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PRODUCTION OF NEW LAGOCHILIN DERIVATIVES

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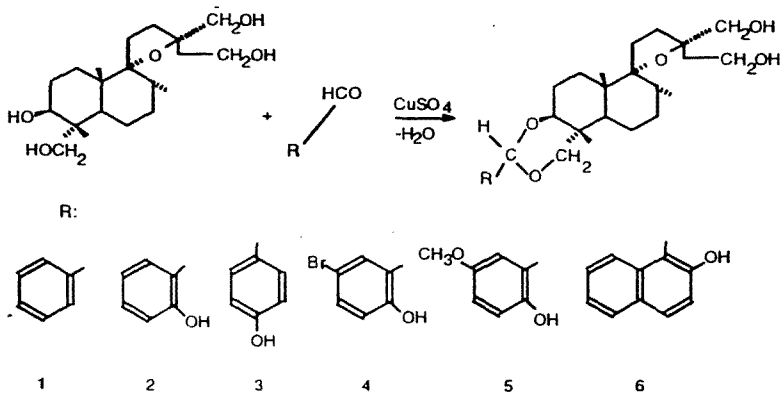
The tetrahydric alcohol lagochilin belongs to the 9,13-epoxylabdane series of diterpenoids. It is produced by many species of plants of the Lagochilus *genus and can be used as the starting material for the synthesis of new compounds with a broad spectrum of physiological action [1, 2]. Many lagochilin derivatives possess hemostatic [3, 4] and antiviral properties. Lagochilin derivatives with aromatic hydroxaldehydes and naphthaldehydes have been synthesized, and the cytotoxic effects of the compounds synthesized in cell cultures have been studied.*

As the starting materials we used lagochilin and the appropriate aromatic aldehydes: benz-, 2-hydroxybenz-, 4-hydroxybenz-, 5-bromo-2-hydroxybenz- and 2-hydroxy-5-methoxybenzaldehydes and 2-hydroxynaphthaldehyde.

The lagochilin derivatives were synthesized by heating with constant stirring an alcoholic solution of lagochilin and the appropriate aldehyde in a ratio of 1:5 in the presence of anhydrous copper sulfate. It was established that the alcohol groups of lagochilin form two types of ketal derivatives. The addition of ketones or aldehydes to the lagochilin molecule takes place first with the participation of the hydroxy groups located at C_3 and C_{18}. A stable 1,3-dioxane ring is formed. Then the addition of the ketones or aldehydes proceeds with the participation of the hydroxy groups at C_{15} and C_{16}, leading to the formation of seven-membered 1,3-dioxane ring [sic]. On reacting with aldehydes (acetaldehyde, benzaldehyde, crotonaldehyde) and ketones (acetone, methyl ethyl ketone and cyclohexanone), lagochilin forms mainly monosubstituted derivatives, but cyclohexanone gives the disubstituted derivative as well [5].

On the interaction of lagochilin with aromatic hydroxyaldehydes only monosubstituted derivatives were formed, their presence being confirmed by IR and PMR spectroscopies. The PMR spectra of the compounds synthesized, taken in CD_3OD, showed the methine proton of an acetal group in the form of a singlet signal in the 5.30-5.50 ppm region. The aromatic protons formed a multiplet signal in the 7.00-7.50 ppm region. In the IR spectrum there were absorption bands in the regions of 3200-3400, 1500-1590, and 1190-1260 cm^{-1} regions, corresponding to the stretching vibration of —OH in an aromatic ring, C=C, and ester groups [sic], respectively.

The cytotoxicity of the compounds synthesized was studied in a culture of chick embryo fibroblasts (CEFs). As standard compounds we used tilorone hydrochloride and the gossypol derivative megosin [6]. The results of the investigation showed that the first reliably expressed cytotoxic change to the cells arose on the addition of 330-450 μg/ml to the culture medium. At the same concentration, tirolone hydrochloride and megosin caused practically complete destruction of the cells.



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EXPERIMENTAL

The individuality of the compounds synthesized was checked by the TLC method on Silufol UV-254 plates in systems 1) chloroform—acetone (5:1) and 2) chloroform—methanol (3:2). For column chromatography we used silica gel L 100/160. The revealing agent was 10% H_2SO_4 in alcohol.

Synthesis of 3,18-O-Benzylidenelagochilin (1). A solution of 0.356 g (0.001 mole) of lagochilin in 15 ml of anhydrous alcohol was added to a solution of 2.0 ml of benzaldehyde, and the mixture was stirred with a magnetic stirrer for 2 h. Then 1 g of anhydrous copper sulfate was added and stirring was continued for another 2 h. After this, the reaction mixture was held at 60°C for 1 h. The course of the reaction was monitored by TLC. After absorption chromatography (system 1) the pure product was obtained. mp 143°C, R_f 0.36, yield 0.14 g (30%).

The following were synthesized analogously:

3,18-O-(2-Hydroxybenzylidene)lagochilin (2). Yield 0.20 g (35%), mp 136°C, R_f 0.5 (system 2).

3,18-O-(4-hydroxybenzylidene)lagochilin (3). Yield 0.18 g (30%), mp 130°C, R_f 0.35 (system 2).

3,18-O-(5-Bromo-2-Hydroxybenzylidene)lagochilin (4). Yield 0.15 g (26%), mp 173°C, R_f 0.4 (system 1).

3,18-O-(2-Hydroxy-5-methoxybenzylidene)lagochilin (5). Yield 0.10 g (17%), mp 150°C, R_f 0.45 (system 1).

3,18-O-(2-Hydroxynaphthylidene)lagochilin (6). Yield 0.10 g (17%), mp 160°C, R_f 0.34 (system 2).

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