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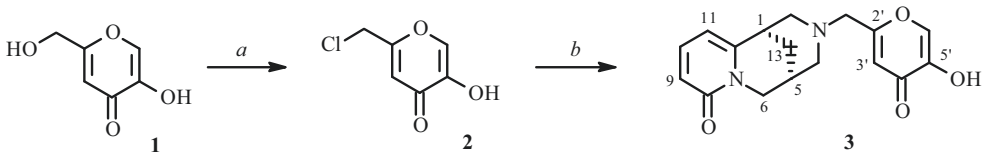
SYNTHESIS OF THE CONJUGATE OF CYTISINE AND KOJIC ACID

O. I. Muzychuk and M. M. Garazd*

N-*(5-Hydroxypyran-4-on-2-ylmethyl)cytisine was synthesized.*

Keywords: cytisine, kojic acid, pyran-4-one, *N*-alkylation.

Chemical modification of biologically active natural compounds is a promising and effective method for new drug discovery. The quinolizidine alkaloid cytisine is especially interesting among such compounds [1, 2]. Kojic acid (5-hydroxy-2-hydroxymethylpyran-4-one) (**1**) is a biologically important fungal secondary metabolite that is produced by various genera of fungi, e.g., *Aspergillus*, *Acetobacter*, and *Penicillium*, and possesses various pharmacological properties [3]. Kojic acid contains several reactive centers and is a very convenient synthon for synthesizing various derivatives and heterocyclic compounds [4].



1 **2** **3**

a. $SOCl_2$, room temp., 2 h, 65%; *b*. cytisine, Et_3N, MeCN, reflux, 6 h, 76%

In continuation of research on the synthesis of cytisine derivatives [5–8], we synthesized *N*-(5-hydroxypyran-4-on-2-ylmethyl)cytisine (**3**).

Chlorokojic acid (**2**) was produced in 65% yield via treatment of kojic acid with thionylchloride at room temperature [9, 10]. Considering the structural features of alkylating agent **2**, we optimized the conditions for cytisine *N*-alkylation. The bases were NaOH solution, K_2CO_3, and tertiary amines [Et_3N, *N*-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and di-isopropylethylamine]. The reaction was carried out in Me_2CO, EtOH, and MeCN. The most satisfactory results were obtained using Et_3N in anhydrous MeCN. Under these conditions, cytisine was monoalkylated on N-3 to give *N*-(5-hydroxypyran-4-on-2-ylmethyl)cytisine (**3**) in high yield.

Synthesized conjugate **3** was of interest as a key polyfunctional synthon for organic synthesis because it contained an active phenol and pyran-4-one ring. This provided new possibilities for subsequent modification of cytisine derivatives.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Merck 60 F254 plates. The eluent was $CHCl_3$–MeOH (9:1 and 95:5). Melting points were determined on a Kofler block. NMR spectra were recorded on Varian VXR-300 and Bruker Avance DRX-500 spectrometers vs. TMS (internal standard). Optical rotation was measured on a PerkinElmer 341 polarimeter. LC-MS spectra were recorded using an Agilent 1100 Series HPLC-MS equipped with a diode-array and Agilent LC\MSD SL mass-selective detectors with chemical ionization at atmospheric pressure (APCI). Elemental analyses of all compounds agreed with those calculated.

Eximed, Khar′kovskoe Shosse, Kiev, 50, Ukraine, 02160, e-mail: gmm@i.com.ua. Translated from *Khimiya Prirodnykh Soedinenii*, No. 3, May–June, 2017, pp. 439–440. Original article submitted July 14, 2016.

Pharmacopoeial (–)-cytisine {$[\alpha]_D^{20}$ –110° (*c* 0.5%, EtOH)} isolated from *Thermopsis lanceolata* and commercial kojic acid (Chemos GmbH & Co. KG, Germany) were used.

2-(Chloromethyl)-5-hydroxypyran-4-one (2) was prepared in 65% yield by treating kojic acid with thionylchloride at room temperature [9, 10]. Mp 161–162°C (lit. 146–147°C [11–13], 165–166°C [14], 165–168°C [15], 166–167°C [9, 16–24]), $C_6H_5ClO_3$. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 9.15 (1H, br.s, 5-OH), 8.11 (1H, s, H-6), 6.56 (1H, s, H-3), 4.65 (2H, s, CH_2-2).

(1*R*,5*S*)-3-(5-Hydroxy-4-oxo-4*H*-pyran-2-ylmethyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3). A solution of chlorokojic acid (**2**, 0.80 g, 5 mmol), cytisine (0.95 g, 5 mmol), and Et_3N (0.2 mL) in anhydrous MeCN (5 mL) was refluxed under N_2 for 6 h (course of reaction monitored by TLC) and cooled. The solvent was distilled off at reduced pressure in a rotary evaporator. The oily residue was treated with distilled H_2O (10 mL). The resulting precipitate was filtered, rinsed with H_2O, and crystallized from EtOH. Yield 1.19 g (76%), mp 182–183°C, $C_{17}H_{18}N_2O_4$, $[\alpha]_D^{20}$ –206.5° (*c* 1%, EtOH). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 9.00 (1H, br.s, 5′-OH), 7.93 (1H, s, H-6′), 7.33 (1H, dd, J = 6.5, 9.0, H-10), 6.24 (1H, d, J = 9.0, H-9), 6.08 (1H, d, J = 6.5, H-11), 5.94 (1H, s, H-3′), 3.82 (1H, d, J = 15.5, H-6_{endo}), 3.70 (1H, dd, J = 15.9, 6.5, H-6_{exo}), 3.31 and 3.35 (2H, two d, J = 15.5, CH_2-2′), 2.98–3.07 (1H, m, H-1), 2.90 (1H, d, J = 10.0, H-2_{endo}), 2.79 (1H, d, J = 10.0, H-4_{endo}), 2.34–2.45 (3H, m, H-5, H-2_{exo}, 4_{exo}), 1.80 (1H, d, J = 12.5, H-13_{syn}), 1.69 (1H, d, J = 12.5, H-13_{anti}). ^{13}C NMR spectrum (126 MHz, DMSO-d_6, δ, ppm): 173.99 (C-4′), 165.12 (C-2′), 162.67 (C-8), 152.18 (C-12), 146.14 (C-5′), 139.89 (C-6′), 139.30 (C-10), 115.91 (C-9), 112.39 (C-3′), 104.40 (C-11), 60.05 (C-2), 59.65 (C-4), 58.17 (C-2a′), 49.97 (C-6), 34.92 (C-1), 27.79 (C-5), 25.29 (C-13). LC-MS: 315.2 $[MH]^+$ (100%).

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