Chemistry of Natural Compounds, Vol. 48, No. 1, March, 2012 [Russian original No. 1, January-February, 2012]

SYNTHESIS OF AMINOMETHYL DERIVATIVES OF SOPHORICOSIDE

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UDC 547.814.5

*Aminomethylation of the natural isoflavonoid sophoricoside (genistein-4-*O*-β-D-glucoside) was studied. It was shown that the most convenient method for performing the aminomethylation was the use of aminals. 6,8-bis-Substituted derivatives of sophoricoside were synthesized.*

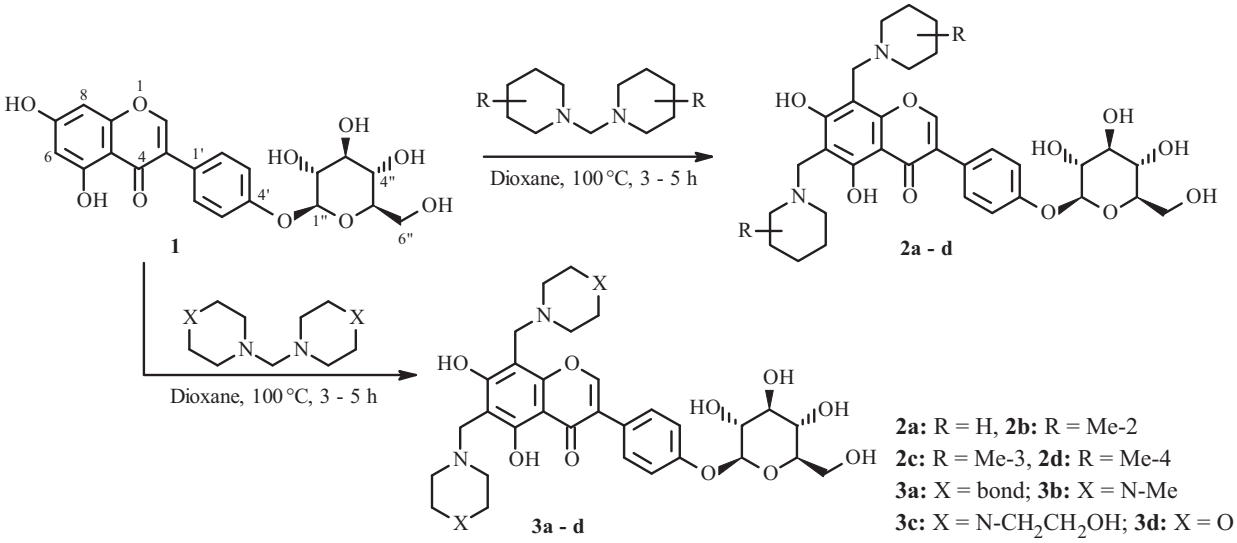
Keywords: isoflavone, sophoricoside, electrophilic substitution, aminomethylation, aminal.

Heightened interest in the study of natural flavonoids and their various modifications is due to the important role of these compounds in metabolic processes of plants and animals, their broad range of physiological activity, and their low toxicity.

In continuation of research on the modification of natural compounds, we decided to study sophoricoside (genistein-4-*O*-*β*-D-glucoside) (**1**), which occurs in *Sophora japonica* [1–5], *Piptanthus nepalensis* [6], and *Lupinus albus* [7]. Sophoricoside is known to exhibit anti-inflammatory [8], antioxidant [5, 9], and anticancer [4, 10] activity and to inhibit the activity of cyclooxygenase [8] and aldehyde reductase [11].

A promising pathway for modifying natural phenolic compounds and their analogs is aminomethylation because Mannich bases of flavones and isoflavones regulate the activity of the central nervous system and respiratory pathways; exhibit high anticonvulsant, anti-allergic, and analgesic activity [12, 13]; and act as CDK1/Cyclin B inhibitors [14].

Therefore, we selected aminomethylation for modification of sophoricoside extracted from fruit of *S. japonica* using the published method [15]. Considering the presence of the labile glycoside bond in sophoricoside and the mechanism of the Mannich reaction [16], the reaction was carried out using the aminal method that was applied successfully to several flavonoids [17].



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 0009-3130/12/4801-0026

Like for aminomethylation of the natural isoflavones biochanin A, the 3′-*O*-methyl ether of pratensein, and their derivatives [18], the action on genistein-4-*O*-glucoside of one equivalent of aminal in refluxing dioxane formed a complicated product mixture. Changing the reaction conditions (solvent, temperature, reaction time) did not cause the electrophilic substitution in the benzopyrone ring to become regioselective. Increasing the amount of aminal to two equivalents produced 6,8-*bis*-aminomethyl derivatives of sophoricoside. This indicated that the C atoms in the 6- and 8-positions of the chromone ring had practically identical reactivities toward electrophilic reagents.

