Chemistry of Natural Compounds, Vol. 39, No. 4, 2003

MODIFIED COUMARINS. 11. SYNTHESIS AND BIOLOGICAL ACTIVITY OF MANNICH BASES OF SUBSTITUTED 2,3-DIHYDROCYCLOPENTA[*c*]CHROMEN-4-ONES

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UDC 547.814.5

Mannich bases containing the dialkylaminomethyl group in the 6- and 8-positions of 2,3-dihydrocyclopenta[c]chromen-4-ones were prepared by condensation of 7- and 9-hydroxy-2,3-dihydrocyclopenta[c]chromen-4-ones with substituted 1,1-diaminomethanes. The effects of 8-chloro-7-hydroxy-6-(1-pyrrolidinylmethyl)-2,3-dihydrocyclopenta[c]chromen-4-one and 8-chloro-7-hydroxy-6-(morpholinomethyl)-2,3-dihydrocyclopenta[c]chromen-4-one on the central and peripheral nervous system were defined and enable the presence of tranquilizing and neuroleptic properties to be predicted.

Key words: coumarins, 2,3-dihydrocyclopenta[*c*]chromen-4-one, Mannich reaction, synthesis.

Natural coumarins and their synthetic analogs provide a platform for creating new pharmacologically active compounds owing to their high biological activity. The Mannich reaction is one method of chemical modification that introduces into a molecule a pharmacophoric base that renders the molecule water-soluble when converted to the ammonium salt. According to the literature, most aminomethylated coumarin derivatives are central-nervous-system stimulants, barbiturate antagonists, anticonvulsants, analgesics, antipyretics, and anti-inflammatory agents [1, 2].

In continuation of research on the synthesis and properties of Mannich bases [3, 4], we prepared and performed a preliminary pharmacologic screening of aminomethyl derivatives of 7-hydroxy- and 9-hydroxy-2,3-dihydrocyclopenta[*c*]chromen-4-ones.

Hydroxycoumarins **1-4** were necessary for further conversions and were prepared by Pechmann condensation of polyphenols (resorcinol, 2-methylresorcinol, 4-chlororesorcinol, orcine) and ethyl-2-oxocyclopentanecarboxylate in the presence of H_2SO_4 (conc.).

Classical conditions of the Mannich reaction for hydroxycompounds, upon which the benzopyran skeleton is based, include reaction of the substrate, amine, and formaldehyde in alcohol with prolonged heating [5]. In our opinion, a more convenient method involves introduction of the aminomethyl group into the benzopyran system by using substituted 1,1-diaminomethanes [3, 4] because this reaction typically has a fast rate and lacks side products [6, 7].

The position ortho to the hydroxyl is known to be the most preferred for attack under Mannich-reaction conditions for all phenolic derivatives. This is explained by the reaction mechanism, according to which a H-bond is first formed between the Mannich reagent and substrate, after which the *o*-position is attacked [5].

The C-aminomethylation reaction was carried out by refluxing hydroxycoumarins with substituted 1,1-diaminomethanes in absolute dioxane. The aminomethyl group enters the 6-position of the 2,3-dihydrocyclopenta[*c*]chromen-4-one upon reacting with coumarins **1** and **2**; the 8-position, with coumarins **3** and **4**. This is consistent with the PMR spectroscopy data.

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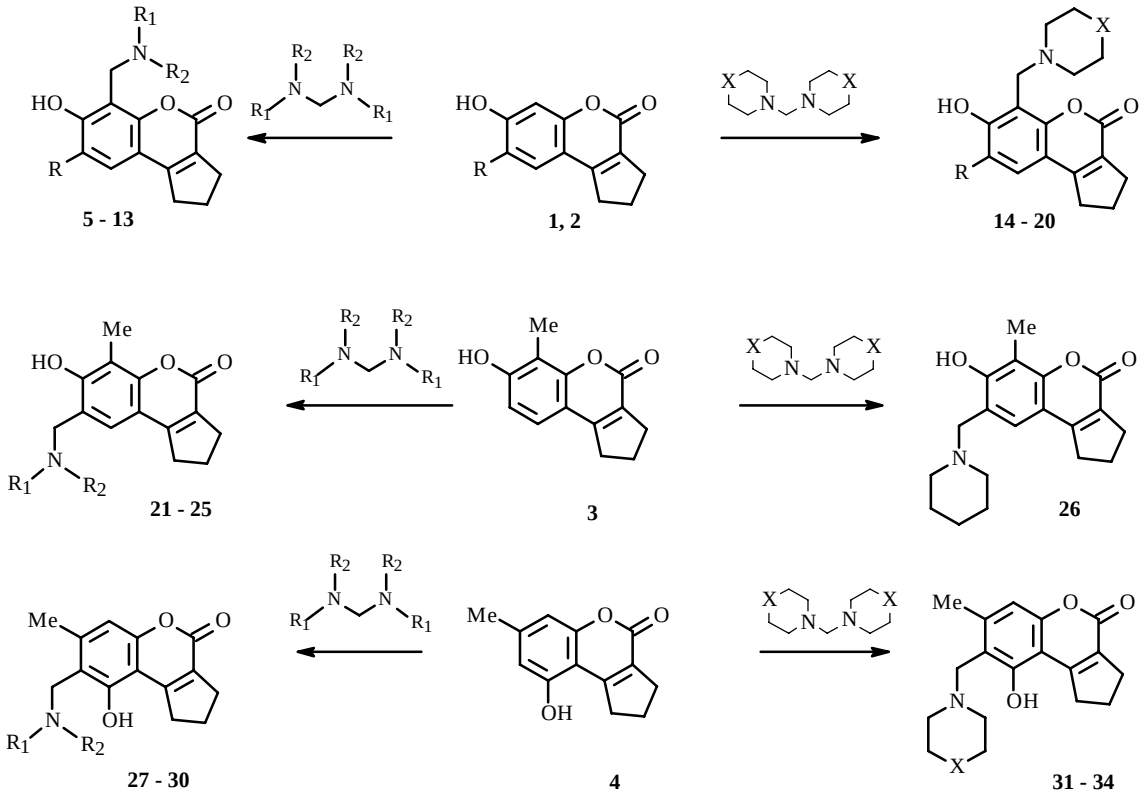
Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 264-269, July-August, 2003. Original article submitted July 31, 2003.

