CHOLESTERYL ESTERS OF FUROCOUMARIN AND COUMARIN CARBOXYLIC ACIDS

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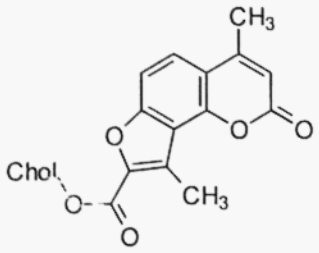
Abstract: Cholesteryl esters of angelicin and psoralen carboxylic acids have been prepared by condensation of o-acetyl(hydroxy)coumarins with cholesteryl chloroacetate in acetonitrile in presence of potassium carbonate. Attempts to prepare these esters starting from furocoumarin carboxylic acids turned to be unsuccessful. Cholesteryl ester of 2-(4-methyl-7-coumarinyloxy)butanoic acid has been prepared via alkylation of the acid by cholesteryl tosylate. The resulted cholesteryl esters form thin films fitted for the Langmuir technology.

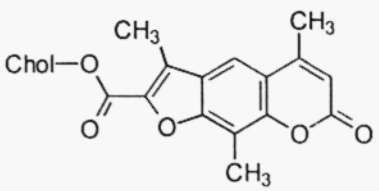
Introduction

Cholesteryl esters of benzene carboxylic acids are well known for their mesomorphic behavior and use in liquid crystal devices (1,2). Cholesteryl esters of coumarin and furocoumarin carboxylic acids have not been synthesized yet, although cholesteryl ethers of hydroxycoumarins have been obtained and showed marked mesomorphism (3). Cholesteryl derivatives seem to be much of interest also in the Langmuir thin film technology, since many furocoumarins and coumarins are famous for their good photosensitive properties (4-6).

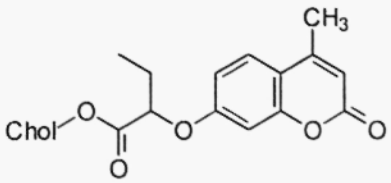
We have prepared cholesteryl ester of 4,9-dimethylangelicin-8-carboxylic acid **1a**, cholesteryl ester of 4,6,8-trimethylpsoralen-7-carboxylic acid **2** and cholesteryl ester of 2-(4-methyl-7-coumarinyloxy)butanoic acid **3a** and have performed a preliminary screening of their thin films formation ability.



1a



2



3a

Results and Discussion

Syntheses of esters 1a, 2, 3a have been firstly planned with initial preparation of the corresponding carboxylic acids. With this aim we have modified synthesis of 4,9-dimethylangelicin-8-carboxylic acid 1c (7) shown in the Scheme 1. The Fries rearrangement of 7-hydroxy-4-methylcoumarin acetate 5 has been done by the ordinary way with good yield of 8-acetyl-7-hydroxy-4-methylcoumarin 6. However, we have changed the experimental conditions of condensation of coumarin 6 with esters of α-halogenocarboxylic acids. This condensation is a key step of many furocoumarins syntheses. Use of acetonitrile (instead of 2-butanone recommended by (7)) as a solvent and potassium carbonate as a base reagent led to certain improvement of the reaction results. Condensation of 6 with diethyl bromomalonate underwent for 0.5 hr (instead of 6 hr) with a fairly good yield, 83% (instead of 30%). Resulted ethyl 4,9-dimethylangelicin-8-carboxylate 1b has been treated by aqueous potassium hydroxide solution, then acidified with formation of acid 1c.

