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MODIFIED COUMARINS. 20. FUROCOUMARIN DERIVATIVES OF CYTISINE

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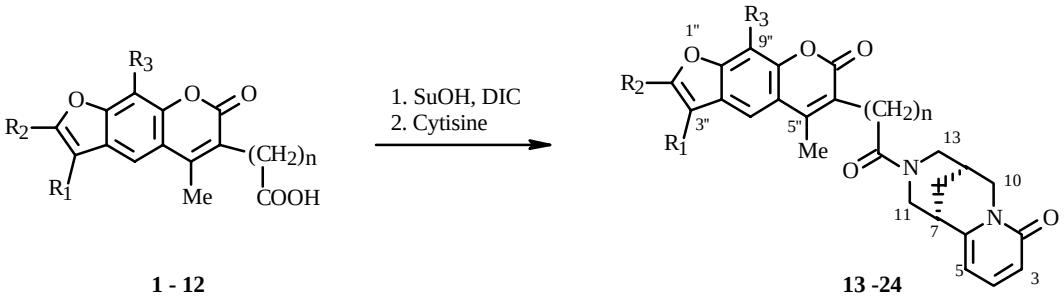
Cytisine derivatives modified by furocoumarins were synthesized using activated esters.

Key words: cytisine, coumarins, furocoumarins, acylation, activated esters.

Many important natural compounds are based on the furocoumarin structure [1]. Highly active pharmacological compounds are known among natural and synthetic furocoumarins [2].

On the other hand, the alkaloid cytisine and its derivatives possess a broad spectrum of biological activity [3, 4]. Therefore, a large number of publications on the chemical modification and study of the properties of cytisine have appeared [5-8]. Thus, addition to cytisine of a furocoumarin ring as a substituent is interesting both to the chemistry of alkaloids and coumarins and to the targeted search for new biologically active compounds.

Starting furocoumarins **1-12** that contain a carboxylic acid were prepared by the MacLeod method [9, 10]. Cytisine was *N*-acylated using activated esters [11], a method that is widely employed in peptide synthesis. The carboxylic acid was activated as the highly reactive *N*-hydroxysuccinimide ester [12]. Activated esters were prepared by reacting the corresponding acids **1-12** and *N*-hydroxysuccinimide (SuOH) in absolute dioxane using diisopropylcarbodiimide (DIC) as the condensing agent. Condensation of the resulting activated esters with cytisine in dioxane at room temperature gives in high yields the *N*-acyl cytisine derivatives **13-24**, the molecules of which contain furocoumarin moieties.



1 - 12 **13 -24**

1, 13: R_1 = Me, R_2 = R_3 = H, n = 1; **2, 14:** R_1 = R_3 = Me, R_2 = H, n = 1; **3, 15:** R_1 = R_2 = Me, R_3 = H, n = 1; **4, 16:** R_1 = R_2 = R_3 = Me, n = 1; **5,17:** R_1R_2 = $(CH_2)_4$, R_3 = H, n = 1; **6, 18:** R_1R_2 = $(CH_2)_4$, R_3 = Me, n = 1; **7, 19:** R_1 = Me, R_2 = R_3 = H, n = 2; **8, 20:** R_1 = R_3 = Me, R_2 = H, n = 2; **9, 21:** R_1 = R_2 = Me, R_3 = H, n = 2; **10, 22:** R_1 = R_2 = R_3 = Me, n = 2; **11, 23:** R_1R_2 = $(CH_2)_4$, R_3 = H, n = 2; **12, 24:** R_1R_2 = $(CH_2)_4$, R_3 = Me, n = 2

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The PMR spectra revealed that a doubled set of signals was observed for all prepared compounds. Obviously invertomers with hindered rotation about the N–C bond that could be viewed as *Z*- and *E*-isomers were formed as a result of amide conjugation in these systems. The presence of amide conjugation was confirmed by variable temperature experiments. Thus, heating samples of the prepared compounds to 100°C caused the PMR signals to coalesce owing to free rotation around the N–C bond.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck 60 F254 plates using $CHCl_3$:CH_3OH (9:1 and 1:9) as eluent. Melting points were determined on a Kofler block. PMR spectra were recorded on a Varian VXR-300 spectrometer at 300 MHz relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

Furocoumarins **1-12** were synthesized as before [9, 10]. We used pharmacopeic cytisine isolated from *Thermopsis lanceolata*.