0009-3130/03/3904-0330$25.00



1: R = H; **2:** R = Cl; **5:** R = H, $R_1 = R_2 = CH_3$; **6:** R = Cl, $R_1 = R_2 = CH_3$; **7:** R = H, $R_1 = R_2 = CH_2CH_3$;
8: R = Cl, $R_1 = R_2 = CH_2CH_3$; **9:** R = H, $R_1R_2 = (CH_2)_4$; **10:** R = Cl, $R_1R_2 = (CH_2)_4$;
11: R = Cl, $R_1R_2 = CH_2CH(CH_3)CH_2CH_2$; **12:** R = H, $R_1R_2 = CH(CH_2CH_3)CH_2CH_2CH_2CH_2$;
13: R = Cl, $R_1R_2 = CH(CH_2CH_3)CH_2CH_2CH_2CH_2$; **14:** R = H, X = CH_2; **15:** R = Cl, X = CH_2;
16: R = Cl, X = $CH(CH_3)$; **17:** R = H, X = O; **18:** R = Cl, X = O; **19:** R = H, X = NCH_3;
20: R = Cl, X = NCH_3; **21, 27:** $R_1 = R_2 = CH_3$; **22, 28:** $R_1 = R_2 = CH_2CH_3$; **23, 29:** $R_1R_2 = (CH_2)_4$;
24, 30: $R_1R_2 = CH_2CH(CH_3)CH_2CH_2$; **25:** $R_1R_2 = CH(CH_2CH_3)CH_2CH_2CH_2CH_2$;
31: X = CH_2; **32:** X = $CH(CH_3)$; **33:** X = O; **34:** X = NCH_3

According to the experimental results, 7-hydroxy-2,3-dihydrocyclopenta[*c*]chromen-4-one (**1**) is the most reactive substrate toward aminomethylation. The reaction occurs over 0.5-1 h. A longer heating period of 2-4 h is necessary if **2** is used. The fact that an even longer period (5-10 h) is needed to carry out the Mannich reaction with **3**, in our opinion, proves that the 8-position of 2,3-dihydrocyclopenta[*c*]chromen-4-one is rather unreactive toward aminomethylation. The reactivity of the 8-position increases significantly upon introducing a 9-hydroxy because the reaction with 9-hydroxy-7-methyl-2,3-dihydrocyclopenta[*c*]chromen-4-one (**4**) is complete after heating for 1-3 h.

Aminals of dimethylamine (**5**, **6**, **21**, **27**), diethylamine (**7**, **8**, **22**, **28**), pyrrolidine (**9**, **10**, **23**, **29**), piperidine (**14**, **15**, **26**, **31**), 2-ethylpiperidine (**12**, **13**, **25**), 3-methylpiperidine (**11**, **24**, **30**), 4-methylpiperidine (**16**, **32**), morpholine (**17**, **18**, **33**), and 1-methylpiperazine (**19**, **20**, **34**) were used in the Mannich reaction. Bis(dimethylamino)methane exhibited the highest reactivity of the 1,1-diaminomethanes. Use of the other aminals required longer heating.

The structures of the resulting Mannich bases were confirmed by elemental analyses and PMR spectroscopy. The PMR spectra of **5**-**20**, which contain a dialkylaminomethyl group in the 6-position, lack signals in the range 6.9-7.0 ppm for the H-6 proton of the 2,3-dihydrocyclopenta[*c*]chromen-4-one. As a result of the lack of coupling with H-6, the PMR spectrum in the range of the aromatic protons is simplified. The H-8 and H-9 positions of **5**, **7**, **9**, **12**, **14**, **17**, and **19** resonate as doublets with spin—spin coupling constants of 8.7-8.8 Hz at 6.70-6.76 and 7.21-7.26 ppm, respectively. For the 8-chloroderivatives **6**, **8**, **10**, **11**, **13**, **15**, **16**, **18**, and **20**, H-9 resonates at 7.32-7.36 ppm as a 1H singlet. The analogous trend is noted for the 8-dialkylaminomethyl derivatives **21**-**34**. Proton H-9 in PMR spectra of Mannich bases **21**-**26** appears as a singlet at 6.89-6.91 ppm; for 9-hydroxy-7-methyl derivatives **27**-**34**, H-6 resonates as a singlet at 6.61-6.65 ppm.