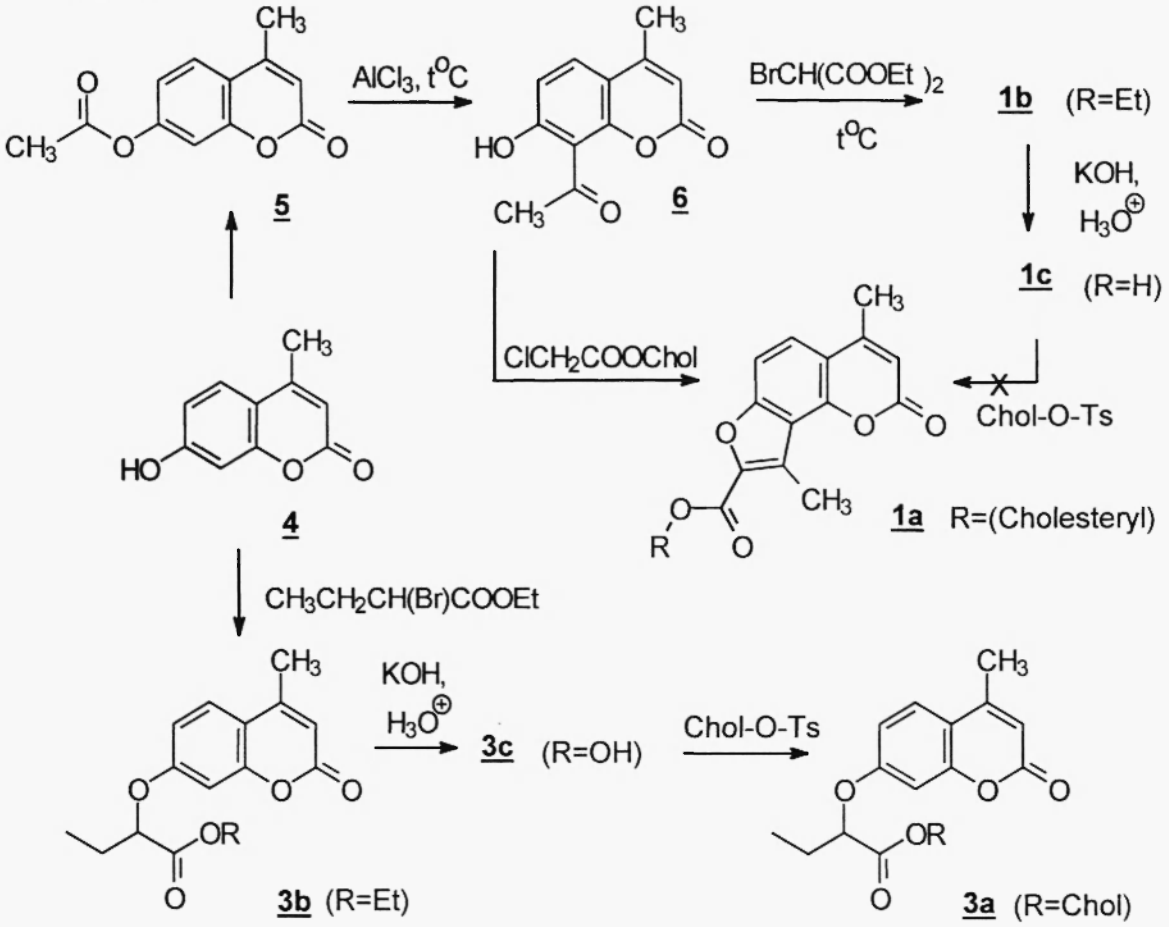
Unfortunately, both procedures of the ester 1a preparation started from acid 1c turned to be unsuccessful. We could not isolate ester 1a among products of interaction of potassium salts of acid 1c with cholesteryl tosylate 7. We could not get ester 1a with good yield neither by interaction of the corresponding acid chloride with cholesterol.

Ester 1a became available via condensation reaction of cholesteryl chloroacetate 8 with coumarin 6 (Scheme 1). This reaction has been performed in boiling acetonitrile in presence of potassium carbonate. Moderate yield of 1a has been achieved (catalytic amount of the crown ether18-dibenzocrown-6 improves the reaction results). However, this procedure has provided rather poor yield of the overcrowded ester 2, when 6-acetyl-7-hydroxy-4,8-dimethylcoumarin 9 has been treated by chloroacetate 8.

Ester 3a has been prepared from 7-hydroxy-4-methylcoumarin 4 as it is shown in the Scheme 1. O-Alkylation of coumarin 4 by ethyl 2-bromobutanoate in presence of potassium carbonate in

acetonitrile gave ester **3b**. Followed basic hydrolysis of ester **3b** gave 2-(4-methyl-7-coumarinyloxy)butanoic acid **3c**. Direct alkylation of acid **3c** by tosylate 7 was successful and led to ester **3a** with a rather good yield.

Scheme 1



Esters **1a** and **3a** have been tested in the Langmuir thin film technology. The formed samples of films turned to have a good quality.

Experimental

The coumarin and furocoumarin derivatives **4**-**6**, **1b**, **1c**, **9**, **3b** and **3c** were obtained by previously reported procedures (7-11). These compounds have been identified by their melting points and spectral data. The compounds numbers, the measured melting points (in °C) and references are listed below: **4**, 194-195, (8); **5**, 153-154, (9); **6**, 162-163, (9); **1b**, 188-189, (7); **1c**, 312-313, (7); **9**, 193-194, (10); **3b**, 52-53, (11); **3c**, 167-168, (11).

