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# REACTION OF FRANGULA-EMODIN WITH α-BROMOALKYLMETHYLKETONES

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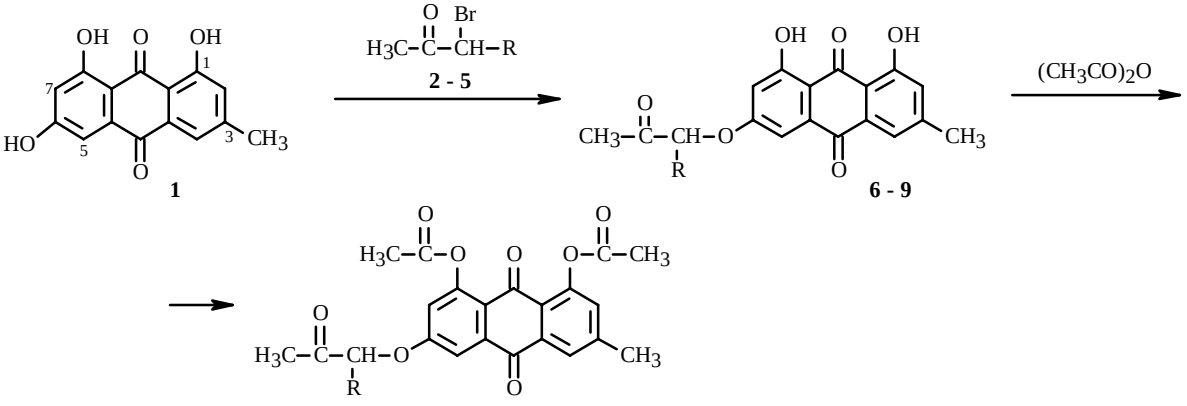
*The alkylation of 1,6,8-trihydroxy-3-methylanthraquinone (frangula-emodin) by α-bromoalkylmethylketones was investigated. Hydroxyls in the 1- and 8-positions of the β-derivatives were O-acylated. The compositions and structures of the prepared compounds were confirmed by elemental analysis and UV, IR, PMR, and $^{13}C$ NMR spectroscopy.*

**Key words:** frangula-emodin, α-bromoalkylmethylketones.

Natural anthraquinones are widely distributed in nature and participate in important vital processes of plants. Research on the biological activity and other practically valuable properties of anthraquinone derivatives has enabled them to be widely used in various branches of industry and especially in medicine [1-3].

We studied certain transformations of 1,6,8-trihydroxy-3-methylanthraquinone (frangula-emodin) (**1**) that was isolated and processed from subterranean organs (roots and rhizomes) of *Rumex tianschanicus* A. Los [4]. Compound **1** was isolated from plant material as before [5, 6]. The physicochemical and spectral properties of **1** are given in the Experimental.

Introduction into **1** of fragments containing a carbonyl group would enable the preparation of an extensive series of polyfunctional derivatives and make it possible to use them in further syntheses. Alkylation of **1** by α-bromoketones **2**-**5**, which were prepared by the literature method [7] and brominated by dioxane-dibromide, produced the *O*-substituted derivatives.




**2, 6, 10:** R = H; **3, 7, 11:** R = $CH_3$; **4, 8, 12:** R = $C_2H_5$; **5, 9, 13:** $C_3H_7$

The reaction of **1** with **2**-**5** can form various compounds because of the presence of three hydroxyls. The reactions of **1** were carried out in acetone with added $K_2CO_3$. Products of alkylation of the β-hydroxyl, **6**-**9**, were formed first in all instances whether an equimolar ratio of reactants or an excess of the α-bromoketone was used. Performing the reaction with an excess of bromide or increasing the duration of the reaction for **7**-**9** led to the formation of additional products that were lemon-yellow in visible light and orangish-brown in UV light and differed from **6**-**9** by a smaller $R_f$ value. Alkylation of **1** by α-bromoacetone

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(**2**) did not produce a second product because the solution became cloudy after 1.5 h and reaction product **6** precipitated under the synthesis conditions after 3 h.

The purity of **6-9** was confirmed by TLC. They were identified using elemental analyses and UV, IR, PMR, and $^{13}C$ NMR spectra. They were crystalline orange solids that were very soluble in ethylacetate and dioxane, less soluble in ether and $CHCl_3$, and insoluble in water.