TABLE 1. Neurotropic Effects of **18** in Animal Tests

Compound	Rectal temperature with apomorphine, °C		Extent of nicotine cramps, ball	Hexenal sleep, min	
	initial	after 90 min		latent period	duration
Control	37.1±0.1	33.4±0.5	3.3±0.4	3.6±0.7	35.0±2.3
18	37.9±0.3	32.7±0.6	2.4±0.3	2.0±0.3	51.0±6.8

The PMR spectra of the prepared Mannich bases also contains 2H signals for the methylene and signals typical of dialkylamine substituents. The methylene group of the 6-dialkylaminomethyl derivatives **5-11** and **14-20** appears as a singlet at 4.04-4.26 ppm; for Mannich bases **21-23** and **26-34**, which contain an 8-dialkylaminomethyl, at stronger field of 3.68-3.88 ppm.

It should be noted that the methylene protons in **12**, **13**, **24**, and **25** are diastereotopic and appear as two doublets with spin—spin coupling constant 15.0-15.6 Hz. The hydroxyl protons 7-OH and 9-OH resonate at weak field (8.60-10.50 ppm) because they are involved in the formation of stable intramolecular H-bonds to the N atom of the dialkylaminomethyl group.

The toxicity and biological activities of **10**, **18**, and **29** were studied in animal (mice, rats) experiments. It has been found that the average lethal doses (LD_{50}) of these compounds administered orally to mice are less than 5000 mg/kg, which corresponds to class IV toxicity (mildly toxic compounds).

Pharmacological screening has shown that **10** and **18** exhibit distinct neurotropic activity. Thus, single administration of **10** at doses of 200 and 400 mg/kg reduced the spontaneous motor activity, (elicited adynamia), weakened the reaction to forced body positioning, and elicited hypotonicity of skeletal muscle and an inadequate reaction to stimulation of ear and eye iris. Compound **18** increased statistically significantly apomorphine hypothermia, potentiated the activity of soporific substances (increased by 46% the duration of hexenal sleep), and reduced the neuromuscular threshold as evaluated by nicotine hyperkinesis (Table 1). Compound **29** at the studied doses did not affect the central nervous system.

Thus, the observed effects confirm that **10** and **18** have an influence on the central and peripheral nervous systems and can predict the presence of tranquilizing and neuroleptic properties. These compounds may be promising for further study as potential medicinal preparations.

EXPERIMENTAL

The course of the reactions and the purity of the products were monitored using TLC on Merck 60 F254 plates. The eluent was $CHCl_3$:CH_3OH (9:1) and hexane:ethylacetate (7:3). Melting points were determined on a Kofler block. IR and UV spectra were measured on a Nicolet FTIR Nexus 475 spectrometer and a Specord M40 spectrophotometer, respectively. 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**, **3**, and **4** were prepared as before [8].

8-Chloro-7-hydroxy-2,3-dihydrocyclopenta[*c*]chromen-4-one (2). A cooled (0°C) solution of 4-chlororesorcinol (28.9 g, 0.2 mol) and ethyl-2-oxocyclopentacarboxylate (29 mL, 0.2 mol) in absolute ethanol (50 mL) was vigorously stirred, cooled, and treated dropwise with H_2SO_4 (conc., 20 mL). The reaction mixture was stirred until thickened and then left overnight at room temperature. The mixture was poured into icewater (500 mL). The resulting precipitate was filtered off and crystallized from acetonitrile. Yield 73%, $C_{12}H_{11}ClO_3$, mp 255-256°C (lit. 245-247°C [9]). IR spectrum (KBr, cm^{-1}): 3168, 1676, 1636, 1600, 1568, 1408, 1256, 1212, 1160, 1080, 952, 848. UV (EtOH, λ_{max}, nm, log ε): 206 (4.71), 221 (4.25), 327 (4.29).

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm): 2.15 (2H, m, CH_2-2), 2.76 (2H, m, CH_2-1), 2.95 (2H, m, CH_2-3), 6.90 (1H, s, H-6), 7.47 (1H, s, H-9), 10.99 (1H, br.s, OH-7).

General Method for Synthesizing Mannich Bases 5-34. A solution of **1-4** (4 mmol) in absolute dioxane (30 mL) was treated with the appropriate substituted 1,1-diaminomethane (5 mmol). The reaction mixture was stored at 100°C for 0.5-10 h (completion of the reaction determined using TLC). After the reaction was complete the solvent was removed in vacuum. The solid or oily residue was crystallized from hexane:propan-2-ol (3:1).

6-[(Dimethylamino)methyl]-7-hydroxy-2,3-dihydrocyclopenta[*c*]chromen-4-one (5), yield 87%, $C_{15}H_{17}NO_3$, mp 158-159°C. IR spectrum (ν, cm^{-1}): 3424, 2964, 1720, 1664, 1612, 1504, 1440, 1388, 1356, 1292, 1252, 1052, 1020, 972. UV (EtOH, λ_{max}, nm, log ε): 206 (4.51), 220 (4.10), 335 (4.17).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.18 (2H, m, CH_2-2), 2.40 [6H, s, $N(CH_3)_2$], 2.89 (2H, m, CH_2-1), 3.03 (2H, m, CH_2-3), 4.04 (2H, s, CH_2-6), 6.76 (1H, d, J = 8.7, H-8), 7.26 (1H, d, J = 8.7, H-9), 10.20 (1H, s, OH-7).

