

MODIFIED COUMARINS. 25. *N*-ACYL CYTISINE DERIVATIVES CONTAINING A COUMARIN FRAGMENT

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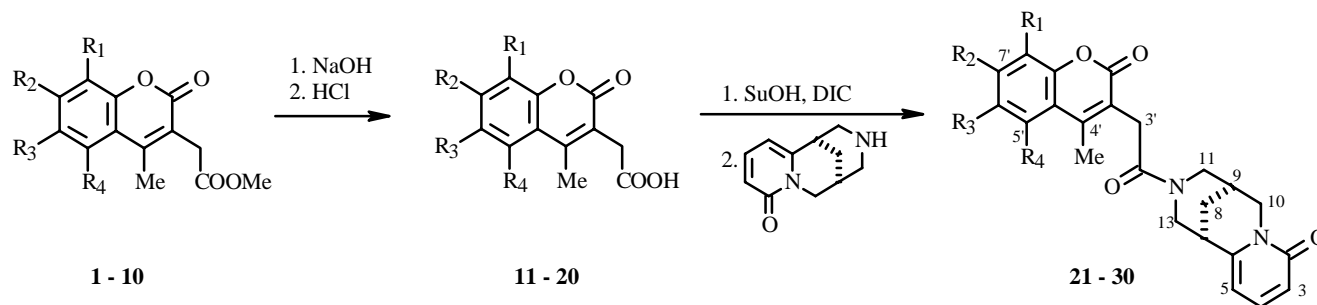
UDC 547.814.5

New modified cytosine derivatives were prepared by acylation with coumarin-3-acetic acids.

Key words: cytosine, coumarins, acylation, activated esters.

Addition of a natural alkaloid fragment to organic molecules leads in most instances to the appearance of new pharmacological properties in the synthesized compounds. Research on the chemical modification of cytosine is interesting because of the broad spectrum of its biological activity. In continuation of our work on modification of the cytosine structure by introducing the benzopyran structure into it [1, 2], herein we report the preparation of new *N*-acyl cytosine derivatives containing the widely distributed coumarin fragment.

Methyl esters of coumarin-3-acetic acid (**1-5**) that were required for further transformations were prepared by Pechmann condensation of polyphenols (resorcinol, 2-methylresorcinol, 4-chlororesorcinol, phloroglucinol, and orcinol) with dimethylacetylsuccinate in the presence of dry HCl as a condensing agent at 0°C [3]. Alkylation of **1-5** under Williamson reaction conditions by dimethylsulfate formed methoxy derivatives **6-10**. Saponification of **1-10** by NaOH solution (1 M) in aqueous propan-2-ol with subsequent acidolysis synthesized the corresponding coumarin-3-acetic acids **11-20**.



1, 6, 11, 16, 21, 26: R₁ = R₃ = R₄ = H; **2, 7, 12, 17, 22, 27:** R₁ = Me, R₃ = R₄ = H; **1 - 4, 11 - 14, 21 - 24:** R₂ = OH;

3, 8, 13, 18, 23, 28: R₁ = R₄ = H, R₃ = Cl; **4, 14, 24:** R₁ = R₃ = H, R₄ = OH; **9, 19, 29:** R₁ = R₃ = H, R₄ = OMe;

5, 15, 25: R₁ = R₃ = H, R₂ = Me, R₄ = OH; **6 - 9, 16 - 19, 26 - 29:** R₂ = OMe; **10, 20, 30:** R₁ = R₃ = H, R₂ = Me, R₄ = OMe

The method of activated esters [4] that is widely used in peptide synthesis was used for *N*-acylation of the secondary N atom of cytosine. The carboxylic acid was activated using typically highly reactive *N*-hydroxysuccinimide ester [5].

Activated esters were prepared by reacting the corresponding acids **11-20** and *N*-hydroxysuccinimide (SuOH) in absolute dioxane using diisopropylcarbodiimide (DIC) as a condensing agent. The resulting activated esters were condensed with cytosine in dioxane at room temperature to form in high yields (62-91%) *N*-acyl cytosine derivatives **21-30**, which contain coumarin moieties.