IR spectra of **6-9** exhibited characteristic bands for stretching vibrations of carbonyls in the 9- and 10-positions of anthraquinone at 1624-1680 cm $^{-1}$. Stretching vibrations of the carbonyl of the substituent in the $\beta$-position corresponded to a band at 1712-1736 cm $^{-1}$. The C=C stretches of aromatic rings of anthraquinone were found at 1576-1592 cm $^{-1}$.

PMR spectra of **6-9** contained resonances for aromatic $\alpha$- and $\beta$-protons at 6.51-7.61 ppm. Protons of methyl directly bonded to the aromatic ring resonated at 2.37-2.48 ppm (C-3, $CH_3$). The $\alpha$-hydroxyl protons gave singlets at 11.85-12.22 ppm. Resonances of the $\beta$-hydroxyl were missing. Instead of them, resonances of protons of the 6-substituent were observed in the PMR spectra.

Alkylation of **1** by $\alpha$-bromoketones at the 6-hydroxyl was confirmed by preparing acylated derivatives **10-13**. IR spectra of these compounds contained characteristic absorption bands due to C=O stretching vibrations. Thus, stretching vibrations of carbonyls of substituents in the 1- and 8-positions were observed at 1776-1730 cm $^{-1}$; of the substituent in the 6-position, at 1724-1708 cm $^{-1}$; of the anthraquinone C=O, at 1680-1632 cm $^{-1}$.

PMR spectra of the acylated products lacked resonances for hydroxyl protons in the 1- and 8-positions. Instead of them, the spectra contained resonances for methyl protons (–OCO$\underline{CH}_3$) at 2.35-2.36 ppm as 6H-singlets. The aromatic $\alpha$- and $\beta$-protons resonated at 6.62-7.95 ppm. Compared with starting compounds **6-9**, these resonances shifted to weak field. Protons of 3-methyls corresponded with singlets at 2.43-2.51 ppm.

Thus, the study of the reaction of frangula-emodin (**1**) with $\alpha$-bromomethylalkylketones (**2-5**) indicates that the main alkylation products are substituted at the $\beta$-hydroxyl and are convenient intermediates for synthesizing new compounds based on them.

## EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using various solvent systems. UV spectra in ethanol for **1** and in $CH_3CN$ for **6-9** were recorded on a Perkin—Elmer Lambda 35 UV/Vis spectrometer; IR spectra, on a Specord M-80 spectrometer in KBr disks. PMR and $^{13}C$ NMR spectra at room temperature were recorded on a Mercury-300 spectrometer at operating frequency 300 MHz for protons and 75 MHz for $^{13}C$ with HMDS internal standard. Melting points were determined on a Boetius apparatus. Reaction products were separated on grade L 40/100 (Czech Rep.) silica gel.

**1,6,8-Trihydroxy-3-methylanthraquinone (frangula-emodin) (1).** Mp 254-256°C. UV spectrum ($\lambda_{max}$, nm): 224, 254, 267, 290, 440. IR spectrum (KBr, $\nu$, cm $^{-1}$): 3390 ($\beta$-OH); 1675, 1631 (C=$O_{anth}$); 1595 (Ar).

PMR spectrum ($d_6$-acetone, ppm, J/Hz): 7.06 (s, H-2), 7.48 (s, H-4), 7.18 (d, J = 2.4, H-5), 6.60 (d, J = 2.4, H-7), 2.42 (s, C-3, C$\underline{H}_3$), 10.58 (br.s, $\beta$-OH), 12.00 (s, $\alpha$-OH), 12.13 (s, $\alpha$-OH).

$^{13}C$ NMR spectrum (DMSO-$d_6$, ppm): 161.32 (C-1), 124.02 (C-2), 148.15 (C-3), 120.34 (C-4), 108.75 (C-5), 165.91 (C-6), 107.80 (C-7), 164.37 (C-8), 189.44 (C-9), 180.92 (C-10); nodal atoms: 134.77, 108.68, 112.99, 132.51, 21.44 (C-3, $CH_3$).