8-Chloro-6-[(dimethylamino)methyl]-7-hydroxy-2,3-dihydrocyclopenta[*c*]chromen-4-one (6), yield 91%, $C_{15}H_{16}ClNO_3$, mp 185-186°C. IR spectrum (ν, cm^{-1}): 3420, 2962, 1700, 1596, 1548, 1436, 1392, 1308, 1264, 1148, 1068, 1024, 976. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.52), 241 (4.04), 370 (4.31).

PMR (400 MHz, $CDCl_3$, δ, ppm): 2.19 (2H, m, CH_2-2), 2.42 [6H, s, $N(CH_3)_2$], 2.88 (2H, m, CH_2-1), 3.00 (2H, m, CH_2-3), 4.08 (2H, s, CH_2-6), 7.35 (1H, s, H-9), 9.57 (1H, s, OH-7).

6-[(Diethylamino)methyl]-7-hydroxy-2,3-dihydrocyclopenta[*c*]chromen-4-one (7), yield 76%, $C_{17}H_{21}NO_3$, mp 116-117°C. IR spectrum (ν, cm^{-1}): 3424, 2976, 1716, 1656, 1608, 1500, 1460, 1416, 1388, 1364, 1276, 1196, 1064. UV spectrum (EtOH, λ_{max}, nm, log ε): 207 (4.55), 227 (4.05), 331 (4.07).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.15 (6H, t, J = 7.2, two CH_3-2′), 2.18 (2H, m, CH_2-2), 2.69 (4H, q, J = 7.2, two CH_2-1′), 2.88 (2H, m, CH_2-1), 3.03 (2H, m, CH_2-3), 4.13 (2H, s, CH_2-6), 6.73 (1H, d, J = 8.7, H-8), 7.23 (1H, d, J = 8.7, H-9), 8.60 (1H, s, OH-3).

8-Chloro-6-[(diethylamino)methyl]-7-hydroxy-2,3-dihydrocyclopenta[*c*]chromen-4-one (8), yield 96%, $C_{17}H_{20}ClNO_3$, mp 191-192°C. IR spectrum (ν, cm^{-1}): 3428, 2976, 1716, 1656, 1600, 1392, 1308, 1148, 1068, 924. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.54), 240 (4.08), 366 (4.23).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.19 (6H, t, J = 7.2, two CH_3-2′), 2.18 (2H, m, CH_2-2), 2.76 (4H, q, J = 7.2, two CH_2-1′), 2.87 (2H, m, CH_2-1), 2.99 (2H, m, CH_2-3), 4.18 (2H, s, CH_2-6), 7.33 (1H, s, H-9), 9.65 (1H, s, OH-7).

7-Hydroxy-6-(1-pyrrolidinylmethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (9), yield 64%, $C_{17}H_{19}NO_3$, mp 155-156°C. IR spectrum (ν, cm^{-1}): 3448, 2952, 1720, 1664, 1608, 1500, 1436, 1388, 1288, 1052. UV spectrum (EtOH, λ_{max}, nm, log ε): 206 (4.74), 225 (4.38), 328 (4.24).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.89 (4H, m, CH_2-3′, CH_2-4′), 2.17 (2H, m, CH_2-2), 2.74 (6H, m, CH_2-7, CH_2-2′, CH_2-5′), 2.88 (2H, m, CH_2-1), 3.02 (2H, m, CH_2-3), 4.20 (2H, s, CH_2-6), 6.74 (1H, d, J = 8.8, H-8), 7.24 (1H, d, J = 8.8, H-9), 9.82 (1H, s, OH-7).

8-Chloro-7-hydroxy-6-(1-pyrrolidinylmethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (10), yield 84%, $C_{17}H_{18}ClNO_3$, mp 202-203°C. IR spectrum (ν, cm^{-1}): 3400, 2964, 1716, 1656, 1592, 1500, 1476, 1432, 1404, 1348, 1164. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.61), 239 (4.20), 370 (4.44).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.93 (4H, m, CH_2-3′, CH_2-4′), 2.18 (2H, m, CH_2-2), 2.82 (6H, m, CH_2-7, CH_2-2′, CH_2-5′), 2.88 (2H, m, CH_2-1), 3.00 (2H, m, CH_2-3), 4.26 (2H, s, CH_2-6), 7.34 (1H, s, H-9), 9.50 (1H, s, OH-7).

8-Chloro-7-hydroxy-6-[(3-methylpiperidino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (11), yield 88%, $C_{19}H_{22}ClNO_3$, mp 183-184°C. IR spectrum (ν, cm^{-1}): 3428, 2944, 1724, 1656, 1600, 1484, 1416, 1388, 1308, 1068, 976. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.59), 242 (4.07), 364 (4.24).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, t, J = 6.4, CH_3-3′), 0.95 (1H, m, CH_2-4′α), 1.64-1.85 (5H, m, H-3′, CH_2-5′, CH_2-4′β, CH_2-2′α, CH_2-6′α), 2.18 (2H, m, CH_2-2), 2.87 (2H, m, CH_2-1), 2.93 (2H, m, CH_2-2′β, CH_2-6′β), 2.99 (2H, m, CH_2-3), 4.08 (2H, s, CH_2-6), 7.33 (1H, s, H-9), 9.35 (1H, s, OH-7).

