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SYNTHESIS OF CYTISINE DERIVATIVES OF FLAVONOIDS. 2. AMINOMETHYLATION OF 7-HYDROXYISOFLAVONES

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Aminomethylation of natural 7-hydroxyisoflavones and their analogs by the alkaloid (–)cytisine was studied. Substituted 8-(cytisin-12-yl)methyl-7-hydroxyisoflavones were synthesized.

Keywords: isoflavone, cytisine, electrophilic substitution, aminomethylation.

Considering the valuable biological properties of cytisine and its alkyl derivatives [1], the search for new pathways for chemical modification of this alkaloid is certainly timely. The combination in one molecule of various fragments of natural compounds stimulates interest in studying their mutual influence on the biological activity. Therefore, our goal was to investigate the possibility of using cytisine for aminomethylation of natural 7-hydroxyisoflavones and their analogs methylated on ring B that are known to be natural antioxidants [2], are used to treat cardiovascular diseases [3], and exhibit hypolipidemic activity [4].

We found earlier that aminomethylation of 3-hetaryl-7-hydroxycoumarins and 3-hetaryl-7-hydroxychromones occurred via reaction with the aminal synthesized using cytisine [5, 6]. We studied the aminomethylation of analogs of natural 7-hydroxy-3-arylcoumarins by this alkaloid [7].

Considering the complexity of isolating the desired 8-cytisinylmethylbenzopyranones upon reaction with methylene-*bis*-cytisine, we decided to study aminomethylation of natural isoflavones and their analogs using cytisine and formalin because the presence of electron-donating substituents in their molecules favored the occurrence of the electrophilic substitution reaction.

The starting natural 7-hydroxyisoflavones **1a** [8], **1b** [9], and **2a** [10] and their analogs **1c** [11], **2b** [12], and **3a** and **3b** [13] were synthesized from the corresponding 2-hydroxydeoxybenzoins that were prepared under Hoesch reaction conditions by acylation of the methylene using Vilsmeier reagent or acetic or trifluoroacetic anhydrides with subsequent heterocyclization that formed the chromone ring.

The search for the optimum conditions for performing the aminomethylation of the natural flavonoids and their analogs by cytisine consisted of selecting the appropriate solvent and catalyst.

It is known that the Mannich reaction can occur under base- or acid-catalyzed conditions [14]. The most satisfactory results for introducing cytisine via aminomethylation of the natural isoflavones and their analogs, like for 7-hydroxy-3-arylcoumarins [7], were obtained using 4-*N*,*N*-dimethylaminopyridine (DMAP) as the catalyst. The most suitable solvent in this instance was propanol-2.

Aminomethylation of the chromone ring occurred upon heating **1a**–**c**, **2a**, **2b**, **3a**, or **3b**, cytisine, and formalin in propanol-2 in the presence of a catalytic amount of DMAP. This formed 8-(cytisin-12-yl)methyl-7-hydroxyisoflavones **4a**–**c**, **5a**, **5b**, **6a**, and **6b**.

As we supposed, a 3-aryl substituent with electron-donating methoxyls increased significantly the reactivity of the chromone ring to electrophilic attack. The reaction of 7-hydroxyisoflavones **1a**–**c**, **2a**, **2b**, **3a**, or **3b** with formalin and cytisine occurred in 3–7 h. This provided evidence of the significant reactivity of the benzopyrone ring in the Mannich reaction.