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The PMR spectra of **21-30** contained signals characteristic of both cytosine and benzopyran-2-one. All prepared compounds exhibited a doubled set of proton signals in the PMR spectra. Obviously rotation about the N–C bond was hindered as a result of the formation of amide conjugation in invertomers that could be viewed as *Z*- and *E*-isomers. Amide conjugation in the synthesized compounds was confirmed by variable temperature experiments. Heating the products to 100°C caused coalescence of signals in the PMR spectrum as a result of free rotation of substituents about the N–C bond.

EXPERIMENTAL

The course of reactions and the purity of products were monitored by TLC on Merck 60 F254 plates with elution by CHCl₃:CH₃OH (9:1 and 19:1). Melting points were determined on a Kofler block. PMR spectra were recorded on Varian VXR-300 and Varian Mercury 400 spectrometers at 300 and 400 MHz, respectively, relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

Hydroxycoumarins **1** and **2** were prepared as before [3]. We used pharmacopeic cytosine isolated from *Thermopsis lanceolata*.

Methyl-2-(6-chloro-7-hydroxy-4-methyl-2-oxochromen-3-yl)acetate (3). A cooled (0°C) solution of 4-chlororesorcinol (14.46 g, 0.1 mol) and dimethylacetylsuccinate (16.2 mL, 0.1 mol) in absolute methanol (50 mL) was stirred vigorously with cooling. A stream of dry HCl was passed through for 3 h. The mixture was stirred until thick, left overnight at room temperature, and poured into icewater (500 mL). The resulting precipitate was filtered off and crystallized from aqueous methanol, yield 65%, mp 240–241°C, C₁₃H₁₁ClO₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm): 2.34 (3H, s, Me-4'), 3.62 (2H, s, CH₂-2), 3.64 (3H, s, COOMe), 6.87 (1H, s, H-8'), 7.73 (1H, s, H-5'), 11.17 (1H, s, OH-7').

Methyl-(5,7-dihydroxy-4-methyl-2-oxochromen-3-yl)acetate (4) was prepared analogously to **3** starting with phloroglucinol dihydrate (16.21 g, 0.1 mol) and dimethylacetylsuccinate (18.82 g, 0.1 mol), yield 86%, mp 259–260°C, C₁₃H₁₂O₆.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.49 (3H, s, Me-4'), 3.60 (2H, s, CH₂-3'), 3.61 (3H, s, COOMe), 6.18 (1H, d, J = 2.0, H-6'), 6.29 (1H, d, J = 2.0, H-8'), 10.29 and 10.57 (2H, two s, OH-5' and OH-7').

Methyl-(5-hydroxy-4,7-dimethyl-2-oxochromen-3-yl)acetate (5) was prepared analogously to **3** starting with orcinol monohydrate (14.2 g, 0.1 mol) and dimethylacetylsuccinate (18.82 g, 0.1 mol), yield 73%, mp 233–234°C, C₁₄H₁₄O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm): 2.29 (3H, s, Me-7'), 2.54 (3H, s, Me-4'), 3.61 (2H, s, CH₂-3'), 3.63 (3H, s, COOMe), 6.56 (2H, s, H-6', H-8'), 10.38 (1H, s, OH-5').

General Method of Synthesizing Methoxycoumarins 6-10. A hot solution of **1-5** (10 mmol) in absolute acetone (50 mL) was treated with freshly calcined potash (4.14 g, 30 mmol), stirred vigorously and heated (50–56°C), and treated with dimethylsulfate (1.1 mL, 11 mmol) [for **4**, potash (5.52 g, 40 mmol) and dimethylsulfate (2.2 mL, 22 mmol)]. The mixture was heated for 2–4 h and vigorously stirred (course of reaction monitored by TLC). After the reaction was complete, the mixture was cooled, poured into icewater (500 mL), and acidified to pH 5–6. The resulting precipitate was filtered off and crystallized from methanol.

Methyl-(7-methoxy-4-methyl-2-oxochromen-3-yl)acetate (6). Yield 89%, mp 136–137°C, lit. [6] mp 122°C, C₁₄H₁₄O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.37 (3H, s, Me-4'), 3.65 (5H, s, CH₂-3', COOMe), 3.86 (3H, s, MeO-7'), 6.87 (1H, dd, J = 2.4, 8.7, H-6'), 6.93 (1H, d, J = 2.4, H-8'), 7.68 (1H, d, J = 8.7, H-5').