7-Hydroxy-6-[(2-ethylpiperidino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (12), yield 69%, $C_{20}H_{25}NO_3$, mp 96-97°C. IR spectrum (ν, cm^{-1}): 3400, 2936, 1720, 1664, 1608, 1500, 1384, 1284, 1052, 922. UV spectrum (EtOH, λ_{max}, nm, log ε): 207 (4.56), 227 (4.08), 335 (4.15).

PMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.96 (3H, t, J = 7.2, CH_3-2″), 1.45-1.85 (9H, m, CH_2-3′, CH_2-4′, CH_2-5′, CH_2-6′α, CH_2-1″, 2.17 (2H, m, CH_2-2), 2.30 (1H, m, H-2′), 2.87 (2H, m, CH_2-1), 3.02 (2H, m, CH_2-3), 3.08 (1H, m, CH_2-6′β), 3.98 (1H, d, J = 15.6, CH_2-6α), 4.35 (1H, d, J = 15.6, CH_2-6β), 6.70 (1H, d, J = 8.8, H-2), 7.21 (1H, d, J = 8.8, H-1), 9.40 (1H, s, OH-7).

8-Chloro-7-hydroxy-6-[(2-ethylpiperidino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (13), yield 83%, $C_{20}H_{24}ClNO_3$, mp 194-195°C. IR spectrum (ν, cm^{-1}): 3436, 2940, 1716, 1656, 1596, 1524, 1476, 1384, 1296, 1100, 1044. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.64), 240 (4.09), 358 (4.16).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95 (3H, t, J = 7.2, CH_3-2″), 1.45-1.85 (9H, m, CH_2-3′, CH_2-4′, CH_2-5′, CH_2-6′α, CH_2-1″), 2.17 (2H, m, CH_2-2), 2.30 (1H, m, H-2′), 2.86 (2H, m, CH_2-1), 2.99 (2H, m, CH_2-3), 3.05 (1H, m,

CH_2-6′β), 4.02 (1H, d, J = 15.6, CH_2-6α), 4.38 (1H, d, J = 15.6, CH_2-6β), 7.32 (1H, s, H-9), 9.30 (1H, s, OH-7).

7-Hydroxy-6-(piperidinylmethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (14), yield 68%, $C_{18}H_{21}NO_3$, mp 159-160°C. IR spectrum (ν, cm^{-1}): 3420, 2920, 1720, 1668, 1608, 1500, 1380, 1348, 1292, 1152, 1052, 960. UV spectrum (EtOH, λ_{max}, nm, log ε): 207 (4.49), 226 (4.05), 335 (4.12).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.66 (6H, m, CH_2-3′, CH_2-4′, CH_2-5′), 2.17 (4H, m, CH_2-2, CH_2-2′α, CH_2-6′α), 2.80-2.90 (2H, m, CH_2-2′β, CH_2-6′β), 2.86 (2H, m, CH_2-1), 3.01 (2H, m, CH_2-3), 4.06 (2H, s, CH_2-6), 6.72 (1H, d, J = 8.8, H-8), 7.24 (1H, d, J = 8.8, H-9), 10.14 (1H, s, OH-7).

8-Chloro-7-hydroxy-6-(piperidinylmethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (15), yield 89%, $C_{18}H_{20}ClNO_3$, mp 203-204°C. IR spectrum (ν, cm^{-1}): 3400, 2936, 1720, 1660, 1600, 1384, 1308, 1152, 1064, 968. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.63), 239 (4.17), 366 (4.31).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.71 (6H, m, CH_2-3′, CH_2-4′, CH_2-5′), 2.18 (2H, m, CH_2-2), 2.20-2.30 (2H, m, CH_2-2′α, CH_2-6′α), 2.80-2.90 (2H, m, CH_2-2′β, CH_2-6′β), 2.87 (2H, m, CH_2-1), 2.99 (2H, m, CH_2-3), 4.09 (2H, s, CH_2-6), 7.33 (1H, s, H-9), 9.25 (1H, s, OH-7).

8-Chloro-7-hydroxy-6-[(4-methylpiperidino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (16), yield 86%, $C_{19}H_{22}ClNO_3$, mp 173-174°C. IR spectrum (ν, cm^{-1}): 3444, 2932, 1720, 1656, 1596, 1384, 1340, 1308, 1148, 1064, 968. UV spectrum (EtOH, λ_{max}, nm, log ε): 212 (4.59), 241 (4.09), 366 (4.31).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95 (3H, t, J = 6.4, CH_3-4′), 1.38 (2H, m, CH_2-3′α, CH_2-5′α), 1.49 (1H, m, H-4′), 1.73 (2H, m, CH_2-3′β, CH_2-5′β), 2.18 (2H, m, CH_2-2), 2.31 (2H, m, CH_2-2′α, CH_2-6′α), 2.87 (2H, m, CH_2-1), 2.99 (2H, m, CH_2-3), 3.05 (2H, m, CH_2-2′β, CH_2-6′β), 4.10 (2H, s, CH_2-6), 7.33 (1H, s, H-9), 9.50 (1H, s, OH-7).

7-Hydroxy-6-(morpholinomethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (17), yield 60%, $C_{17}H_{19}NO_4$, mp 160-161°C. IR spectrum (ν, cm^{-1}): 3432, 2952, 1720, 1668, 1604, 1500, 1464, 1416, 1384, 1276, 1116, 1052. UV spectrum (EtOH, λ_{max}, nm, log ε): 206 (4.45), 225 (4.02), 328 (4.10).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.18 (2H, m, CH_2-2), 2.65 (4H, m, CH_2-2′, CH_2-6′), 2.88 (2H, m, CH_2-1), 3.03 (2H, m, CH_2-3), 3.78 (4H, m, CH_2-3′, CH_2-5′), 4.08 (2H, s, CH_2-6), 6.76 (1H, d, J = 8.8, H-8), 7.26 (1H, d, J = 8.8, H-9), 10.50 (1H, s, OH-7).