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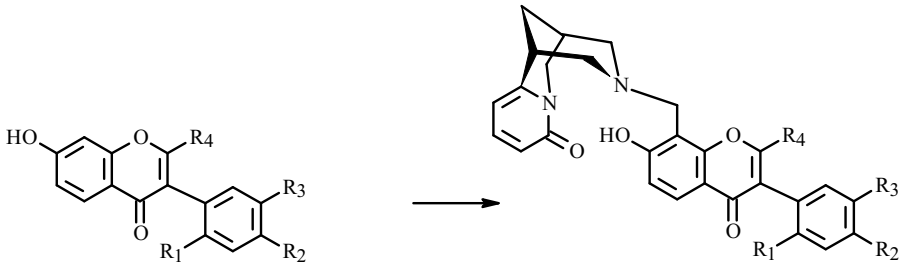
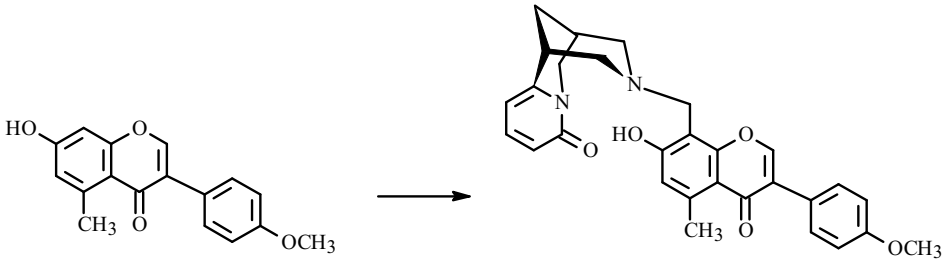


1a - c, 2a,b, 3a,b **4a - c, 5a,b, 6a,b**

1a, 4a: $R_1 = R_3 = R_4 = H$, $R_2 = OCH_3$; **1b, 4b:** $R_1 = R_4 = H$, $R_2 = R_3 = OCH_3$; **1c, 4c**: $R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$
2a, 5a: $R_1 = R_2 = R_3 = H$, $R_4 = CH_3$; **2b, 5b:** $R_1 = H$, $R_2 = R_3 = OCH_3$, $R_4 = CH_3$; **3a, 6a:** $R_1 = R_3 = H$, $R_2 = OCH_3$, $R_4 = CF_3$
3b, 6b: $R_1 = OCH_3$, $R_2 = R_3 = H$, $R_4 = CF_3$

We showed previously that aminomethylation of 5,7-dihydroxyisoflavones [15] using aminals formed 6,8-*bis*-aminomethyl derivatives. We used 5-methylformononetin (**1d**) to study the influence of the substituents in ring A on the course of the aminomethylation of the natural isoflavones and their analogs.

As it turned out, the presence of the electron-donating methyl in **1d** accelerated its reaction with cytisine and formalin. The 8-cytisinylmethyl derivative **4d** was formed exclusively.



1d **4d**

The structures of the synthesized compounds were confirmed by PMR spectroscopy. Thus, PMR spectra of **4**–**6** contained resonances for protons of both cytisine and the isoflavone fragments. Resonances of the CH_2-8 protons were observed as two doublets with SSCC 14.9–16.5 Hz, indicating that they were diastereomeric because of the optical centers in the cytisine fragment.

Thus, we developed the optimum conditions for aminomethylation of natural isoflavones and their analogs by cytisine. This enabled compounds containing pharmacophores of these natural compounds in one molecule to be synthesized. This opened new possibilities for chemical modification of the alkaloid cytisine.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on plates (Merck, Germany) with elution by $CHCl_3$:MeOH:Et_2NH (88:10:2) and EtOAc. PMR spectra of **4**–**6** were measured in $CDCl_3$ on a VXR-300 instrument (Varian, 300 MHz) vs. TMS (internal standard) on the δ-scale. Elemental analysis of all compounds agreed with those calculated.

General Method for Preparing 3-Aryl-7-hydroxy-8-(cytisin-12-yl)methylchromones 4a–d, 5a, 5b, 6a, and 6b. A refluxing solution of 7-hydroxyisoflavone **1a**–**d**, **2a**, **2b**, **3a**, or **3b** (2 mmol) in propanol-2 (30 mL) was treated with cytisine (2.5 mmol), formalin (1 mL, 35%), and DMAP (5 mg), refluxed for 3–7 h (end of reaction determined by TLC), cooled, and diluted with hexane. The precipitate was filtered off, dried, and crystallized from propanol-2 or propanol-2:hexane.

