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SYNTHESIS OF FLAVONOID DERIVATIVES OF CYTISINE. 1. AMINOMETHYLATION OF 7-HYDROXY-3-ARYLCOUMARINS

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Aminomethylation involving the natural alkaloid (–)-cytisine of analogs of natural 3-arylbenzopyran-2-ones was studied. Substituted 8-(cytisin-12-yl)methyl-3-aryl-7-hydroxycoumarins were synthesized.

Keywords: cytisine, 3-arylcoumarin, electrophilic substitution, aminomethylation.

The pharmacological properties of the natural alkaloid cytisine, like nicotine, classify it as a ganglionic toxin that stimulates the central nervous system and ganglia of the autonomous nervous system and enhances breathing by reflex [1]. Furthermore, cytisine and its *N*-methyl derivative exhibit hypolipidemic and anti-inflammatory activity [2, 3].

Considering these features, modification of cytisine is interesting from both chemical and biological viewpoints.

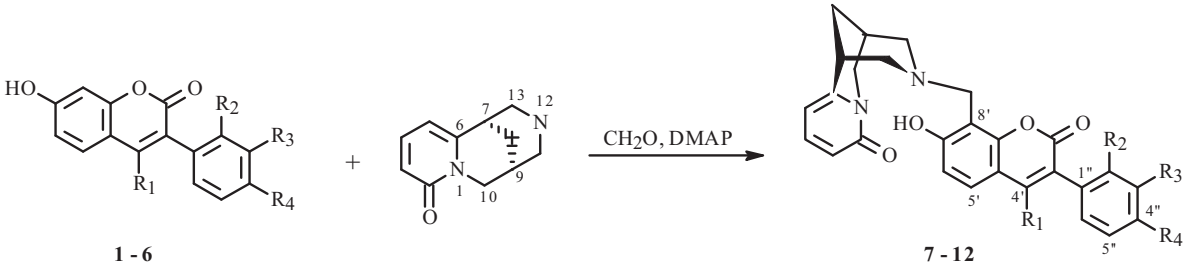
Our goal was to study the possibility of using cytisine in aminomethylation of analogs of natural 3-arylcoumarins methoxylated in ring B.

Aminomethylation of 7-hydroxybenzopyran-2-ones is known to occur at the 8-position of the coumarin core [4–7] or at the 6-position if the 8-position is occupied [4, 8]. The presence of an electron-accepting heterocyclic substituent in the 3-position of the benzopyran ring decreases significantly the reactivity of such compounds toward electrophilic reagents [9] whereas electron-donating groups can steer the reaction to other directions [4, 10].

We have previously studied electrophilic substitution of analogs of natural isoflavonoids [11] containing electron-donating alkoxy groups in the 3-aryl substituent by aminal reagents and found that 7-hydroxyisoflavones methoxylated in ring B are more reactive than 3-hetaryl-7-hydroxychromones toward electrophilic attack.

Considering this and the similarty of the structures of 7-hydroxyisoflavones and 3-aryl-7-hydroxycoumarins, we studied the possibility of using cytosine as the amine and formalin for introducing an aminomethyl group into the benzopyrone ring.

The starting substituted 7-hydroxy-3-arylcoumarins **1**–**6** were prepared by Perkin condensation of substituted phenylacetic acids with 2,4-dihydroxybenzaldehyde or 2,4-dihydroxyacetophenone in acetic anhydride in the presence of KOAc as the base [12] with subsequent deacylation of the 7-acetoxy derivatives.



1 - 6 **7 - 12**

1, 7: $R_1 = R_2 = R_3 = R_4 = H$; **2, 8:** $R_1 = R_2 = R_3 = H$, $R_4 = OMe$; **3, 9:** $R_1 = R_2 = H$, $R_3 = R_4 = OMe$; **4, 10:** $R_1 = R_3 = H$, $R_2 = R_4 = OMe$
5, 11: $R_1 = Me$; $R_2 = R_3 = R_4 = H$; **6, 12:** $R_1 = Me$; $R_2 = R_3 = R_4 = OMe$

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Heating **1–6**, cytisine, and aqueous formalin in dioxane in the presence of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) caused aminomethylation of the coumarin moiety to form 8-(cytisin-12-yl)methyl-3-aryl-7-hydroxycoumarins **7–12**.