8-Chloro-7-hydroxy-6-(morpholinomethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (18), yield 84%, $C_{17}H_{18}ClNO_4$, mp 221-222°C. IR spectrum (ν, cm^{-1}): 3396, 2964, 1712, 1660, 1600, 1464, 1412, 1388, 1308, 1116, 1072, 992. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.59), 238 (4.11), 359 (4.15).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.20 (2H, m, CH_2-2), 2.68 (4H, m, CH_2-2′, CH_2-6′), 2.89 (2H, m, CH_2-1), 3.01 (2H, m, CH_2-3), 3.80 (4H, m, CH_2-3′, CH_2-5′), 4.11 (2H, s, CH_2-6), 7.36 (1H, s, H-9), 10.40 (1H, s, OH-7).

7-Hydroxy-6-[(4-methylpiperazino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (19), yield 82%, $C_{18}H_{22}N_2O_3$, mp 185-186°C. IR spectrum (ν, cm^{-1}): 3426, 2960, 1714, 1661, 1600, 1462, 1426, 1388, 1305, 1068, 1008, 988. UV spectrum (EtOH, λ_{max}, nm, log ε): 208 (4.46), 226 (4.08), 335 (4.14).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.18 (2H, m, CH_2-2), 2.32 (3H, s, NCH_3), 2.40-2.85 (8H, m, CH_2-2′, CH_2-3′, CH_2-5′, CH_2-6′), 2.89 (2H, m, CH_2-1), 3.03 (2H, m, CH_2-3), 4.11 (2H, s, CH_2-6), 6.75 (1H, d, J = 8.7, H-8), 7.26 (1H, d, J = 8.7, H-9), 8.60 (1H, s, OH-7).

8-Chloro-7-hydroxy-6-[(4-methylpiperazino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (20), yield 92%, $C_{18}H_{21}ClN_2O_4$, mp 202-203°C. IR spectrum (ν, cm^{-1}): 3396, 2956, 1724, 1664, 1600, 1460, 1436, 1388, 1300, 1148, 1068, 1008, 988. UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.49), 231 (4.11), 335 (4.04).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.18 (2H, m, CH_2-2), 2.32 (3H, s, NCH_3), 2.40-2.80 (8H, m, CH_2-2′, CH_2-3′, CH_2-5′, CH_2-6′), 2.88 (2H, m, CH_2-1), 3.00 (2H, m, CH_2-3), 4.11 (2H, s, CH_2-6), 7.34 (1H, s, H-9), 9.60 (1H, s, OH-7).

8-[(Dimethylamino)methyl]-7-hydroxy-6-methyl-2,3-dihydrocyclopenta[*c*]chromen-4-one (21), yield 86%, $C_{16}H_{19}NO_3$, mp 175-176°C. IR spectrum (ν, cm^{-1}): 3400, 2924, 1712, 1656, 1616, 1464, 1400, 1260, 1100, 1032, 984. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.56), 229 (4.15), 333 (4.26).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 2.17 (2H, m, CH_2-2), 2.32 (3H, s, CH_3-6), 2.36 [6H, s, $N(CH_3)_2$], 2.87 (2H, m, CH_2-1), 2.99 (2H, m, CH_2-3), 3.70 (2H, s, CH_2-8), 6.90 (1H, s, H-9), 10.19 (1H, s, OH-7).

8-[(Diethylamino)methyl]-7-hydroxy-6-methyl-2,3-dihydrocyclopenta[*c*]chromen-4-one (22), yield 64%, $C_{18}H_{23}NO_3$, mp 188-189°C. IR spectrum (ν, cm^{-1}): 3444, 2964, 1712, 1660, 1616, 1460, 1404, 1324, 1244, 1104, 1052, 992. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.76), 230 (4.28), 335 (4.38).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.13 (6H, t, J = 7.2, two CH_3-2′), 2.17 (2H, m, CH_2-2), 2.31 (3H, s, CH_3-6), 2.65 (4H, q, J = 7.2, two CH_2-1′), 2.88 (2H, m, CH_2-1), 3.00 (2H, m, CH_2-3), 3.83 (2H, s, CH_2-8), 6.90 (1H, s, H-9), 8.78 (1H, s, OH-7).

7-Hydroxy-6-methyl-8-(1-pyrrolidinylmethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (23), yield 88%, $C_{18}H_{21}NO_3$, mp 166-167°C. IR spectrum (ν, cm^{-1}): 3460, 2964, 1716, 1668, 1612, 1396, 1328, 1272, 1188, 1100, 992. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.74), 228 (4.29), 335 (4.31).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.88 (4H, m, CH_2-3′, CH_2-4′), 2.17 (2H, m, CH_2-2), 2.32 (3H, s, CH_3-6), 2.67 (4H, m, CH_2-2′, CH_2-5′), 2.88 (2H, m, CH_2-1), 3.00 (2H, m, CH_2-3), 3.88 (2H, s, CH_2-8), 6.91 (1H, s, H-9), 9.72 (1H, s, OH-7).