**Preparation of 6-9.** A solution of **1** (5.4 g, 0.02 mol) in acetone (100 mL) at room temperature was treated with the appropriate $\alpha$-bromoketone (**2-5**, 0.02 mol) and $K_2CO_3$ (2.76 g, 0.02 mol). The reagents were mixed. The temperature was increased to the boiling point of acetone and then held at 45-50°C for 3-25 h. After the reaction was finished, part of the solvent was distilled off. The reaction mixture was treated with water acidified with HCl. The resulting precipitate was filtered off and dried. The products were isolated by column chromatography over L 40/100 silica gel and crystallized from a suitable solvent.

**6-*O*-(Propan-2′-one)-1,8-dihydroxy-3-methylanthraquinone (6).** $C_{18}H_{14}O_6$, yield 97%, mp 232-233°C (acetone:dioxane, 2:1), $R_f$ 0.42 (hexane:ethylacetate, 2:1), 0.67 ($CCl_4$:ether, 5:2). UV spectrum ($\lambda_{max}$, nm): 223, 254, 265, 284, 433. IR spectrum (KBr, $\nu$, cm $^{-1}$): 1736 (C=$O_{sub}$); 1672, 1632 (C=$O_{anth}$); 1592 (Ar).

PMR spectrum ($d_6$-acetone, ppm, J/Hz): 7.17 (s, H-2), 7.61 (s, H-4), 7.34 (d, J = 3, H-5), 6.77 (d, J = 3, H-7), 2.48 (s, C-3, C$\underline{H}_3$), 12.03 (s, $\alpha$-OH), 12.22 (s, $\alpha$-OH), 5.09 (s, 2H, $CH_2$), 2.27 (s, 3H, $CH_3$).

PMR spectrum (DMSO-$d_6$, ppm, J/Hz): 7.06 (s, H-2), 7.40 (s, H-4), 7.10 (d, J = 3, H-5), 6.78 (d, J = 3, H-7), 2.37 (s, C-3, C$\underline{H}_3$), 11.85 (s, $\alpha$-OH), 12.06 (s, $\alpha$-OH), 5.08 (s, 2H, $CH_2$), 2.19 (s, 3H, $CH_3$).

$^{13}$C NMR spectrum (DMSO-$d_6$, ppm): 161.20 (C-1), 123.95 (C-2), 149.85 (C-3), 121.64 (C-4), 108.99 (C-5), 165.75 (C-6), 108.21 (C-7), 165.28 (C-8), 196.80 (C-9), 184.20 (C-10); nodal atoms: 133.93, 108.79, 113.02, 132.64, 22.59 (C-3, $CH_3$); $\beta$-substituent: 203.74 (C=O), 73.51 (–$CH_2$–), 27.23 (–$CH_3$).

**6-*O*-(1′-Methylpropan-2′-one)-1,8-dihydroxy-3-methylanthraquinone (7)**, $C_{19}H_{16}O_6$, yield 78%, mp 168-170°C (hexane:acetone, 1:4), $R_f$ 0.45 (heptane:ethylacetate, 2:1), 0.46 ($CHCl_3$). UV spectrum ($\lambda_{max}$, nm): 224, 254, 265, 284, 433. IR spectrum (KBr, ν, cm $^{-1}$): 1720 (C=$O_{sub}$); 1676, 1628 (C=$O_{anth}$); 1590 (Ar).

PMR spectrum ($CDCl_3$, ppm, J/Hz): 6.96 (s, H-2), 7.47 (s, H-4), 7.20 (d, J = 3, H-5), 6.51 (d, J = 3, H-7), 2.38 (s, C-3, C$\underline{H}_3$), 11.89 (s, $\alpha$-OH), 12.12 (s, $\alpha$-OH), 4.78 (m, 1H, >CH), 2.24 (s, 3H, $CH_3$), 1.57 (t, 3H, $CH_3$).

$^{13}$C NMR spectrum ($CDCl_3$, ppm): 162.43 (C-1), 124.45 (C-2), 148.58 (C-3), 121.23 (C-4), 110.59 (C-5), 164.99 (C-6) 107.52 (C-7), 164.05 (C-8), 190.50 (C-9), 181.28 (C-10); nodal atoms: 135.31, 108.33, 113.34, 132.86, 22.08 (C-3, $CH_3$); $\beta$-substituent: 207.19 (C=O), 79.40 (–CH), 25.05 (–$CH_3$), 17.21 (–$CH_3$).