As we supposed, a 3-aryl substituent with electron-donating methoxyls increased significantly the reactivity of the coumarin ring toward electrophilic attack. Although heating the starting compounds with aminals for 8–10 h was needed in order to introduce the aminomethyl group into 3-hetarylcoumarins [9], the reaction of 7-hydroxy-3-arylcoumarins **1**–**6** with formalin and cytisine occurred in 2–8 h. This indicated that the coumarin ring was very reactive in the Mannich reaction.

The structures of **7**–**12** were confirmed by PMR spectroscopy. Thus, PMR spectra of these compounds exhibited resonances for cytisine and coumarin protons. The resonance of coumarin proton H-8′ was missing whereas resonances of CH_2-8′ in the range 3.88–4.11 ppm were observed as two doublets with SSCC 14.3–14.9 Hz. This was consistent with the existence of diastereomers due to the presence of optical centers in the cytisine moiety.

Thus, the method developed by us for aminomethylation can be used to synthesize compounds containing the (–)-cytisine moiety. This creates new possibilities for chemical modification of cytisine and expands our understanding of its reactivity.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 (Russia) and Merck (Germany) plates. The eluent was toluene:EtOH (9:1, 95:5). PMR spectra (δ scale) were taken in $CDCl_3$ on a VXR-300 instrument (Varian, 300 MHz) with TMS internal standard. Elemental analyses of all compounds agreed with those calculated.

Starting 7-hydroxy-3-arylcoumarins **1–6** were prepared as before [12].

General Method for Preparing 3-Aryl-7-hydroxy-8-(cytisin-12-yl)methylcoumarins 7–12. A solution of 7-hydroxy-3-arylcoumarin (**1**–**6**, 2 mmol) in anhydrous dioxane (30 mL) was refluxed; treated with cytisine (2.5 mmol), formalin (1 mL, 35%), and 4-*N*,*N*-dimethylaminopyridine (5 mg); refluxed for 2–8 h (end of reaction determined by TLC); and cooled. The dioxane was evaporated in vacuo. The solid was crystallized from *i*-PrOH or *i*-PrOH:hexane.

(1*R*,5*S*)-3-[(7-Hydroxy-3-phenyl-2-oxo-2*H*-chromen-8-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanepyrido[1,2-*a*][1,5]diazocin-8-one (7). Yield 71%, $C_{28}H_{26}N_2O_4$, mp 205–207°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.81–2.08 (2H, m, H_2-8), 2.44–2.69 (3H, m, H-9, H-11, H-13), 3.11 (3H, m, H-11, H-13, H-7), 3.92, 4.18 (2H, 2m, ^2J = 15.4, H_2-10), 6.02 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.54 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.34 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); coumarin protons: 3.89, 4.09 (2H, 2d, J = 14.6, H_2-8′), 6.70 (1H, d, J = 8.9, H-6′), 7.28 (1H, d, J = 8.9, H-5′), 7.41–7.66 (5H, 3m, Ph-3), 10.78 (1H, s, OH-7′).

(1*R*,5*S*)-3-{[7-Hydroxy-3-(4-methoxyphenyl)-2-oxo-2*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanepyrido[1,2-*a*][1,5]diazocin-8-one (8). Yield 83%, $C_{28}H_{26}N_2O_5$, mp 243–244°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.84–2.05 (2H, m, H_2-8), 2.47–2.69 (3H, m, H-9, H-11, H-13), 3.10 (3H, m, H-11, H-13, H-7), 3.92, 4.17 (2H, 2m, H_2-10), 6.02 (1H, dd, J = 6.9, J = 1.2, H-5), 6.54 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.33 (1H, dd, J = 6.9, J = 8.7, H-4); coumarin protons: 3.84 (3H, s, OMe-4″), 3.88, 4.08 (2H, 2d, J = 14.3, H_2-8′), 6.69 (1H, d, J = 8.7, H-6′), 6.96 (2H, d, J = 9.0, H-3″, H-5″), 7.26 (1H, d, J = 8.7, H-5′), 7.61 (2H, d, J = 9.0, H-2″, H-6″), 7.65 (1H, s, H-4′).