(1*R*,5*S*)-3-{[7-Hydroxy-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one (4a). Yield 78%, $C_{28}H_{26}N_2O_5$, mp 196–198°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.84–2.08 (2H, m, CH_2-8), 2.45–2.65 (3H, m, H-9, 11, 13), 3.03–3.18 (3H, m, H-11, 13, 7), 3.86, 3.98 (2H, 2d, ^2J = 15.3, CH_2-10), 6.01 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.55 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.32 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); isoflavone protons: 3.83 (3H, s, OMe-4′), 3.95, 4.19 (2H, 2d, ^2J = 14.9, CH_2-8), 6.79 (1H, d, ^3J = 9.0, H-6), 6.96 (2H, d, ^3J = 9.0, H-3′, 5′), 7.47 (2H, d, ^3J = 9.0, H-2′, 6′), 7.85 (1H, s, H-2), 8.06 (1H, d, ^3J = 9.0, H-5).

(1*R*,5*S*)-3-{[7-Hydroxy-3-(3,4-dimethoxyphenyl)-4-oxo-4*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one (4b). Yield 82%, $C_{29}H_{28}N_2O_6$, mp 200–201°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.85–2.08 (2H, m, CH_2-8), 2.46–2.67 (3H, m, H-9, 11, 13), 3.05–3.21 (3H, m, H-11, 13, 7), 3.87, 3.98 (2H, 2d, ^2J = 15.3, CH_2-10), 6.03 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.55 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.32 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); isoflavone protons: 3.90, 3.92 (6H, 2s, OMe-3′, OMe-4′), 3.92, 4.19 (2H, 2d, ^2J = 15.4, CH_2-8), 6.80 (1H, d, ^3J = 9.0, H-6), 6.92 (1H, d, ^3J = 8.4, H-5′), 7.02 (1H, dd, ^3J = 8.4, ^4J = 1.8, H-6′), 7.19 (1H, d, ^4J = 1.8, H-2′), 7.89 (1H, s, H-2), 8.07 (1H, d, ^3J = 9.0, H-5).

(1*R*,5*S*)-3-{[7-Hydroxy-3-(2-methoxyphenyl)-4-oxo-4*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one (4c). Yield 77%, $C_{28}H_{26}N_2O_5$, mp 236–237°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.82–2.07 (2H, m, CH_2-8), 2.45–2.63 (3H, m, H-9, 11, 13), 3.03–3.19 (3H, m, H-11, 13, 7), 3.87, 3.97 (2H, 2d, ^2J = 15.3, CH_2-10), 6.00 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.54 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.29 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); isoflavone protons: 3.78 (3H, s, OMe-2′), 3.89, 4.18 (2H, 2d, ^2J = 15.3, CH_2-8), 6.78 (1H, d, ^3J = 9.0, H-6), 6.98 (2H, m, H-3′, 5′), 7.35 (2H, m, H-4′, 6′), 7.85 (1H, s, H-2), 8.04 (1H, d, ^3J = 9.0, H-5).

(1*R*,5*S*)-3-{[7-Hydroxy-5-methyl-3-(4-methoxyphenyl)-4-oxo-4*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one (4d). Yield 63%, $C_{29}H_{28}N_2O_5$, mp 164–166°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.84–2.06 (2H, m, CH_2-8), 2.43–2.67 (3H, m, H-9, 11, 13), 2.98–3.22 (3H, m, H-11, 13, 7), 3.82, 3.92 (2H, 2d, ^2J = 14.3, CH_2-10), 6.01 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.54 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.32 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); isoflavone protons: 2.74 (3H, s, Me-5), 3.82 (3H, s, OMe-4′), 3.90, 4.19 (2H, 2d, ^2J = 15.4, CH_2-8), 6.57 (1H, s, H-6), 6.95 (2H, d, ^3J = 9.0, H-3′, 5′), 7.42 (2H, d, ^3J = 9.0, H-2′, 6′), 7.75 (1H, s, H-2).