The structures of the synthesized Mannich bases were proved using NMR spectroscopy. Formation of C-6 and C-8 *bis*-aminomethyl derivatives of sophoricoside was confirmed by the disappearance in PMR spectra of resonances for H-6 and H-8 and the appearance of resonances for two methylenes and amines.

Proof of the substitution of the C-6 and C-8 protons was the change of position of the resonances for these atoms in ^{13}C NMR spectra. Thus, instead of characteristic resonances of tertiary C atoms at 94–98 ppm, resonances of quaternary C atoms were observed at 100–103 ppm. Also, resonances of the amines had chemical shifts differing by 0.2–0.6 ppm because of the slight non-equivalence of the aminomethyl moieties in the 6- and 8-positions of the chromone ring.

Thus, we synthesized 6,8-bis-aminomethyl derivatives of sophoricoside. Variation of the amine component (secondary amine) enabled promising biologically active compounds to be prepared. Introducing aminomethyls into sophoricoside increased its solubility and expanded the capability for studying the physiological activity of this isoflavone.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Sorbfil UV-254 (Russia) and Merck (Germany) plates. The eluent was a mixture of $CHCl_3$ and MeOH (95:5 and 9:1). PMR spectra were measured in DMSO-d_6 relative to TMS (internal standard) on a VXR-300 instrument (Varian, 300 MHz) on the δ-scale; ^{13}C NMR spectra, in DMSO-d_6 (internal standard) on a Mercury 400 instrument (Varian, 400 MHz). Melting points were determined on a Buchi B-535 instrument. Elemental analyses of all compounds agreed with those calculated.

General Method for Synthesizing 2a–d and 3a–d. A hot solution of sophoricoside (2 mmol) in dioxane (10 mL) was treated with the appropriate aminal (4.4 mmol), refluxed for 3–5 h, and cooled (TLC monitoring). The solvent was evaporated in vacuo. The solid was ground with Et_2O, dried, and crystallized from *i*-PrOH:hexane.

4-[5,7-Dihydroxy-4-oxo-6,8-bis(piperidin-1-ylmethyl)-4*H*-chromen-3-yl]phenyl-β-D-glucopyranoside (2a). Yield 71%, $C_{33}H_{42}N_2O_{10}$, mp 150–151°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.28–1.60, 2.52–2.68 (12H, 8H, 2m, piperidine protons), 3.12–3.50 (6H, m, H-2″, 3″, 4″, 5″, 6″), 3.67 (2H, s, CH_2-8), 3.75 (2H, s, CH_2-6), 4.90 (1H, d, ^3J = 7.0, H-1″), 7.08 (2H, d, ^3J = 8.8, H-3′, 5′), 7.49 (2H, d, ^3J = 8.8, H-2′, 6′), 8.38 (1H, s, H-2).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): amine: 23.2, 23.7, 25.0, 25.4, 52.7, 53.3; 50.4 (CH_2-8), 51.7 (CH_2-6), 60.7 (C-6″), 69.7 (C-4″), 73.2 (C-2″), 76.6 (C-5″), 77.1 (C-3″), 100.3 (C-1″), 100.8 (C-8), 102.4 (C-6), 103.9 (C-4a), 116.0 (C-3′, 5′), 121.4 (C-3), 124.5 (C-1′), 130.1 (C-2′, 6′), 153.8 (C-2), 155.0 (C-8a), 157.2 (C-7), 158.5 (C-5), 167.7 (C-4′), 179.9 (C-4).

4-{5,7-Dihydroxy-6,8-bis[(2-methylpiperidin-1-yl)methyl]-4-oxo-4*H*-chomen-3-yl}phenyl-β-D-glucopyranoside (2b). Yield 67%, $C_{35}H_{46}N_2O_{10}$, mp 148–149°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.80–1.81, 2.65–2.91 (18H, 6H, 2m, piperidine protons), 3.15–3.54 (6H, m, H-2″, 3″, 4″, 5″, 6″), 3.67 (2H, m, CH_2-8), 4.05 (2H, m, CH_2-6), 4.91 (1H, d, ^3J = 7.2, H-1″), 7.08 (2H, d, ^3J = 8.0, H-3′, 5′), 7.50 (2H, d, ^3J = 8.0, H-2′, 6′), 8.37 (1H, s, H-2).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): amine: 19.6, 19.8, 23.3, 23.8, 25.2, 25.5, 31.0, 31.2, 53.4, 53.8, 60.8, 61.9; 51.2 (CH_2-8), 51.4 (CH_2-6), 60.7 (C-6″), 69.7 (C-4″), 73.2 (C-2″), 76.6 (C-5″), 77.1 (C-3″), 100.3 (C-1″), 100.8 (C-8), 102.3 (C-6), 104.0 (C-4a), 116.0 (C-3′, 5′), 121.4 (C-3), 124.4 (C-1′), 130.1 (C-2′, 6′), 153.8 (C-2), 155.0 (C-8a), 157.2 (C-7), 158.5 (C-5), 167.6 (C-4′), 179.9 (C-4).