7-Hydroxy-6-methyl-8-[(3-methylpiperidino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (24), yield 83%, $C_{20}H_{25}NO_3$, mp 199-200°C. IR spectrum (ν, cm^{-1}): 3448, 2948, 1712, 1656, 1616, 1400, 1348, 1276, 1180, 1100, 1000, 984. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.60), 228 (4.18), 335 (4.23).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, t, J = 6.0, CH_3-3′), 0.95 (1H, m, CH_2-4′α), 1.62 (1H, m, H-3′), 1.70-1.82 (5H, m, CH_2-5′, CH_2-4′β, CH_2-2′α, CH_2-6′α), 2.17 (2H, m, CH_2-2), 2.32 (3H, s, CH_3-6), 2.88 (2H, m, CH_2-1), 2.90 (2H, m, CH_2-2′β, CH_2-6′β), 3.00 (2H, m, CH_2-3), 3.68 (1H, d, J = 15.0, CH_2-8α), 3.76 (1H, d, J = 15.0, CH_2-8′β), 6.90 (1H, s, H-9), 8.50 (1H, s, OH-7).

7-Hydroxy-6-methyl-8-[(2-ethylpiperidino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (25), yield 68%, $C_{21}H_{27}NO_3$, mp 220-221°C. IR spectrum (ν, cm^{-1}): 3400, 2940, 1708, 1660, 1612, 1532, 1400, 1276, 1100, 984. UV spectrum (EtOH, λ_{max}, nm, log ε): 211 (4.60), 227 (4.15), 335 (4.19).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.95 (3H, t, J = 7.2, CH_3-2″), 1.40-1.80 (9H, m, CH_2-8, CH_2-9, CH_2-3′, CH_2-4′, CH_2-5′, CH_2-6′α, CH_2-1″), 2.31 (3H, s, CH_3-6), 2.35 (1H, m, H-2′), 2.88 (2H, m, CH_2-1), 3.00 (2H, m, CH_2-3), 3.08 (1H, m, CH_2-6′β), 3.37 (1H, d, J = 15.0, CH_2-4α), 4.39 (1H, d, J = 15.0, CH_2-4β), 6.89 (1H, s, H-9), 8.40 (1H, s, OH-7).

7-Hydroxy-6-methyl-8-(piperidinylmethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (26), yield 79%, $C_{19}H_{23}NO_3$, mp 173-174°C. IR spectrum (ν, cm^{-1}): 3400, 2932, 1720, 1660, 1616, 1420, 1396, 1276, 1188, 1152, 1128, 984. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.56), 229 (4.09), 333 (4.16).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.66 (6H, m, CH_2-3′, CH_2-4′, CH_2-5′), 2.17 (2H, m, CH_2-2), 2.32 (3H, s, CH_3-6), 2.60-2.70 (4H, m, CH_2-2′, CH_2-6′), 2.88 (2H, m, CH_2-1), 3.00 (2H, m, CH_2-3), 3.72 (2H, s, CH_2-8), 6.89 (1H, s, H-9), 8.74 (1H, s, OH-7).

8-[(Dimethylamino)methyl]-9-hydroxy-7-methyl-2,3-dihydrocyclopenta[*c*]chromen-4-one (27), yield 86%, $C_{16}H_{19}NO_3$, mp 168-169°C. IR spectrum (ν, cm^{-1}): 3432, 2960, 1716, 1660, 1616, 1520, 1460, 1404, 1384, 1144, 1072, 1016, 992. UV spectrum (EtOH, λ_{max}, nm, log ε): 209 (4.50), 259 (3.92), 313 (4.09).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.10 (2H, m, CH_2-2), 2.26 (3H, s, CH_3-7), 2.38 [6H, s, $N(CH_3)_2$], 2.80 (2H, m, CH_2-1), 3.36 (2H, m, CH_2-3), 3.68 (2H, s, CH_2-8), 6.61 (1H, s, H-6), 9.60 (1H, s, OH-9).

8-[(Diethylamino)methyl]-9-hydroxy-7-methyl-2,3-dihydrocyclopenta[*c*]chromen-4-one (28), yield 72%, $C_{18}H_{23}NO_3$, mp 106-107°C. IR spectrum (ν, cm^{-1}): 3416, 2972, 1712, 1660, 1612, 1448, 1380, 1192, 1144, 1068, 984. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.50), 260 (3.92), 311 (4.10).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.16 (6H, t, J = 7.2, two CH_3-2′), 2.10 (2H, m, CH_2-2), 2.26 (3H, s, CH_3-7), 2.69 (4H, q, J = 7.2, two CH_2-1′), 2.80 (2H, m, CH_2-1), 3.36 (2H, m, CH_2-3), 3.70 (2H, s, CH_2-8), 6.62 (1H, s, H-6), 9.55 (1H, s, OH-9).

9-Hydroxy-7-methyl-8-(1-pyrrolidinylmethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (29), yield 87%, $C_{18}H_{21}NO_3$, mp 159-160°C. IR spectrum (ν, cm^{-1}): 3416, 2964, 1716, 1660, 1616, 1456, 1416, 1376, 1324, 1144, 1068. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.43), 260 (3.88), 313 (4.03).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.89 (4H, m, CH_2-3′, CH_2-4′), 2.11 (2H, m, CH_2-2), 2.27 (3H, s, CH_3-7), 2.65 (4H, m, CH_2-2′, CH_2-5′), 2.80 (2H, m, CH_2-1), 3.38 (2H, m, CH_2-3), 3.86 (2H, s, CH_2-8), 6.61 (1H, s, H-6), 9.60 (1H, s, OH-9).