General Method of Cytisine *N*-acylation. A solution of acids **1-12** (3 mmol) and *N*-hydroxysuccinimide (0.38 g, 3.3 mmol) in absolute dioxane (20 mL) was stirred vigorously, treated with diisopropylcarbodiimide (0.52 mL, 3.3 mmol), and stirred for 2 h (course of reaction monitored by TLC). The resulting activated ester was treated with cytisine (0.63 g, 3.3 mmol) and stirred vigorously for 2-4 h (course of reaction monitored by TLC). When the reaction was complete, water (200 mL) was added and acidified to pH 5-6. The resulting precipitate was filtered off and crystallized from propan-2-ol.

***N*-[(3,5)-Dimethyl-7-oxofuro[3,2-*g*]chromen-6-yl)acetyl]cytisine (13).** Yield 84%, $C_{26}H_{24}N_2O_5$, mp 276.5-278°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.99 and 2.08 (2H, 2 br.s, CH_2-8), 2.27 (6H, s, CH_3-3″, CH_3-5″), 2.54 (1H, m, H-9), 2.85-3.06 (2H, m, H-7, H-11a), 3.38-3.85 (4H, m, CH_2-10, CH_2-13), 4.06 and 4.24 (2H, 2 d, J = 15.6, CH_2-1′), 4.48 and 4.58 (1H, 2 d, J = 13.2, H-11e), 6.09 and 6.18 (1H, 2 d, J = 6.9, H-5), 6.22 (1H, d, J = 6.9, H-3), 7.24-7.32 (1H, m, H-4), 7.46 (1H, s, H-9″), 7.74 (1H, br.s, H-4″), 7.86 (1H, br.s, H-2″).

***N*-[(3,5,9-Trimethyl-7-oxofuro[3,2-*g*]chromen-6-yl)acetyl]cytisine (14).** Yield 79%, $C_{27}H_{26}N_2O_5$, mp 307.5-309°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.97 and 2.09 (2H, 2 br.s, CH_2-8), 2.25 (3H, s, CH_3-3″), 2.46 (6H, s, CH_3-5″, CH_3-9″), 2.54 (1H, m, H-9), 2.80-3.02 (2H, m, H-7, H-11a), 3.40-3.86 (4H, m, CH_2-10, CH_2-13), 4.09 and 4.28 (2H, 2 d, J = 15.6, CH_2-1′), 4.44 and 4.58 (1H, 2 d, J = 13.2, H-11e), 6.09 and 6.21 (1H, 2 d, J = 6.9, H-5), 6.22 (1H, d, J = 6.9, H-3), 7.24-7.34 (1H, m, H-4), 7.68 (1H, s, H-2″), 7.74 (1H, s, H-4″).

***N*-[(2,3,5-Trimethyl-7-oxofuro[3,2-*g*]chromen-6-yl)acetyl]cytisine (15).** Yield 86%, $C_{27}H_{26}N_2O_5$, mp 293-294.5°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.95 and 2.04 (2H, 2 br. s, CH_2-8), 2.16 (3H, s, CH_3-3″), 2.36 (3H, s, CH_3-2″), 2.39 (3H, s, CH_3-5″), 2.54 (1H, m, H-9), 2.84-2.98 (2H, m, H-7, H-11a), 3.39-3.86 (4H, m, CH_2-10, CH_2-13), 4.07 and 4.25 (2H, 2 d, J = 15.6, CH_2-1′), 4.42 and 4.59 (1H, 2 d, J = 13.2, H-11e), 6.10 and 6.19 (1H, 2 d, J = 6.9, H-5), 6.22 (1H, d, J = 6.9, H-3), 7.27-7.32 (1H, m, H-4), 7.35 (1H, s, H-9″), 7.67 and 7.69 (1H, 2 s, H-4″).

***N*-[(2,3,5,9-Tetramethyl-7-oxofuro[3,2-*g*]chromen-6-yl)acetyl]cytisine (16).** Yield 86%, $C_{28}H_{28}N_2O_5$, mp 318-319.5°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.95 and 2.04 (2H, 2 br. s, CH_2-8), 2.16 (3H, s, CH_3-3″), 2.39 and 2.43 (9H, 2 s, CH_3-2″, CH_3-5″, CH_3-9″), 2.54 (1H, m, H-9), 2.82-3.02 (2H, m, H-7, H-11a), 3.40-3.85 (4H, m, CH_2-10, CH_2-13), 4.09 and 4.26 (2H, 2 d, J = 15.6, CH_2-1′), 4.39 and 4.58 (1H, 2 d, J = 13.2, H-11e), 6.10 and 6.19 (1H, 2 d, J = 6.9, H-5), 6.22 (1H, d, J = 6.9, H-3), 7.28 (1H, t, J = 6.9, H-4), 7.52 (1H, s, H-4″).

