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# SYNTHESIS OF THE α-MONOGLYCERIDE OF *trans*-O-METHYL-MARMESIC ACID AND ITS MODIFIED DERIVATIVES — THE PHOSPHATE AND CITRATE

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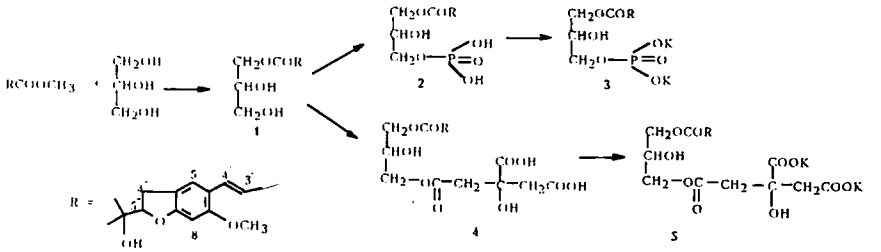
*The α-monoglyceride of trans-O−methylmarmesinic acid and its phosphate and citrate derivatives have been synthesized. The structures of the compounds have been confirmed by IR, UV, PMR and $^{13}C$ and $^{31}P$ spectroscopies.*

Continuing investigations of the chemical modification of natural and synthetic organic carboxylic acids with polyols [1-7], it appeared of interest to obtain ester of *trans*-cinnamic acids with polyhydric alcohols and their derivatives — phosphate and citrate — in the form of the water-soluble potassium salts. These modifications permit an increase in water solubility, a decrease in toxicity, a guarantee of the active transport of substances, and the retention or enhancement of, or even a change in, the physiological activities of the initial organic carboxylic acids.

In the present paper we report the synthesis of the α-monoglyceride of *trans*-O−methylmarmesic acid by the transesterification of its methyl ester with glycerol in the presence of an alkaline catalyst (KOH). The initial methyl *trans*-O−methylmarmesate was synthesized by opening the lactone ring of the dihydrofurocoumarin marmesin and isomerization of the resulting *cis*-cinnamic acid to the *trans*-isomer, followed by methylation with diazomethane [1].



The α-monoglyceride (**1**) was isolated from the reaction product by column chromatography on silica gel. In order to increase hydrophilicity, modified derivatives of the α-monoglyceride (**1**) were obtained in the form of the phosphate and citrate. The phosphorylation of (**1**) was achieved with phosphoric anhydride, and the citrate was obtained by the reaction of (**1**) with an equimolar amount of citric acid. The monophosphate (**2**) and the citrate (**4**) were isolated from the reaction products by column chromatography on silica gel. The potassium salts of the phosphate (**3**) and of the citrate (**5**) were obtained by neutralizing the acid phosphate (**2**) and the acid citrate (**4**) with an alcoholic solution of potassium hydroxide.

In the IR spectrum of the α-monoglyceride (**1**) the stretching vibrations of the C=C bonds of the aromatic ring appeared in the 1490 and 1620 $cm^{-1}$ regions, the vibration of the C=O of the ester group at 1700 $cm^{-1}$, and the vibrations of associated OH groups in the 3100-3600 $cm^{-1}$ region.

The IR spectrum of the monophosphate (**2**) contained absorption bands corresponding to the vibrations of a P=O group (1210 $cm^{-1}$) and of a P−O−C bond (1040 $cm^{-1}$). In the IR spectrum of the citrate (**4**) the vibration of the second ester C=O group appeared in the 1740 $cm^{-1}$ region.

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The PMR spectrum of the α-monoglyceride (1) contained, in addition to the signals of aromatic protons at 6.4-7.5 ppm, signals of the protons of the glycerol residue: a two-proton doublet in the 4.7 ppm region corresponding to the methylene protons of the acylated alcohol group, and a two-proton doublet at 4.0 ppm due to methylene protons present in the geminal position to a hydroxyl. The methine proton of the secondary hydroxy group of glycerol was represented by a multiplet at 4.2-4.6 ppm. Two one-proton doublets due to *trans*-olefinic protons were present at 6.6 and 8.25 ppm ($^3J = 16$ Hz).

The position of the acyl residue in the α-monoglyceride (1) was determined from the $^{13}C$ NMR spectrum. For comparison we took the spectrum of unsubstituted glycerol. Acylation at a primary hydroxy group of the glycerol was confirmed by the fact the signal of the carbon atom (C-1) present in the α-position to the ester group was shifted downfield by 2.7 ppm, while that of the C-2 atom of the glycerol had undergone a diamagnetic shift by 2.0 ppm in comparison with the chemical shifts of unsubstituted glycerol. The chemical shift of the carbon atom of the primary hydroxy group of the glycerol (C-3) had changed only slightly ($\Delta\delta$ + 0.36 ppm).

The $^{13}C$ NMR spectrum of the citrate (4) confirmed that the free primary hydroxy group of the glycerol had been acylated, since the signal of the carbon atom (C-3) present in the α-position to the ester group of citric acid was shifted downfield by 3.8 ppm.

In the $^{31}P$ NMR spectrum of the monophosphate (2) there was a one-proton signal in the −0.07 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 on a Tesla 487 (80 MHz) instrument with HMDS as internal standard in $C_5D_5N$. $^{13}C$ NMR spectra were taken on a Bruker WP-80 instrument with a working frequency of 20.15 MHz ($CD_3OD$, 0 — TMS). $^{31}P$ NMR spectra were recorded on a Bruker WP-80 instrument at a working frequency of 32.44 MHz with 80% orthophosphoric acid as internal standard.

