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SYNTHESIS OF CERTAIN BENZYLIDENE DERIVATIVES OF LAGOCHILIN

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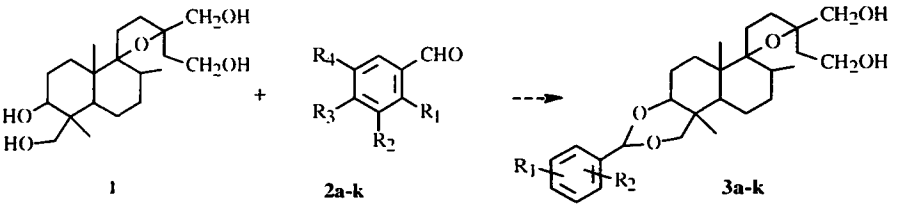
Methods for preparing certain aromatic acetals of 3,15,16,18-tetrahydroxy-9,13-epoxylabdane are described. The structures of the resulting acetals are confirmed by IR and PMR spectra. Certain physicochemical constants of the compounds are presented.

Key words: hemostatics, lagochilin, aromatic aldehydes, aromatic acetals, catalysts, diterpenes.

Lagochilin (**1**) is a diterpene with the grindelane framework. It is a tetra-alcohol [1]. An effective hemostatic preparation and several medicinal formulations are based on lagochilin [2].

The reaction of lagochilin with several aromatic aldehydes, which forms ketals and acetals, and determination of the synthesis conditions seemed interesting. The synthesis of aromatic acetals of lagochilin, which until now had not been studied, followed the scheme:



1 **2a-k** **3a-k**

a: $R_1=R_2=R_3=R_4=H$ **e**: $R_1=R_3=OH$; $R_2=H$
b: $R_1=R_2=R_4=H$; $R_3=OCH_3$ **f**: $R_1=OH$; $R_2=R_4=H$; $R_3=OCH_3$
c: $R_1=R_4=H$; $R_2=R_3=OCH_3$ **i**: $R_1=OH$; $R_2=R_4=H$; $R_3=OC_2H_5$
d: $R_1=OH$; $R_2=R_3=R_4=H$ **k**: $R_1=OH$; $R_2=R_4=H$; $R_3=Br$

Two catalysts, anhydrous $CuSO_4$ and concentrated H_2SO_4, were used for the reaction of lagochilin with aromatic aldehydes containing a hydroxy group in the ring. In the first instance, the yields of the final products were 25-40%; in the second, the final product polymerized.

Aromatic acetals of lagochilin that contain only a methoxy group in the aromatic ring are obtained in rather high yields (55-60%) if H_2SO_4 is used as the catalyst. For anhydrous $CuSO_4$, the yields of final products are low.

All prepared aromatic acetals of lagochilin were purified by column chromatography. The structures of the synthesized compounds were confirmed by IR and PMR spectra. The IR spectra exhibit a broad band at 3300-3400 cm^{-1} for the stretching vibrations of the hydroxyls at the 15- and 16-positions of lagochilin. The hydroxyls are involved in inter- and intramolecular H-bonds. The hydroxyl stretching vibrations in the phenols are observed at 3200 cm^{-1} (compounds **3d-k**). Vibrations characteristic of C=C stretches of the aromatic ring are observed at 1500-1600 cm^{-1}. Deformations of the aromatic CH groups, the frequency of which depend on the type of substituents in the benzene ring, occur at 700-880 cm^{-1}. Symmetric and asymmetric methyl vibrations are observed at 2800-2950 cm^{-1}. In compound **3k**, the C–Br stretching vibration occurs at 620 cm^{-1}.

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The PMR spectra of **3d-k** exhibit singlets for methyl protons of C_8 and C_{10} at 0.80-0.90 ppm. A signal for the methyl protons on C_4 of lagochilin appears at 1 ppm. Signals for $-OCH_2$ protons on C_{15}, C_{16}, and C_{18} are located at 3.4-4.0 ppm. The signal of the tertiary CH proton lies at 5.5 ppm.

The methoxy protons in **3b**, **-c**, and **-f** appear as a singlet at 3.6 ppm. The signal of the $-OCH_2$ proton in the $-OC_2H_5$ group of **3i** is observed at 4.2 ppm as a quartet. The methyl group of the ethoxy group is a triplet at 1.2-1.3 ppm. The remaining protons of the lagochilin framework appear as multiplets at 1.1-1.2 ppm. Signals for the aromatic protons of the synthesized compounds are observed at 6.7-8.0 ppm. The nature of the splitting and the values of the proton signals depend on the position of substituents in the benzene ring.