***N*-[(4-Methyl-2-oxo-6,7,8,9-tetrahydro[1]benzofuro[3,2-*g*]chromen-3-yl)acetyl]cytisine (17).** Yield 84%, $C_{29}H_{28}N_2O_5$, mp 200.5-202°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.85 (2H, m, CH_2-7″), 1.92 (2H, m, CH_2-8″), 1.96 and 2.08 (2H, 2 br. s, CH_2-8), 2.46 (3H, s, CH_3-4″), 2.54 (1H, m, H-9), 2.63 (2H, m, CH_2-6″), 2.73 (2H, m, CH_2-9″), 2.84-3.02 (2H, m, H-7, H-11a), 3.38-3.84 (4H, m, CH_2-10, CH_2-13), 4.09 and 4.27 (2H, 2 d, J = 15.6, CH_2-1′), 4.40 and 4.57 (1H, 2 d, J = 13.2, H-11e), 6.10 and 6.20 (1H, 2 d, J = 6.9, H-5), 6.23 (1H, d, J = 6.9, H-3), 7.28 (1H, t, J = 6,9, H-4), 7.41 (1H, s, H-11″), 7.71 (1H, br. s, H-5″).

***N*-[(4,11-Dimethyl-2-oxo-6,7,8,9-tetrahydro[1]benzofuro[3,2-*g*]chromen-3-yl)acetyl]cytisine (18).** Yield 81%, $C_{30}H_{30}N_2O_5$, mp 287-289°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.84 (2H, m, CH_2-7″), 1.93 (2H, m, CH_2-8″), 1.94 and 2.04 (2H, 2 br. s, CH_2-8), 2.44 (3H, s, CH_3-4″, CH_3-11″), 2.54 (1H, m, H-9), 2.61 (2H, m, CH_2-6″), 2.73 (2H, m, CH_2-9″), 2.85-3.01 (2H, m, H-7, H-11a), 3.39-3.82 (4H, m, CH_2-10, CH_2-13), 4.08 and 4.25 (2H, 2 d, J = 15.6, CH_2-1′), 4.41 and 4.58 (1H, 2 d, J = 13.2, H-11e), 6.12 and 6.21 (1H, 2 d, J = 6.9, H-5), 6.22 (1H, d, J = 6.9, H-3), 7.27 (1H, t, J = 6.9, H-4), 7.52 (1H, br. s, H-5″).

***N*-[3-(3,5-Dimethyl-7-oxofuro[3,2-*g*]chromen-6-yl)propionyl]cytisine (19).** Yield 87%, $C_{27}H_{26}N_2O_5$, mp 185.5-187°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.95-2.04 (2H, m, CH_2-8), 2.29 (3H, s, CH_3-3″), 2.39 (3H, s, CH_3-5″), 2.20-2.75 (5H, m, H-9, CH_2-1′, CH_2-2′), 2.82 (1H, m, H-11a), 3.14 (1H, m, H-7), 3.34 and 3.42 (1H, 2 d, J = 13.2, H-13a), 3.60-3.70 (1H, m, H-10a), 3.82-4.09 (2H, m, H-10e, H-13e), 4.42 and 4.64 (1H, 2 d, J = 13.2, H-11e), 6.12-6.21 (2H, m, H-3, H-5), 7.20-7.28 (1H, m, H-4), 7.48 (1H, br. s, H-9″), 7.76 (1H, s, H-4″), 7.90 (1H, br.s, H-2″).

***N*-[3-(3,5,9-Trimethyl-7-oxofuro[3,2-*g*]chromen-6-yl)propionyl]cytisine (20).** Yield 69%, $C_{28}H_{28}N_2O_5$, mp 153.5-155°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.94-2.05 (2H, m, CH_2-8), 2.25 (3H, s, CH_3-3″), 2.38 (3H, s, CH_3-9″), 2.44 (3H, s, CH_3-5″), 2.20-2.75 (5H, m, H-9, CH_2-1′, CH_2-2′), 2.82 (1H, m, H-11a), 3.14 (1H, m, H-7), 3.34 and 3.42 (1H, 2 d, J = 13.2, H-13a), 3.60-3.70 (1H, m, H-10a), 3.82-4.09 (2H, m, H-10e, H-13e), 4.42 and 4.64 (1H, 2 d, J = 13.2, H-11e), 6.12-6.21 (2H, m, H-3, H-5), 7.20-7.28 (1H, m, H-4), 7.65 (1H, s, H-2″), 7.74 (1H, s, H-4″).