**6-*O*-(1′-Ethylpropan-2′-one)-1,8-dihydroxy-3-methylanthraquinone (8)**, $C_{20}H_{18}O_6$, yield 75%, mp 163-165°C (ethylacetate), $R_f$ 0.45 (heptane:ethylacetate, 2:1), 0.72 ($CCl_4$:ether, 5:2). UV spectrum ($\lambda_{max}$, nm): 224, 254, 265, 283, 434. IR spectrum (KBr, ν, cm $^{-1}$): 1736 (C=$O_{sub}$); 1672, 1632 (C=$O_{anth}$); 1592 (Ar).

PMR spectrum ($CDCl_3$, ppm, J/Hz): 7.03 (s, H-2), 7.56 (s, H-4), 7.28 (d, J = 2.6, H-5), 6.55 (d, J = 3, H-7), 2.41 (s, C-3, C$\underline{H}_3$), 11.98 (s, $\alpha$-OH), 12.22 (s, $\alpha$-OH), 4.68 (m, 1H, >CH), 2.19 (s, 3H, $CH_3$), 1.71 (m, 2H, $CH_2$), 1.05 (t, 3H, $CH_3$).

$^{13}$C NMR spectrum ($CDCl_3$, ppm): 162.47 (C-1), 124.53 (C-2), 148.64 (C-3), 121.33 (C-4), 108.54 (C-5), 164.97 (C-6), 107.83 (C-7), 164.38 (C-8), 190.71 (C-9), 181.58 (C-10); nodal atoms: 135.24, 110.81, 113.45, 132.95, 22.30 (C-3, $CH_3$); $\beta$-substituent: 207.31 (C=O), 84.45 (>CH–), 40.94 (–$CH_2$–), 25.35 (–$CH_3$), 13.90 (–$CH_3$).

**6-*O*-(1′-Propylpropan-2′-one)-1,8-dihydroxy-3-methylanthraquinone (9)**, $C_{21}H_{20}O_6$, yield 85%, mp 154-156°C (acetone), $R_f$ 0.60 (hexane:ethylacetate, 2:1), 0.83 ($CCl_4$:acetone, 8:1). UV spectrum ($\lambda_{max}$, nm): 224, 255, 266, 283, 434. IR spectrum (KBr, ν, cm $^{-1}$): 1712 (C=$O_{sub}$); 1680, 1628 (C=$O_{anth}$); 1576 (Ar).

PMR spectrum ($CDCl_3$, ppm, J/Hz): 7.01 (s, H-2), 7.53 (s, H-4), 7.26 (d, J = 2.4, H-5), 6.53 (d, J = 3, H-7), 2.41 (s, C-3, C$\underline{H}_3$), 11.96 (s, $\alpha$-OH), 12.20 (s, $\alpha$-OH), 4.60 (m, 1H, >CH), 2.20 (s, 3H, $CH_3$), 1.89 (m, 2H, $CH_2$), 1.57 (m, 2H, $CH_2$), 0.98 (t, 3H, $CH_3$).

$^{13}$C NMR spectrum ($CDCl_3$, ppm): 162.43 (C-1), 124.49 (C-2), 148.59 (C-3), 121.27 (C-4), 108.51 (C-5), 164.08 (C-6), 107.40 (C-7), 164.49 (C-8), 190.56 (C-9), 181.48 (C-10); nodal atoms: 135.37, 110.61, 113.40, 132.92, 22.11 (C-3, $CH_3$); $\beta$-substituent: 207.43 (C=O), 84.27 (>CH–), 33.69 (–$CH_2$–), 18.34 (–$CH_2$–), 25.46 (–$CH_3$), 13.67 (–$CH_3$).

Derivatives **10-13** were prepared by heating **6-9** in acetic anhydride in the presence of sodium acetate.