9-Hydroxy-7-methyl-8-[(3-methylpiperidino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (30), yield 92%, $C_{20}H_{25}NO_3$, mp 141-142°C. IR spectrum (ν, cm^{-1}): 3456, 2932, 1720, 1668, 1620, 1456, 1384, 1144, 1068, 976. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.52), 260 (3.97), 311 (4.16).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, t, J = 6.4, CH_3-3′), 0.96 (1H, m, CH_2-4′α), 1.65-1.80 (5H, m, H-3′, CH_2-5′, CH_2-4′β, CH_2-2′α, CH_2-6′α), 2.11 (2H, m, CH_2-2), 2.26 (3H, s, CH_3-7), 2.80 (2H, m, CH_2-1), 2.92 (2H, m, CH_2-2′β, CH_2-6′β), 3.37 (2H, m, CH_2-3), 3.68 (2H, s, CH_2-8), 6.61 (1H, s, H-6), 9.50 (1H, s, OH-9).

9-Hydroxy-7-methyl-8-(piperidinylmethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (31), yield 89%, $C_{19}H_{23}NO_3$, mp 189-190°C. IR spectrum (ν, cm^{-1}): 3400, 2936, 1720, 1656, 1620, 1536, 1480, 1452, 1400, 1372, 1176, 1080, 1040, 988. UV spectrum (EtOH, λ_{max}, nm, log ε): 209 (4.69), 260 (4.11), 313 (4.27).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.66 (6H, m, CH_2-3′, CH_2-4′, CH_2-5′), 2.11 (2H, m, CH_2-2), 2.26 (3H, s, CH_3-7), 2.80 (2H, m, CH_2-1), 2.90-3.10 (4H, m, CH_2-2′, CH_2-5′), 3.38 (2H, m, CH_2-3), 3.69 (2H, s, CH_2-8), 6.61 (1H, s, H-6), 9.50 (1H, s, OH-9).

9-Hydroxy-7-methyl-8-[(4-methylpiperidino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (32), yield 89%, $C_{20}H_{25}NO_3$, mp 173-174°C. IR spectrum (ν, cm^{-1}): 3392, 2948, 1724, 1656, 1620, 1456, 1400, 1384, 1168, 1068. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.45), 260 (3.86), 313 (4.03).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.96 (3H, t, J = 6.4, CH_3-4′), 1.30 (2H, m, CH_2-3′α, CH_2-5′α), 1.50 (1H, m, H-4′), 1.70 (2H, m, CH_2-3′β, CH_2-5′β), 2.11 (4H, m, CH_2-2, CH_2-2′α, CH_2-6′α), 2.26 (3H, s, CH_3-3), 2.80 (2H, m, CH_2-1), 2.97 (2H, m, CH_2-2′β, CH_2-6′β), 3.38 (2H, m, CH_2-3), 3.70 (2H, s, CH_2-8), 6.61 (1H, s, H-6), 9.50 (1H, s, OH-9).

9-Hydroxy-7-methyl-8-(morpholinomethyl)-2,3-dihydrocyclopenta[*c*]chromen-4-one (33), yield 92%, $C_{18}H_{21}NO_4$, mp 159-160°C. IR spectrum (ν, cm^{-1}): 3428, 2848, 1708, 1660, 1620, 1460, 1416, 1384, 1348, 1272, 1144, 1116, 1072, 1000. UV spectrum (EtOH, λ_{max}, nm, log ε): 210 (4.56), 259 (3.97), 311 (4.17).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.12 (4H, m, CH_2-2), 2.29 (3H, s, CH_3-3), 2.50-2.65 (4H, m, CH_2-2′, CH_2-6′), 2.80 (2H, m, CH_2-1), 3.37 (2H, m, CH_2-3), 3.70-3.80 (4H, m, CH_2-3′, CH_2-5′), 3.74 (2H, s, CH_2-8), 6.65 (1H, s, H-6), 9.30 (1H, s, OH-9).

9-Hydroxy-7-methyl-8-[(4-methylpiperazino)methyl]-2,3-dihydrocyclopenta[*c*]chromen-4-one (34), yield 84%, $C_{19}H_{24}N_2O_3$, mp 189-190°C. IR spectrum (ν, cm^{-1}): 3436, 2936, 1716, 1660, 1564, 1456, 1416, 1352, 1284, 1160, 1140, 1068, 1008. UV spectrum (EtOH, λ_{max}, nm, log ε): 209 (4.56), 260 (3.96), 311 (4.16).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 2.11 (4H, m, CH_2-2), 2.27 (3H, s, CH_3-3), 2.32 (3H, s, NCH_3), 2.40-2.80 (4H, m, CH_2-2′, CH_2-3′, CH_2-5′, CH_2-6′), 2.80 (2H, m, CH_2-1), 3.38 (2H, m, CH_2-3), 3.73 (2H, s, CH_2-8), 6.63 (1H, s, H-6), 9.10 (1H, s, OH-9).

ACKNOWLEDGMENT

We thank OAO "Eximed" (Kiev, Ukraine) for assistance with the work.

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