Thus, we prepared several new aromatic acetals of lagochilin that contain various alkoxy groups as substituents on the aromatic ring. The suggested catalyst is H_2SO_4 or anhydrous $CuSO_4$ if the substituents are OH groups.

EXPERIMENTAL

Silica gel (100×160 μ) was used for column chromatography. Silufol UV-264 plates were used for TLC. The developer was H_2SO_4 (10%) in alcohol. PMR spectra were recorded on a Varian-XL-100-15 instrument; IR spectra, on a UR-20 instrument.

Synthesis of 3,18-Benzyliden-15,16-dihydroxy-9,13-epoxylabdane (3a). Lagochilin (0.356 g) was dissolved in absolute ethanol (15 ml) and treated with benzaldehyde (3 ml). The solution was stirred by a magnetic stirrer for 6 h, treated with anhydrous $CuSO_4$ (1 g), and stirred at 60 C for 24 h. Then the solution was filtered. The filtrate was distilled. The solid was separated on a silica-gel column. Yield of **3a**, 30%, mp 143-144 C, R_f 0.36 [$CHCl_3$—$(CH_3)_2CO$, 1:1].

Synthesis of 3,18-(4-Methoxybenzyliden)-15,16-dihydroxy-9,13-epoxylabdane (3b). Lagochilin (1 g) was dissolved in dioxane (20 ml) and treated with 4-methoxybenzaldehyde (0.76 g) and dropwise with H_2SO_4 (0.2 ml). The reaction was carried out for 7 h in boiling dioxane. The mixture was cooled and treated with Na_2CO_3 solution (5%) until neutral. The precipitate of Na_2SO_4 was filtered off. The dioxane was distilled off. The solid was chromatographed on a column. Yield of **3b**, 55%, R_f 0.73 [$CHCl_3$—$(CH_3)CO$, 5:1].

Synthesis of 3,18-(3,4-Dimethoxybenzyliden)-15,16-dihydroxy-9.13-epoxylabdane (3c). This was performed analogously to that of **3b**. Products were separated by column chromatography. The main product has R_f 0.26 (ethylacetate—acetone, 8:2).

Synthesis of 3,18-(2-Hydroxybenzyliden)-15,16-dihydroxy-9,13-epoxylabdane (3d). This was performed analogously to that of **3a**. The principal product was separated by column chromatography (silica gel, 40×100 μ). Yield of **3d**, 35%, mp 136 C, R_f 0.5 [$CHCl_3$—$(CH_3)_2CO$, 5:1].

Synthesis of 3,18-(2,5-Dihydroxybenzyliden)-15,16-dihydroxy-9,13-epoxylabdane (3e). This was performed analogously to that of **3a** and **3d** in the presence of anhydrous $CuSO_4$. The product was purified on a silica-gel column. Yield of **3e**, 27%, mp 138-139 C, R_f = 0.38 [$CHCl_3$—$(CH_3)_2CO$, 1:1].

Synthesis of 3,18-(2-Hydroxy-4-methoxybenzyliden)-15,16-dihydroxy-9,13-epoxylabdane (3f). This was performed analogously to that of **3a**. The principal product was separated by column chromatography (silica gel, 100×160 μ). Yield of **3f**, 25%, mp 150 C, R_f 0.45 (C_6H_6—CH_3OH, 5:1).

Synthesis of 3,18-(2-Hydroxy-4-ethoxybenzyliden)-15,16-dihydroxy-9,13-epoxylabdane (3i). This was performed analogously to that of **3a**. The principal product was separated by column chromatography (silica gel, 100×160 μ). Yield of **3i**, 30%, mp 167-168 C, R_f 0.42 [$CHCl_3$—$(CH_3)_2CO$, 1:1].

Synthesis of 3,18-(2-Hydroxy-4-bromobenzyliden)-15,16-dihydroxy-9,13-epoxylabdane (3k). This was performed analogously to that of **3a**. The product was separated by column chromatography (silica gel, 100×160 μ). Yield of **3k**, 36%, mp 173-174 C, R_f 0.40 [$CHCl_3$—$(CH_3)_2CO$, 5:1].

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