectrum (KBr, ν, cm^{-1}): 1715 (CO, α-pyrone), 1730 (CO, ester), 1615, 1510 (Ar). PMR spectrum (δ, ppm, $CDCl_3$): 0.88 (3H, d, J = 7 Hz), 1.08 (3H, s, 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, $-CH_2-O-Ar$), 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″).

Synthesis of the α-Monoglycerides of Karatavic and Galbanic Acids (3 and 4). In an atmosphere of argon, 10 g (0.024 mole) of methyl karatavate or galbanate was heated with 33.6 g (0.36 mole) of glycerol at 190-200°C for 3-4 h in the presence of 0.15 g (0.0027 mole) of KOH. After the end of the reaction, the product was extracted with ethyl acetate, the extract was washed free from glycerol with water and dried over $MgSO_4$, and the solvent was driven off. The α-monoglycerides were isolated from the reaction products by column chromatography on silica gel L (0.04-0.1 mm) with elution by chloroform–methanol (9.5:0.5). This gave 5.7 g (50%) of substance (**3**). R_f 0.50 (chloroform–methanol (4:1)), mp 68-69°C. Found, %: C 68.72; H 7.12; $C_{27}H_{34}O_7$. Calculated, %: C 68.94; H 7.23.

UV spectrum (EtOH, λ_{max}, nm): 325 (log ε 4.25). IR spectrum (KBr, cm^{-1}): 1715 (CO, α-pyrone), 1740 (CO, ester), 1615 (Ar) 3200-3600 (OH). PMR (δ, ppm, C_5D_5N): 0.85 (3H, s), 1.68 (6H, d), 3.8 (2H, d, J = 6.5 Hz, $-CH_2O-Ar$), 4.08 (2H, d, J = 5 Hz, C-3), 4.2-4.5 (1H, m, C-2), 4.6 (2H, d, J = 5 Hz, C-1), 4.8 (2H, d, CH_2, C-11′), 5.4 (1H, d, CH=, H-3′), 6.25 (1H, d, J = 10 Hz, H-3″), 6.9-7.4 (3H, Ar), 7.6 (1H, d, J = 10 Hz, H-4″).

^{13}C NMR (δ, ppm, CD_3OH, 0-TMS) for the glycerol part of the molecule: C-1 66.0 (Δδ +3.16); 70.25 (Δδ − 2.15); C-3 63.30 (Δδ +0.46). Substance 4, yield 5.96 g (52%), mp 71-73°, R_f 0.48 (chloroform–methanol; 4:1). Found, %: C 68.36; H 7.48; $C_{27}H_{36}O_7$. Calculated, %: C 68.64; H 7.63.

UV spectrum (EtOH, λ_{max}, nm): 326 (log ε 4.20). IR spectrum (KBr, cm^{-1}): 1720 (CO, α-pyrone), 1735 (CO, ester), 1590, 1500 (Ar), 3200-3600 (OH), PMR (δ, ppm, C_5D_5N), glycerol part of the molecule: 4.0 (d, 2H, J = 5 Hz, C-3), 4.2-4.5 (1H, m, C-2), 4.6 (d, 2H, J = 5 Hz, C-1): coumarin part: 0.85 (3H, CH_3), 1.68 (6H, CH_3), 2.6-3.8 (2H, Ar $-O-CH_2-$), 6.25 (1H, H-3″, d, CH=, J = 9 Hz), 6.6-6.8 (2H, Ar), 7.2 (1H, d, Ar), 7.5 (1H, d, CH=, J = 9 Hz, H-4″).

^{13}C NMR (δ, ppm, CD_3OH, 0-TMS) for the glycerol part of the molecule C-1 65.65 (Δδ +2.8), C-2 70.10 (Δδ −2.1), C-3 63.20 (Δδ +0.36).

Monophosphates of the α-Monoglycerides (5 and 6) and Their Potassium Salts (7 and 8). To 4.7 g (0.1 mole) of the α-monoglyceride of the appropriate acid (karatavic or galbanic) was added 1.44 g (0.1 mole) of phosphoric anhydride, and the reaction mixture was heated at 75-80°C with stirring in an atmosphere of argon for 2-3 h and was then poured into water and extracted with ethyl acetate. The ethyl acetate solution was washed with water and dried over $MgSO_4$. The solvent was distilled off, and the monophosphates were isolated from the reaction products by adsorption column chromatography on silica gel L (0.04-0.1 mm) using chloroform–methanol (9:1) as eluent. This gave 0.97 g (17.6%) of substance (**5**), R_f 0.22 (chloroform–methanol (4:1)), mp 141-143°C. Found, %: C 58.82; H 6.28; P 5.52; $C_{27}H_{35}O_{10}P$. Calculated, %: C 58.91; H 6.36; P 5.64.

IR spectrum (KBr, ν, cm^{-1}): 1240 (P=O), 1060, 930 (P–O–C), 3200-3600 (OH). ^{31}P NMR (δ, ppm): 2.55 (P–O–C).

Potassium salt of the phosphate (**7**), mp 219-221°C. Found, %: P 4.83; K 12.28. $C_{27}H_{33}K_2O_{10}P$. Calculated, %: P 4.95; K 12.46.

We similarly obtained 1.1 g (20%) of substance (**6**), R_f 0.20 (chloroform–methanol (4:1)), mp 128-130°C. Found, %: C 58.64, H 6.54; P 5.67. $C_{27}H_{37}O_{10}P$. Calculated, %: C 58.70; H 6.70; P 5.80.

IR spectrum (KBr, ν, cm^{-1}): 1235 (P=O), 1060 (P–O–C), 3200-3600 (OH), ^{31}P NMR (δ, ppm): 2.36 (P–O–C). Potassium salt (**8**): mp 174-175°. Found, %: P 5.02; K 12.30; $C_{27}H_{35}K_2O_{10}P$. Calculated, %: P 5.10; K 12.42.

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