Methyl-(7-methoxy-4,8-dimethyl-2-oxochromen-3-yl)acetate (7). Yield 92%, mp 153–154°C, C₁₅H₁₆O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.20 (3H, s, Me-8'), 2.37 (3H, s, Me-4'), 3.63 (5H, s, CH₂-3', COOMe), 3.91 (3H, s, MeO-7'), 7.01 (1H, d, J = 9.0, H-6'), 7.62 (1H, d, J = 9.0, H-5').

Methyl-(6-chloro-7-methoxy-4-methyl-2-oxochromen-3-yl)acetate (8). Yield 87%, mp 162–163°C, C₁₄H₁₃ClO₅.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm): 2.36 (3H, s, Me-4'), 3.63 (2H, s, CH₂-3'), 3.67 (3H, s, COOMe), 3.95 (3H, s, MeO-7'), 7.18 (1H, s, H-6'), 7.83 (1H, s, H-5').

Methyl-(5,7-dimethoxy-4-methyl-2-oxochromen-3-yl)acetate (9). Yield 79%, mp 149–150°C, C₁₅H₁₆O₆.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.46 (3H, s Me-4'), 3.62 (3H, s, COOMe), 3.64 (2H, s, CH₂-3'), 3.85 and 3.87 (6H, two s, MeO-5', MeO-7'), 6.51 (1H, d, J = 2.4, H-8'), 6.58 (1H, d, J = 2.4, H-6').

Methyl-(5-methoxy-4,7-dimethyl-2-oxochromen-3-yl)acetate (10). Yield 86%, mp 173-174°C, C₁₅H₁₆O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm): 2.38 (3H, s, Me-7'), 2.49 (3H, s, Me-4'), 3.63 (5H, s, CH₂-3', COOMe), 3.88 (3H, s, MeO-5'), 6.73 (2H, s, H-6', H-8').

General Method for Synthesizing Acids 11-20. A solution or suspension of ester **1-10** (5 mmol) in propan-2-ol (10 mL) was treated with NaOH solution (20 mL, 20 mmol, 1 M). The mixture was heated and stirred for 0.5-1 h (course of reaction monitored by TLC). After the reaction was complete the mixture was cooled, poured into icewater (100 mL), and acidified to pH 5-6. The resulting precipitate was filtered and crystallized from aqueous propan-2-ol.

(7-Hydroxy-4-methyl-2-oxochromen-3-yl)acetic Acid (11). Yield 72%, mp 268-269°C, lit. [6] mp 265°C, [7, 8] 265-268, [9] 268, C₁₂H₁₀O₅.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.33 (3H, s, Me-4'), 3.51 (2H, s, CH₂-3'), 6.66 (1H, d, J = 1.8, H-8'), 6.76 (1H, dd, J = 1.8, 9.0, H-6'), 7.57 (1H, d, J = 9.0, H-5'), 10.29 (1H, s, OH-7'), 12.26 (1H, br.s, COOH).

(7-Hydroxy-4,8-dimethyl-2-oxochromen-3-yl)acetic Acid (12). Yield 83%, mp 255-256°C, C₁₃H₁₂O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.18 (3H, s, Me-8'), 2.31 (3H, s, Me-4'), 3.52 (2H, s, CH₂-3'), 6.83 (1H, d, J = 9.0, H-6'), 7.40 (1H, d, J = 9.0, H-5'), 10.16 (1H, s, OH-7'), 12.25 (1H, br.s, COOH).

(6-Chloro-7-hydroxy-4-methyl-2-oxochromen-3-yl)acetic Acid (13). Yield 83%, mp 265-266°C, lit. [7] mp 263°C, C₁₂H₉ClO₅.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm): 2.34 (3H, s, Me-4'), 3.56 (2H, s, CH₂-3'), 6.89 (1H, s, H-6'), 7.79 (1H, s, H-5'), 10.15 (1H, s, OH-7'), 12.10 (1H, br.s, COOH).