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

**Monoglyceride of *trans*-O-Methylmarmesic Acid (1).** A mixture of 10.0 g (0.034 mole) of methyl *trans*-O-methylmarmesate and 9.46 g (0.103 mole) of glycerol was heated at 195-200°C for 8 h in an atmosphere of nitrogen in the presence of 0.39 g (0.007 mole) of KOH. The course of the reaction was monitored by TLC on Silufol plates with the use of chloroform−methanol (9:1) as eluent. After the end of the reaction, the product was extracted with ethyl acetate and the extract was freed from glycerol by washing with saturated sodium chloride solution and was dried with $MgSO_4$ and evaporated. The α-monoglyceride (1) was isolated by column chromatography on silica gel with elution by chloroform−methanol (9:1).

This gave 4.16 g (34.5%) of substance (1), mp 108-110°C, $R_f$ 0.45 [chloroform−methanol (9:1)]. Found, %: C 61.42; H 6.94; $C_{18}H_{24}O_7$. Experimental, %: C 61.36; H 6.82.

UV spectrum (EtOH, $\lambda_{max}$, nm): 247, 300, 345 ($\log \varepsilon$ 3.98; 3.93; 4.08).

IR spectrum (KBr, $\gamma$, $cm^{-1}$): 1700 (C=O, ester); 1620, 1575, 1490 (Ar); 3100-3650 (−OH).

PMR ($\delta$, ppm): 3.2 (2H, t, C-4″); 3.5 (3H, s, $OCH_3$); 4.05 (2H, d, J = 5 Hz, C-3); 4.2-4.6 (1H, m, C-2); 4.7 (2H, d, J = 5 Hz, C-1); 5.85 (2H, s, 2OH, gr.); 6.38 (1H, s, C-8′); 6.6 (1H, d, J = 16 Hz, C-4′); 7.4 (1H, s, C-5′); 8.25 (1H, d, J = 16 Hz, C-3′).

**Phosphate of the α-Monoglyceride of *trans*-O-Methylmarmesic Acid (2).** A mixture of 0.1 g (0.0028 mole) of the α-monoglyceride (1) and 0.40 g (0.0028 mole) of phosphoric anhydride was heated at 75-80°C in an atmosphere of argon with stirring until it thickened (4 h), and it was then poured into water and extracted with ethyl acetate. The ethyl acetate solution was washed with saturated NaCl solution and then with water and was dried with $MgSO_4$. The ethyl acetate was distilled off, and the monophosphate was isolated from the reaction product by column chromatography with elution by chloroform−methanol (9:1).

This gave 0.3 g (24.4%) of substance (2), mp 89-92°C, $R_f$ 0.13 [chloroform−methanol (9:1)]. Found, %: C 50.12; H 5.93; P 7.22; $C_{18}H_{25}O_{10}P$. Experimental, %: C 50.0; H 5.78; P 7.17.

UV spectrum (EtOH, $\lambda_{max}$, nm): 248, 300, 345 ($\log \varepsilon$ 3.96; 3.93; 4.04).

IR spectrum (KBr, $\nu$, $cm^{-1}$): 1735 (C=O, ester); 1635, 1515, 1475 (Ar); 3200-3600 (−OH); 1210 (P=O); 1040 (P−O−C).

$^{31}P$ NMR ($\delta$, ppm): −0.07 (P−O−C).

Salt (**3**), mp 260-265°C. Found, %: K 15.32. $C_{18}H_{23}K_2O_{10}P$. Experimental, %: K 15.41.

**Citrate of the α-Monoglyceride of *trans*-O-Methylmarmesic Acid (4).** With stirring, 0.65 g (0.0034 mole) of citric acid was added to 1.2 g (0.0034 mole) of the α-monoglyceride (**1**) that had been heated to 100°C, and the temperature was then raised to 160°C. The formation of compound (**4**) took 1.5-2.0 h. The citrate (**4**) was isolated by column chromatography on silica gel L (0.04-0.1 mm) with elution by chloroform−methanol (9:1).

This gave 0.43 g (24.0%) of substance (**4**), mp 47-49°C, $R_f$ 0.30 [chloroform−methanol (4:1)]. Found, %: C 54.68; H 5.63. $C_{24}H_{30}O_{13}$. Experimental, %: C 54.75; H 5.70.

UV spectrum (EtOH, $\lambda_{max}$, nm): 250, 302; 347 ($\log \varepsilon$ 4.01; 3.95; 4.10).

IR spectrum (KBr, $\nu$, $cm^{-1}$): 1700, 1740 (C=O, ester), 1632, 1544, 1456 (Ar); 3050-3700 (−OH).

PMR ($\delta$, ppm): 3.15 (4H, s, $2CH_2$ citr. gp.); 3.35 (2H, t, C-4″); 3.65 (3H, s, $OCH_3$); 4.25-4.9 (5H, s, C-1, C-2, C-3); 6.0 (5H, s, 5 OH gr.); 6.48 (1H, s, C-8′); 6.9 (1H, d, J = 16 Hz, C-4′); 7.45 (1H, s, C-5′); 8.55 (1H, d, J = 16 Hz, C-3′). Salt (**5**), mp 162-165°C. Found, %: K 12.83. $C_{24}H_{28}K_2O_{13}$. Experimental, %: K 13.0.

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