(1*R*,5*S*)-3-{[7-Hydroxy-3-(3,4-dimethoxyphenyl)-2-oxo-2*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanepyrido[1,2-*a*][1,5]diazocin-8-one (9). Yield 67%, $C_{29}H_{28}N_2O_6$, mp 229–231°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.86–2.05 (2H, m, H_2-8), 2.48-2.68 (3H, m, H-9, H-11, H-13), 3.11 (3H, m, H-11, H-13, H-7), 3.88, 4.18 (each 1H, m, H_2-10), 6.02 (1H, dd, J = 6.9, J = 1.2, H-5), 6.54 (1H, dd, J = 8.7, J = 1.2, H-3), 7.32 (1H, dd, J = 6.9, J = 8.7, H-4); coumarin protons: 3.91, 3.93 (each 3H, s, OMe-3″, OMe-4″), 3.84, 4.08 (each 1H, d, ^2J = 14.6, H_2-8′), 6.69 (1H, d, ^3J = 8.7, H-6), 6.92 (1H, m, H-5″), 7.23 (1H, m, H-6″), 7.26 (1H, m, H-2″), 7.27 (1H, d, J = 8.7, H-5′), 7.67 (1H, s, H-4′).

(1*R*,5*S*)-3-{[7-Hydroxy-3-(2,4-dimethoxyphenyl)-2-oxo-2*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanepyrido[1,2-*a*][1,5]diazocin-8-one (10). Yield 54%, $C_{29}H_{28}N_2O_6$, mp 196–197°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.84–2.08 (2H, m, H_2-8), 2.47–2.69 (3H, m, H-9, H-11, H-13), 3.11 (3H, m, H-11, H-13, H-7), 3.93, 4.21 (2H, 2m, ^2J = 15.4, H_2-10), 6.06 (1H, dd, ^3J = 6.9, ^4J = 1.2,

H-5), 6.57 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.35 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); coumarin protons: 3.78, 3.79 (6H, 2s, OMe-2″, OMe-4″), 3.89, 4.09 (2H, 2d, J = 14.5, H_2-8′), 6.69 (1H, d, J = 8.7, H-6′), 6.90 (3H, m, H-3″, H-5″, H-6′), 7.25 (1H, d, J = 8.7, H-5′), 7.64 (1H, s, H-4′).

(1*R*,5*S*)-3-[(7-Hydroxy-2-methyl-3-phenyl-2-oxo-2*H*-chromen-8-yl)methyl]-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanepyrido[1,2-*a*][1,5]diazocin-8-one (11). Yield 49%, $C_{27}H_{24}N_2O_4$, mp 253–255°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.87–2.07 (2H, m, H_2-8), 2.49–2.69 (3H, m, H-9, H-11, H-13), 3.11 (3H, m, H-11, H-13, H-7), 3.87, 4.17 (2H, 2m, H_2-10), 5.97 (1H, dd, J = 6.9, J = 1.2, H-5), 6.53 (1H, dd, J = 8.7, J = 1.2, H-3), 7.35 (1H, dd, J = 6.9, J = 8.7, H-4); coumarin protons: 2.24 (3H, s, Me-4′), 3.90, 4.10 (2H, 2d, ^2J = 14.9, CH_2-8′), 6.70 (1H, d, J = 8.8, H-6′), 7.23-7.41 (5H, 3m, Ph–H), 7.24 (1H, d, ^3J = 8.8, H-5′), 10.72 (1H, s, OH-7′).

(1*R*,5*S*)-3-{[7-Hydroxy-3-(4-methoxyphenyl)-2-oxo-2*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanepyrido[1,2-*a*][1,5]diazocin-8-one (12). Yield 62%, $C_{29}H_{28}N_2O_5$, mp 251–252°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.85–2.06 (2H, m, H_2-8), 2.47–2.68 (3H, m, H-9, H-11, H-13), 3.11 (3H, m, H-11, H-13, H-7), 3.92, 4.19 (2H, 2m, J = 14.9, H_2-10), 6.03 (1H, dd, J = 6.9, J = 1.2, H-5), 6.56 (1H, dd, J = 8.7, J = 1.2, H-3), 7.34 (1H, dd, J = 6.9, J = 8.7, H-4); coumarin protons: 2.24 (3H, s, Me-4′), 3.84 (3H, s, OMe-4″), 3.88, 4.11 (2H, 2d, J = 14.9, H_2-8′), 6.72 (1H, d, J = 9.0, H-6′), 6.97 (2H, d, J = 8.8, H-3″, H-5″), 7.20 (2H, d, J = 8.8, H-2″, H-6″), 7.43 (1H, d, J = 9.0, H-5′).

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