(5,7-Dihydroxy-4-methyl-2-oxochromen-3-yl)acetic Acid (14). Yield 78%, mp 271-272°C, lit. [10] mp 264°C, [11] 285, C₁₂H₁₀O₆.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.47 (3H, s, Me-4'), 3.60 (2H, s, CH₂-3'), 6.15 (1H, d, J = 2.0, H-6'), 6.27 (1H, d, J = 2.0, H-8'), 10.29 and 10.57 (2H, two s, OH-5' and OH-7'), 11.50 (1H, br.s, COOH).

(5-Hydroxy-4,7-dimethyl-2-oxochromen-3-yl)acetic Acid (15). Yield 82%, mp 259°C, lit. [7] mp 270°C, [10] 271, C₁₃H₁₂O₅.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm): 2.27 (3H, s, Me-7'), 2.52 (3H, s, Me-4'), 3.55 (2H, s, CH₂-3'), 6.59 and 6.62 (2H, two s, H-6', H-8'), 10.45 (1H, s, OH-5'), 12.30 (1H, br.s, COOH).

(7-Methoxy-4-methyl-2-oxochromen-3-yl)acetic Acid (16). Yield 78%, mp 208-209°C, lit. [8] mp 196-197°C, [6] 198°C, [12] 199°C, C₁₃H₁₂O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.36 (3H, s, Me-4'), 3.54 (2H, s, CH₂-3'), 3.85 (3H, s, MeO-7'), 6.92 (2H, m, H-6', H-8'), 7.71 (1H, d, J = 8.7, H-5'), 12.30 (1H, br.s, COOH).

(7-Methoxy-4,8-dimethyl-2-oxochromen-3-yl)acetic Acid (17). Yield 84%, mp 247-248°C, C₁₄H₁₄O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.18 (3H, s, Me-8'), 2.34 (3H, s, Me-4'), 3.54 (2H, s, CH₂-3'), 3.89 (3H, s, MeO-7'), 6.95 (1H, d, J = 9.0, H-6'), 7.56 (1H, d, J = 9.0, H-5'), 12.31 (1H, br.s, COOH).

(6-Chloro-7-methoxy-4-methyl-2-oxochromen-3-yl)acetic Acid (18). Yield 89%, mp 236-237°C, C₁₃H₁₁ClO₅.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.36 (3H, s, Me-4'), 3.59 (2H, s, CH₂-3'), 3.95 (3H, s, MeO-7'), 7.21 (1H, s, H-6'), 7.86 (1H, s, H-5'), 12.40 (1H, br.s, COOH).

(5,7-Dimethoxy-4-methyl-2-oxochromen-3-yl)acetic Acid (19). Yield 73%, mp 228-229°C, lit. [10] mp 218-220°C, C₁₄H₁₄O₆.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 2.46 (3H, s, Me-4'), 3.51 (2H, s, CH₂-3'), 3.83 and 3.89 (6H, two s, MeO-5', MeO-7'), 6.41 (1H, d, J = 2.4, H-8'), 6.49 (1H, d, J = 2.4, H-6'), 12.24 (1H, br.s, COOH).

(5-Methoxy-4,7-dimethyl-2-oxochromen-3-yl)acetic Acid (20). Yield 89%, mp 221-222°C, lit. [10] mp 225°C, C₁₄H₁₄O₅.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm): 2.37 (3H, s, Me-7'), 2.47 (3H, s, Me-4'), 3.57 (2H, s, CH₂-3'), 3.87 (3H, s, MeO-5'), 6.78 and 6.80 (2H, two s, H-6', H-8'), 12.40 (1H, br.s, COOH).

General Method for N-Acylation of Cytisine. A solution of **11-20** (3 mmol) and *N*-hydroxysuccinimide (0.38 g, 3.3 mmol) in absolute dioxane (20 mL) was stirred vigorously and treated with diisopropylcarbodiimide (0.52 mL, 3.3 mmol). The mixture was stirred for 2 h (course of reaction monitored by TLC). The resulting activated ester was treated with cytosine (0.63 g, 3.3 mmol) and stirred vigorously for 4-6 h (course of reaction monitored by TLC). When the reaction was complete the mixture was diluted with water (200 mL) and acidified to pH 5-6. The resulting solid was filtered off and crystallized from propan-2-ol.