**6-*O*-(Propan-2′-one)-1,8-diacetoxy-3-methylanthraquinone (10)**, $C_{22}H_{18}O_8$, yield 93%, mp 158-160°C ($CHCl_3$), $R_f$ 0.51 ($CCl_4$:ether, 5:2). IR spectrum (KBr, ν, cm $^{-1}$): 1776, 1752 [C=O in –OC(O)$CH_3$]; 1728 (C=$O_{sub}$); 1672, 1632 (C=$O_{anth}$); 1600 (Ar).

PMR spectrum (DMSO-$d_6$, ppm, J/Hz): 7.20 (s, H-2), 7.92 (s, H-4), 7.48 (d, J = 3, H-5), 6.92 (d, J = 3, H-7), 2.43 (s, C-3, C$\underline{H}_3$), 2.36 [s, 6H, –O–C(O)$CH_3$], 5.14 (s, 2H, $CH_2$), 2.17 (s, 3H, $CH_3$).

**6-*O*-(1′-Methylpropan-2′-one)-1,8-diacetoxy-3-methylanthraquinone (11)**, $C_{23}H_{20}O_8$, yield 68%, mp 142-144°C ($CHCl_3$), $R_f$ 0.40 (hexane:ethylacetate, 2:1), 0.18 (benzene:$CHCl_3$, 5:4). IR spectrum (KBr, ν, cm $^{-1}$): 1774, 1748 [C=O in –OC(O)$CH_3$]; 1714 (C=$O_{sub}$); 1674, 1634 (C=$O_{anth}$); 1590 (Ar).

PMR spectrum ($CDCl_3$, ppm, J/Hz): 7.12 (s, H-2), 7.65 (s, H-4), 7.42 (d, J = 3, H-5), 6.62 (d, J = 3, H-7), 2.44 (s, C-3, C$\underline{H}_3$), 2.36 [s, 6H, –O–C(O)$CH_3$], 4.82 (m, 1H, >CH), 2.28 (s, 3H, $CH_3$), 1.62 (t, 3H, $CH_3$).

**6-*O*-(1′-Ethylpropan-2′-one)-1,8-diacetoxy-3-methylanthraquinone (12)**, $C_{24}H_{22}O_8$, yield 75%, mp 128-130°C ($CHCl_3$), $R_f$ 0.50 (pentane:ethylacetate, 2:1), 0.28 (benzene:$CHCl_3$, 7:4). IR spectrum (KBr, ν, cm $^{-1}$): 1774, 1740 [C=O in –OC(O)$CH_3$]; 1710 (C=$O_{sub}$); 1676, 1634 (C=$O_{anth}$); 1580 (Ar).

PMR spectrum ($CDCl_3$, ppm, J/Hz): 7.20 (s, H-2), 7.82 (s, H-4), 7.48 (d, J = 2.7, H-5), 6.84 (d, J = 2.4, H-7), 2.46 (s, C-3, C$\underline{H}_3$), 2.35 [s, 6H, –O–C(O)$CH_3$], 4.94 (m, 1H, >CH), 2.22 (s, 3H, $CH_3$), 1.91 (m, 2H, $CH_2$), 1.11 (t, 3H, $CH_3$).

**6-*O*-(1′-Propylpropan-2′-one)-1,8-diacetoxy-3-methylanthraquinone (13)**, $C_{25}H_{24}O_8$, yield 87%, mp 112-114°C ($CHCl_3$), $R_f$ 0.62 (heptane:ethylacetate, 2:1), 0.67 ($CCl_4$:acetone, 8:1). IR spectrum (KBr, ν, cm $^{-1}$): 1774, 1730 [C=O in –OC(O)$CH_3$]; 1704 (C=$O_{sub}$); 1680, 1638 (C=$O_{anth}$); 1580 (Ar).

PMR spectrum ($CDCl_3$, ppm, J/Hz): 7.34 (s, H-2), 7.95 (s, H-4), 7.53 (d, J = 2.7, H-5), 7.04 (d, J = 2.4, H-7), 2.51 (s, C-3, $C\underline{H}_3$), 2.35 [s, 6H, –O–C(O)$CH_3$], 5.10 (m, 1H, >CH), 2.22 (s, 3H, $CH_3$), 1.92 (m, 2H, $CH_2$), 1.52 (m, 2H, $CH_2$), 0.96 (t, 3H, $CH_3$).

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