^{1}H NMR and Mass spectra

^{1}H-NMR spectra were recorded on a WP 200 (Bruker) spectrometer at 200 MHz in $CDCl_3$ solutions using TMS as an internal standard. Chemical shifts are given in ppm.

The FAB mass spectra were determined on a SSQ-710 (Finnigan MAT) spectrometer.

Cholesteryl ester of 4,9-dimethyl-8-angelicin carboxylic acid 1a:

To a solution of coumarin **6** (2 mmol, 0.4 g) and potassium carbonate (6 mmol, 0.83 g) in 50 ccm of acetonitrile cholesteryl chloroacetate **8** (2.2 mmol, 1,02 g) in 15 ccm of acetonitrile was added. Then the reaction mixture was refluxed, with stirring, for 24 h. After end of the reaction (TLC-control) the solvent was distilled off. The residue was treated by water (75 ccm) and diluted HCl to pH 3. The precipitate was washed with water. Then it was purified by a silica gel column chromatography (chloroform:n-hexane=1:1), yielding white crystals (25%); m.p.229-230°C; ^{1}H NMR: δ 0.697 (s, 3H, 18-CH_3), 0.871 (d, J=6.4 Hz, 6H, $CH(\underline{CH_3})_2$), 0.927 (d, J=6.0 Hz, 3H, 21-CH_3), 1.087 (s, 3H, 19-CH_3), 2.496 (d, J=1.06 Hz, 3H, 4-CH_3), 2.896 (s, 3H, 9-CH_3), 4.930 (m, 1H, 3-H-chol), 5.445 (d, J=4.14 Hz, 1H, 6-H-chol), 6.286 (d, J=1.06 Hz, 1H, 3-H), 7.455 (d, J=8.82 Hz, 1H, 6-H), 7.630 (d, J=8.82 Hz,1H, 5-H).

MS: m/z (%) 627 (M^++1, 40), 369 ($C_{27}H_{45}$,60), 259 ($C_{14}H_{11}O_5$,100).

Cholesteryl ester of 4,6,8-trimethylpsoralen-7- carboxylic acid 2:

Ester **2** has been prepared and purified by similar procedure, white crystals, m.p.232-233°C, ^{1}H NMR: δ 0.698 (s, 3H, 18-CH_3), 0.869 (d, J=6.62 Hz, 6H, $CH(\underline{CH_3})_2$), 0.925 (d, J=6.02 Hz, 3H, 21-CH_3), 2.529 (d, J=1.08 Hz, 3H, 5-CH_3), 2.618 (s, 3H, 9-CH_3), 2.644 (s, 3H, 3-CH_3), 4.95 (m, 1H, 3-H-chol), 5.445 (d, J=4.52 Hz, 1H, 6-H-chol), 6.286 (d, J=1.08 Hz, 1H, 6-H-coum), 7.656 (s, 1H, 4-H-coum).

MS: m/z (%) 640 (M^+1,19).

Cholesteryl ester of 2-(4-methyl-7-coumarinyloxy) butanoic acid 3a:

To a solution of acid **3c** (2 mmol, 0.52 g) and potassium carbonate (6 mmol, 0.83 g) in 50 ccm of acetonitrile cholesteryl tosylate **7** (2.2 mmol, 1,19 g) in 15 ccm of acetonitrile was added. Then the reaction mixture was refluxed, with stirring, for 8 h. After end of the reaction (TLC-control) the solvent was distilled off. The residue was treated by water (75 ccm) and diluted HCl to pH 3. The precipitate was washed with water, then it was purified by a silica gel column chromatography

(chloroform:n-hexane=1:1), yielding white oil (35%); ^{1}H NMR: δ 0.671 (s, 3H, 18-CH$_3$), 0.861 (d, J=6.4 Hz, 6H, CH(C<u>H</u>$_3$)$_2$), 0.926 (d, J=6.32 Hz, 3H, 21-CH$_3$), 2.393 (d, J=0.94 Hz, 3H, 4-CH$_3$), 4.612 (m, 4H, 3-H-chol + -OCH- + -OCH-C<u>H</u>$_2$-), 6.130 (d, J=0.94 Hz, 1H, 3-H-coum), 5.364 (d, J=5.12 Hz, 1H, 6-H-chol), 6.76 (d, J=2.54 Hz, 1H, 8-H), 6.866 (dd, J=8.84 Hz, J=2.54 Hz, 1H, 6-H), 7.488 (d, J=8.84 Hz, 1H, 5-H).

MS: m/z (%) 631 (M^++1, 30), 369 ($C_{27}H_{45}$, 40), 263 ($C_{14}H_{15}O_5$, 100).

Acknowledgments

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