4-{5,7-Dihydroxy-6,8-bis[(3-methylpiperidin-1-yl)methyl]-4-oxo-4*H*-chromen-3-yl}phenyl-β-D-glucopyranoside (2c). Yield 56%, $C_{35}H_{46}N_2O_{10}$, mp 148–150°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.92, 1.65–2.00, 2.63–3.08 (6H, 10H, 4H, 3m, piperidine protons), 3.16–3.51 (10H, m, H-2″, 3″, 4″, 5″, 6″ and 4H of piperidines), 4.38 (2H, m, CH_2-8), 4.49 (2H, m, CH_2-6), 4.98 (1H, d, ^3J = 7.1, H-1″), 7.18 (2H, d, ^3J = 8.0, H-3′, 5′), 7.54 (2H, d, ^3J = 8.0, H-2′, 6′), 8.54 (1H, s, H-2).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): amine: 19.7, 19.9, 25.3, 25.6, 31.1, 31.2, 32.6, 32.9, 53.3, 53.8, 60.9, 61.8; 51.1 (CH_2-8), 51.3 (CH_2-6), 60.7 (C-6″), 69.7 (C-4″), 73.2 (C-2″), 76.6 (C-5″), 77.1 (C-3″), 100.3 (C-1″), 100.8 (C-8), 102.3 (C-6), 104.0 (C-4a), 116.0 (C-3′, 5′), 121.4 (C-3), 124.4 (C-1′), 130.1 (C-2′, 6′), 153.8 (C-2), 155.0 (C-8a), 157.2 (C-7), 158.5 (C-5), 167.6 (C-4′), 180.0 (C-4).

4-{5,7-Dihydroxy-6,8-bis[(4-methylpiperidin-1-yl)methyl]-4-oxo-4*H*-chromen-3-yl}phenyl-β-D-glucopyranoside (2d). Yield 70%, $C_{35}H_{46}N_2O_{10}$, mp 179–180°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.90, 1.04–1.71, 2.07–2.34, 2.84–3.01 (6H, 10H, 4H, 4H, 4m, piperidine protons), 3.13–3.53 (6H, m, H-2″, 3″, 4″, 5″, 6″), 3.72 (2H, s, CH_2-8), 3.79 (2H, s, CH_2-6), 4.91 (1H, d, ^{3}J = 7.1, H-1″), 7.10 (2H, d, ^{3}J = 8.5, H-3′, 5′), 7.49 (2H, d, ^{3}J = 8.5, H-2′, 6′), 8.38 (1H, s, H-2).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): amine: 21.5, 21.7, 29.6, 30.0, 33.2, 33.7, 52.1, 52.7; 50.0 (CH_2-8), 51.3 (CH_2-6), 60.7 (C-6″), 69.7 (C-4″), 73.2 (C-2″), 76.6 (C-5″), 77.1 (C-3″), 100.3 (C-1″), 100.8 (C-8), 102.3 (C-6), 104.0 (C-4a), 116.0 (C-3′, 5′), 121.4 (C-3), 124.4 (C-1′), 130.1 (C-2′, 6′), 153.8 (C-2), 155.0 (C-8a), 157.2 (C-7), 158.5 (C-5), 167.6 (C-42), 179.9 (C-4).

4-{5,7-Dihydroxy-4-oxo-6,8-bis[(pyrrolidin-1-yl)methyl]-4*H*-chromen-3-yl}phenyl-β-D-glucopyranoside (3a). Yield 45%, $C_{31}H_{38}N_2O_{10}$, mp >250°C (dec).

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.85–1.97, 2.65–2.99 (8H, 4H, 2m, pyrrolidine protons), 3.10–3.50 (10H, m, H-2″, 3″, 4″, 5″, 6″ and 4H of pyrrolidines), 3.70 (2H, m, CH_2-8), 3.96 (2H, m, CH_2-6), 4.90 (1H, d, ^{3}J = 8.0, H-1″), 7.08 (2H, d, ^{3}J = 8.5, H-3′, 5′), 7.47 (2H, d, ^{3}J = 8.5, H-2′, 6′), 8.27 (1H, s, H-2).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): amine: 23.6 (CH_2), 23.7 (CH_2), 53.6 (CH_2), 54.0 (CH_2); glucose: 60.7 (C-6″), 69.7 (C-4″), 73.2 (C-2″), 76.6 (C-5″), 77.1 (C-3″), 100.3 (C-1″); aglycon: 49.7 (CH_2-8), 50.9 (CH_2-6), 100.7 (C-8), 103.2 (C-6), 104.2 (C-4a), 116.0 (C-3′, 5′), 121.6 (C-3), 124.3 (C-1′), 130.1 (C-2′, 6′), 154.2 (C-2), 154.7 (C-8a), 157.3 (C-7), 158.5 (C-5), 165.5 (C-4′), 180.1 (C-4).