***N*-[3-(2,3,5-Trimethyl-7-oxofuro[3,2-*g*]chromen-6-yl)propionyl]cytisine (21).** Yield 78%, $C_{28}H_{28}N_2O_5$, mp 221.5-223°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.90-2.05 (2H, m, CH_2-8), 2.19 (3H, s, CH_3-3″), 2.36 (3H, s, CH_3-2″), 2.39 (3H, s, CH_3-5″), 2.20-2.69 (5H, m, H-9, CH_2-1′, CH_2-2′), 2.82 (1H, m, H-11a), 3.14 (1H, m, H-7), 3.32 and 3.43 (1H, 2 d, J = 13.2, H-13a), 3.60-3.70 (1H, m H-10a), 3.83-4.09 (2H, m, H-10e, H-13e), 4.43 and 4.62 (1H, 2 d, J = 13.2, H-11e), 6.08-6.19 (2H, m, H-3, H-5), 7.20-7.30 (1H, m, H-4), 7.34 and 7.38 (1H, 2 d, H-9″), 7.70 (1H, s, H-4″).

***N*-[3-(2,3,5,9-Tetramethyl-7-oxofuro[3,2-*g*]chromen-6-yl)propionyl]cytisine (22).** Yield 87%, $C_{29}H_{30}N_2O_5$, mp 146-147.5°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.86-2.04 (2H, m, CH_2-8), 2.16 (3H, s, CH_3-3″), 2.33 (3H, s, CH_3-2″), 2.42 (6H, s, CH_3-5″, CH_3-9″), 2.20-2.70 (5H, m, H-9, CH_2-1′, CH_2-2′), 2.81 (1H, m, H-11a), 3.14 (1H, m, H-7), 3.30 and 3.39 (1H, 2 d, J = 13.2, H-13a), 3.58-3.70 (1H, m, H-10a), 3.83-4.10 (2H, m, H-10e, H-13e), 4.42 and 4.64 (1H, 2 d, J = 13.2, H-11e), 6.05-6.16 (2H, m, H-3, H-5), 7.20-7.28 (1H, m, H-4), 7.50 (1H, s, H-4″).

***N*-[3-(4-Methyl-2-oxo-6,7,8,9-tetrahydro[1]benzofuro[3,2-*g*]chromen-3-yl)propionyl]cytisine (23).** Yield 73%, $C_{30}H_{30}N_2O_5$, mp 239.5-241°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.80-2.05 (6H, m, CH_2-8, CH_2-7″, CH_2-8″), 2.33 (3H, s, CH_3-4″), 2.20-2.70 (7H, m, H-9, CH_2-1′, CH_2-2′, CH_2-6″), 2.73 (2H, m, CH_2-9″), 2.82 (1H, m, H-11a), 3.14 (1H, m, H-7), 3.31 and 3.40 (1H, 2 d, J = 13.2, H-13a), 3.60-3.70 (1H, m, H-10a), 3.84-4.09 (2H, m, H-10e, H-13e), 4.44 and 4.62 (1H, 2 d, J = 13.2, H-11e), 6.06-6.17 (2H, m, H-3, H-5), 7.20-7.28 (1H, m, H-4), 7.38 and 7.40 (1H, 2 s, H-9″), 7.68 (1H, s, H-5″).

***N*-[3-(4,11-Dimethyl-2-oxo-6,7,8,9-tetrahydro[1]benzofuro[3,2-*g*]chromen-3-yl)propionyl]cytisine (24).** Yield 86%, $C_{31}H_{32}N_2O_5$, mp 192-193.5°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.80-2.05 (6H, m, CH_2-8, CH_2-7″, CH_2-8″), 2.31 (3H, s, CH_3-11″), 2.42 (3H, s, CH_3-4″), 2.20-2.70 (7H, m, H-9, CH_2-1′, CH_2-2′, CH_2-6″), 2.74 (2H, m, CH_2-9″), 2.83 (1H, m, H-11a), 3.14 (1H, m, H-7), 3.30 and 3.39 (1H, 2 d, J = 13.2, H-13a), 3.58-3.66 (1H, m, H-10a), 3.83-4.08 (2H, m, H-10e, H-13e), 4.44 and 4.64 (1H, 2 d, J = 13.2, H-11e), 6.06-6.17 (2H, m, H-3, H-5), 7.20-7.28 (1H, m, H-4), 7.48 (1H, s, H-5″).

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