(1*R*,5*S*)-3-[(7-Hydroxy-2-methyl-3-phenyl-4-oxo-4*H*-chromen-8-yl)methyl]-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one (5a). Yield 82%, $C_{28}H_{26}N_2O_4$, mp 246–248°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.87–2.02 (2H, m, CH_2-8), 2.44–2.61 (3H, m, H-9, 11, 13), 3.03–3.18 (3H, m, H-11, 13, 7), 3.83, 3.93 (2H, 2d, ^2J = 15.4, CH_2-10), 5.94 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.50 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.30 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); isoflavone protons: 2.25 (3H, s, Me-2), 3.89, 4.16 (2H, 2d, ^2J = 15.4, CH_2-8), 6.73 (1H, d, ^3J = 9.0, H-6), 7.21, 7.27, 7.38 (5H, m, Ph-3), 7.95 (2H, d, ^3J = 9.0, H-5).

(1*R*,5*S*)-3-{[7-Hydroxy-2-methyl-3-(3,4-dimethoxyphenyl)-4-oxo-4*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one (5b). Yield 78%, $C_{30}H_{30}N_2O_6$, mp 229–230°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.84–2.09 (2H, m, CH_2-8), 2.47–2.66 (3H, m, H-9, 11, 13), 3.05–3.22 (3H, m, H-11, 13, 7), 3.86, 3.98 (2H, 2d, ^2J = 15.3, CH_2-10), 6.01 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.55 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.33 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); isoflavone protons: 2.28 (3H, s, Me-2), 3.86, 3.90 (6H, 2s, OMe-3′, OMe-4′), 3.91, 4.20 (2H, 2d, ^2J = 15.4, CH_2-8), 6.75 (1H, d, ^3J = 9.0, H-6), 6.81 (2H, m, H-2′, 6′), 6.92 (1H, d, ^3J = 8.4, H-5), 7.98 (1H, d, ^3J = 9.0, H-5).

(1*R*,5*S*)-3-{[7-Hydroxy-3-(4-methoxyphenyl)-4-oxo-2-trifluoromethyl-4*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one (6a). Yield 56%, $C_{29}H_{25}F_3N_2O_5$, mp 228-230°C.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): cytisine protons: 1.87–2.09 (2H, m, CH_2-8), 2.54–2.69 (3H, m, H-9, 11, 13), 3.13–3.22 (3H, m, H-11, 13, 7), 3.87, 3.99 (2H, 2d, ^2J = 14.2, CH_2-10), 6.03 (1H, dd, ^3J = 6.9, ^4J = 1.2, H-5), 6.55 (1H, dd, ^3J = 8.7, ^4J = 1.2, H-3), 7.34 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); isoflavone protons: 3.84 (3H, s, OMe-4′), 3.92, 4.21 (2H, 2d, ^2J = 16.5, CH_2-8), 6.84 (1H, d, ^3J = 9.0, H-6), 6.95 (2H, d, ^3J = 8.2, H-3′, 5′), 7.17 (2H, d, ^3J = 8.2, H-2′, 6′), 7.99 (1H, d, ^3J = 9.0, H-5).

(1*R*,5*S*)-3-{[7-Hydroxy-3-(2-methoxyphenyl)-4-oxo-2-trifluoromethyl-4*H*-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2-*a*][1,5]diazocin-8-one Hydrochloride (6b). Yield 47%, $C_{29}H_{25}F_3N_2O_5 \cdot HCl$, mp 291–292°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.72–2.03 (2H, m, CH_2-8), 2.73 (3H, m, H-9, 11, 13), 3.12–3.62 (3H, m, H-11, 13, 7), 3.83, 4.03 (2H, 2d, ^2J = 15.3, CH_2-10), 6.32 (2H, m, H-3, 5), 7.47 (1H, dd, ^3J = 6.9, ^3J = 8.7, H-4); isoflavone protons: 3.80 (3H, s, OMe-2′), 4.36 (2H, s ,CH_2-8), 6.40 (1H, d, ^3J = 9.0, H-6), 7.13 (2H, m, H-3′, 5′), 7.44 (2H, m, H-4′, 6′), 8.05 (1H, d, ^3J = 9.0, H-5).

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