***N*-[(7-Hydroxy-4-methyl-2-oxochromen-3-yl)acetyl]cytisine (21).** Yield 91%, mp >350°C (dec.), C₂₃H₂₂N₂O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.86 and 1.96 (3H, two s, CH₃-4'), 1.95-2.05 (2H, m, CH₂-8), 2.70-2.90 (2H, m, H-7, H-9), 3.40-3.75 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.44 and 3.79 (2H, two d, J = 15.6, CH₂-10), 4.04-4.58 (2H, CH₂-11β, CH₂-13β), 6.08 and 6.18 (2H, two d, J = 8.1, H-5, H-3), 6.61 (1H, d, J = 2.1, H-8'), 6.72 (1H, dd, J = 2.1, 9.0, H-6'), 7.24 (1H, t, J = 8.1, H-4), 7.47 (1H, d, J = 9.0, H-5'), 10.24 (1H, br.s, OH-7').

***N*-[(7-Hydroxy-4,8-dimethyl-2-oxochromen-3-yl)acetyl]cytisine (22).** Yield 83%, mp 309-310.5°C, C₂₄H₂₄N₂O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.84 and 1.94 (3H, two s, CH₃-4'), 1.95-2.05 (2H, m, CH₂-8), 2.15 (3H, s, CH₃-8'), 2.70-2.90 (2H, m, H-7, H-9), 3.35-3.70 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.44 and 3.79 (2H, two d, J = 15.6, CH₂-10), 4.00-4.58 (2H, CH₂-11β, CH₂-13β), 6.08 and 6.18 (2H, two m, H-5, H-3), 6.79 (1H, d, J = 8.4, H-6'), 7.20-7.35 (2H, m, H-4, H-5'), 10.11 (1H, br.s, OH-7').

***N*-[(6-Chloro-7-hydroxy-4-methyl-2-oxochromen-3-yl)acetyl]cytisine (23).** Yield 87%, mp >355°C (dec.), C₂₃H₂₁ClN₂O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.85 and 1.96 (3H, two s, CH₃-4'), 1.95-2.05 (2H, m, CH₂-8), 2.82-2.95 (2H, m, H-7, H-9), 3.36-3.71 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.42 and 3.79 (2H, two d, J = 15.6, CH₂-10), 4.00-4.60 (2H, CH₂-11β, CH₂-13β), 6.08 and 6.18 (2H, two d, J = 6.9, H-5, H-3), 6.82 (1H, s, H-8'), 7.27 (1H, t, J = 6.9, H-4), 7.61 (1H, s, H-5'), 11.13 (1H, br.s, OH-7').

***N*-[(5,7-Dihydroxy-4-methyl-2-oxochromen-3-yl)acetyl]cytisine (24).** Yield 62%, mp >350°C (dec.), C₂₃H₂₂N₂O₆.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.95-2.05 (2H, m, CH₂-8), 1.96 and 2.04 (3H, two s, CH₃-4'), 2.80-2.92 (2H, m, H-7, H-9), 3.34-3.72 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.43 and 3.76 (2H, two d, J = 15.6, CH₂-10), 4.05-4.58 (2H, CH₂-11β, CH₂-13β), 6.07 and 6.20 (4H, two m, H-5, H-3, H-6', H-8'), 7.24 (1H, m, H-4), 10.00 and 10.35 (2H, two br.s, OH-5', OH-7').

***N*-[(5-Hydroxy-4,7-dimethyl-2-oxochromen-3-yl)acetyl]cytisine (25).** Yield 71%, mp 320-322°C, C₂₄H₂₄N₂O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.95-2.05 (2H, m, CH₂-8), 2.01 and 2.13 (3H, two s, CH₃-4'), 2.27 (3H, s, CH₃-7'), 2.80-2.95 (2H, m, H-7, H-9), 3.35-3.75 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.45 and 3.80 (2H, two d, J = 15.6, CH₂-10), 4.05-4.60 (2H, CH₂-11β, CH₂-13β), 6.08 and 6.20 (2H, two d, J = 6.6, H-5, H-3), 6.52 (2H, br.s, H-6', H-8'), 7.26 (1H, m, H-4), 10.27 (1H, br.s, OH-5').