4-{5,7-Dihydroxy-6,8-bis[(4-methylpiperazin-1-yl)methyl]-4-oxo-4*H*-chromen-3-yl}phenyl-β-D-glucopyranoside (3b). Yield 68%, $C_{33}H_{44}N_4O_{10}$, mp 165–166°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.20–2.70 (22H, m, piperazine protons), 3.13–3.50 (6H, m, H-2″, 3″, 4″, 5″, 6″), 3.74 (2H, m, CH_2-8), 3.80 (2H, m, CH_2-6), 4.91 (1H, d, ^{3}J = 7.2, H-1″), 7.09 (2H, d, ^{3}J = 8.4, H-3′, 5′), 7.50 (2H, d, ^{3}J = 8.4, H-2′, 6′), 8.40 (1H, s, H-2).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): amine: 45.7, 51.7, 51.8, 54.3, 54.4; 49.7 (CH_2-8), 50.9 (CH_2-6), 60.7 (C-6″), 69.7 (C-4″), 73.2 (C-2″), 76.6 (C-5″), 77.1 (C-3″), 100.3 (C-1″), 100.7 (C-8), 103.2 (C-6), 104.3 (C-4a), 116.0 (C-3′, 5′), 121.6 (C-3), 124.3 (C-1′), 130.1 (C-2′, 6′), 154.1 (C-2), 154.7 (C-8a), 157.3 (C-7), 158.5 (C-5), 165.5 (C-4′), 180.2 (C-4).

4-(5,7-Dihydroxy-6,8-bis{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}-4-oxo-4*H*-chromen-3-yl)phenyl-β-D-glucopyranoside (3c). Yield 53%, $C_{35}H_{48}N_4O_{12}$, mp 148–150°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.20–2.70 (20H, m, piperazine protons), 3.13–3.81 (14H, m, H-2″, 3″, 4″, 5″, 6″ and 4H of piperazines, CH_2-8 and CH_2-6), 4.91 (1H, d, ^{3}J = 6.7, H-1″), 7.08 (2H, d, ^{3}J = 8.4, H-3′, 5′), 7.49 (2H, d, ^{3}J = 8.4, H-2′, 6′), 8.42 (1H, s, H-2).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): amine: 52.6 (CH_2), 52.8 (CH_2), 53.0 (CH_2), 57.8, 57.9 (CH_2), 59.2 (CH_2); 49.8 (CH_2-8), 50.9 (CH_2-6), 60.7 (C-6″), 69.7 (C-4″), 73.2 (C-2″), 76.6 (C-5″), 77.1 (C-3″), 100.3 (C-1″), 100.7 (C-8), 103.2 (C-6), 104.3 (C-4a), 116.0 (C-3′, 5′), 121.6 (C-3), 124.3 (C-1′), 130.1 (C-2′, 6′), 154.1 (C-2), 154.7 (C-8a), 157.3 (C-7), 158.4 (C-5), 165.5 (C-4′), 180.0 (C-4).

4-[5,7-Dihydroxy-6,8-bis(morpholin-1-ylmethyl)-4-oxo-4*H*-chromen-3-yl]phenyl-β-D-glucopyranoside (3d). Yield 78%, $C_{31}H_{38}N_2O_{12}$, mp 239–240°C.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.40–2.63 (8H, m, morpholine protons), 3.05–3.84 (18H, m, H-2″, 3″, 4″, 5″, 6″ and 8H of morpholines, CH_2-8 and CH_2-6), 4.92 (1H, d, ^{3}J = 7.2, H-1″), 7.10 (2H, d, ^{3}J = 8.8, H-3′, 5′), 7.50 (2H, d, ^{3}J = 8.8, H-2′, 6′), 8.46 (1H, s, H-2).

^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): amine: 52.4, 52.7, 65.0, 65.1; 50.2 (CH_2-8), 51.2 (CH_2-6), 60.7 (C-6″), 69.7 (C-4″), 73.2 (C-2″), 76.6 (C-5″), 77.1 (C-3″), 100.3 (C-1″), 100.3 (C-8), 103.5 (C-6), 104.2 (C-4a), 116.0 (C-3′, 5′), 121.7 (C-3), 124.2 (C-1′), 130.1 (C-2′, 6′), 154.3 (C-2), 154.4 (C-8a), 157.3 (C-7), 158.8 (C-5), 164.8 (C-4′), 180.3 (C-4).

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