***N*-[(7-Methoxy-4-methyl-2-oxochromen-3-yl)acetyl]cytisine (26).** Yield 85%, mp 348-349°C, C₂₄H₂₄N₂O₅.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.88 and 1.99 (3H, two s, CH₃-4'), 1.95-2.05 (2H, m, CH₂-8), 2.60-2.95 (2H, m, H-7, H-9), 3.35-3.75 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.45 and 3.78 (2H, two d, J = 15.6, CH₂-10), 3.83 (3H, s, OCH₃-7'), 4.04-4.58 (2H, CH₂-11β, CH₂-13β), 6.08 and 6.22 (2H, two d, J = 6.6, H-5, H-3), 6.91 (2H, m, H-6', H-8'), 7.24 (1H, m, H-4), 7.63 (1H, m, H-5').

***N*-[(7-Methoxy-4,8-dimethyl-2-oxochromen-3-yl)acetyl]cytisine (27).** Yield 89%, mp 325-326°C, C₂₅H₂₆N₂O₅.

PMR spectrum (400 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.87 and 1.98 (3H, two s, CH₃-4'), 1.95-2.05 (2H, m, CH₂-8), 2.15 (3H, s, CH₃-8'), 2.82-2.99 (2H, m, H-7, H-9), 3.35-3.70 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.44 and 3.79 (2H, two d, J = 15.6, CH₂-10), 3.88 (3H, s, OCH₃-7'), 4.00-4.58 (2H, CH₂-11β, CH₂-13β), 6.10 and 6.22 (2H, d, J = 6.4, H-5, H-3), 7.01 (1H, d, J = 8.8, H-6'), 7.29 (1H, m, H-4), 7.58 (1H, m, H-5').

***N*-[(6-Chloro-7-methoxy-4-methyl-2-oxochromen-3-yl)acetyl]cytisine (28).** Yield 83%, mp 301.5-303°C, C₂₄H₂₃ClN₂O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.88 and 1.98 (3H, two s, CH₃-4'), 1.95-2.05 (2H, m, CH₂-8), 2.85-2.95 (2H, m, H-7, H-9), 3.36-3.71 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.45 and 3.79 (2H, two d, J = 15.6, CH₂-10), 3.93 (3H, s, OCH₃-7'), 4.00-4.60 (2H, CH₂-11β, CH₂-13β), 6.08 and 6.20 (2H, two d, J = 6.6, H-5, H-3), 7.11 (1H, s, H-8'), 7.27 (1H, t, H-4), 7.68 (1H, s, H-5').

***N*-[(5,7-Dimethoxy-4-methyl-2-oxochromen-3-yl)acetyl]cytisine (29).** Yield 81%, mp 318-319°C, C₂₅H₂₆N₂O₆.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.96 and 2.07 (3H, two s, CH₃-4'), 1.95-2.05 (2H, m, CH₂-8), 2.80-2.95 (2H, m, H-7, H-9), 3.35-3.75 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.45 and 3.75 (2H, two d, J = 15.6, CH₂-10), 3.82 and 3.84 (6H, two s, OCH₃-5', OCH₃-7'), 4.03-4.58 (2H, CH₂-11β, CH₂-13β), 6.08 and 6.18 (2H, two d, J = 6.6, H-5, H-3), 6.41 and 6.45 (2H, two d, J = 2.1, H-6', H-8'), 7.25 (1H, m, H-4).

***N*-[(5-Methoxy-4,7-dimethyl-2-oxochromen-3-yl)acetyl]cytisine (30).** Yield 76%, mp 337-338°C, C₂₅H₂₆N₂O₅.

PMR spectrum (300 MHz, DMSO-d₆, δ, ppm, J/Hz): 1.97 and 2.09 (3H, two s, CH₃-4'), 1.95-2.05 (2H, m, CH₂-8), 2.35 (3H, s, CH₃-7'), 2.80-2.95 (2H, m, H-7, H-9), 3.35-3.75 (4H, m, CH₂-3', CH₂-11α, CH₂-13α), 3.45 and 3.80 (2H, two d,

J = 15.6, CH₂-10), 3.85 (3H, s, OCH₃-7'), 4.05-4.60 (2H, CH₂-11 β , CH₂-13 β), 6.11 and 6.25 (2H, two d, J = 6.6, H-5, H-3), 6.75 and 6.81 (2H, two s, H-6', H-8'), 7.32 (1H, m, H-4).

ACKNOWLEDGMENT

We thank OAO Eximed (Ukraine, Kiev) for help with this work.

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