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NEW FLAVONOID-CONTAINING DERIVATIVES OF LUPININE

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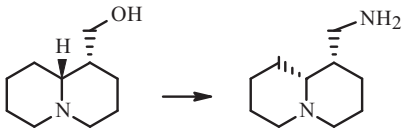
*An oxazine ring was annelated to benzopyran-4-one and benzopyran-2-one cores by reacting 7-hydroxyisoflavones and 7-hydroxycoumarins with lupinylamine and formalin. The new derivatives 9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one and 9,10-dihydro-2*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-2-one containing a lupinine moiety in the 9-position were prepared.*

Keywords: alkaloid, lupinine, lupinylamine, flavonoid, isoflavone, coumarin.

In continuation of research on the modification of natural templates, we decided to study the alkaloid lupinine (1-hydroxymethyl-*trans*-quinolizidine, **1**), which occurs in large quantities in and is extracted from middle-Asian *Lupinus* species (Leguminosae) and *Anabazis aphilla* L. (Chenopodiaceae) [1, 2].



1 **2**

The presence of a hydroxyl in lupinine enabled several esters of carboxylic and dicarboxylic acids [3-5] with antiviral, antitumor, hepatoprotective, antituberculosis, anticholinesterase, and anesthetic properties [6, 7] to be prepared from it. A series of new derivatives of 4-aminoquinoline that included a lupinylamine moiety (**2**) exhibited antimalarial activity [8]. Salts of lupinine with 3- or 4-azomethinebenzoic acids were also synthesized [9]. Several azomethines of lupinylamine [10] and its phosphorylated derivatives [11] were prepared.

The goal of the present work was to introduce the lupinine moiety into natural flavonoids and their analogs because the combination in one molecule of two natural heterocyclic groups could facilitate the manifestation of properties important for practical use.

The appropriate ratio of substrate, amine, and formaldehyde in the presence of a basic catalyst under Mannich reaction conditions is known to form derivatives of 3,4-dihydro-1,3-benzoxazines as a result of electrophilic substitution [12–14]. We considered it interesting to study the reaction features of flavonoids with lupinylamine and formalin.

Heating formononetin (**3a**) [15], 7-hydroxy-2′-methoxyisoflavone (**3b**) [16] and its 2-methyl derivative **3d** [17], and 7-hydroxy-2-methylisoflavone (**3c**), which was isolated from *Glycyrrhiza glabra* [18], with an equivalent amount of **2** and a two-fold excess of formalin in propan-2-ol in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) produced derivatives of 9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (**4a**–**d**) in satisfactory yields without preliminary preparation of *N*,*N*-*bis*-(hydroxymethyl)amine. Thus, we synthesized several new derivatives **4a**–**d** containing a lupinine moiety in the 9-position as a result of simultaneous C- and O-aminomethylation of the benzopyran-4-one core.

3-Arylcoumarins, certain representatives of which were isolated from plant material, are flavonoids according to their biogenetic origin. We studied the reaction features of 3-aryl-7-hydroxycoumarins (**5a**–**c**) with **2** and formalin. Like for the 7-hydroxyisoflavones, the Mannich reaction occurred with satisfactory yield without preliminary preparation of *N*,*N*-*bis*-(hydroxymethyl)amine. Derivatives of the isomeric system 9,10-dihydro-2*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-2-one (**6a**–**c**)

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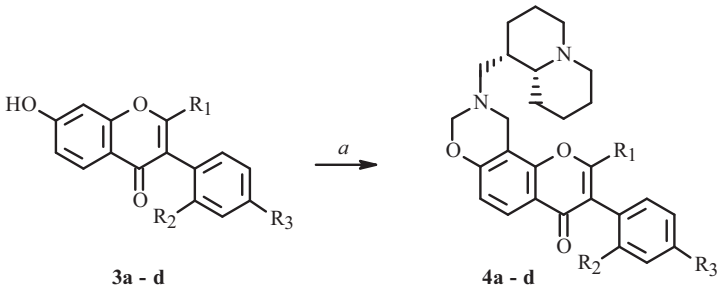
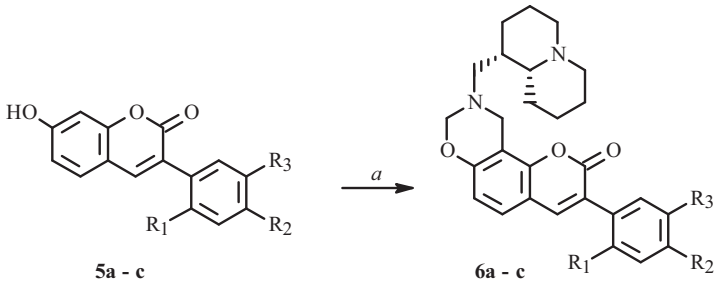
were synthesized by aminomethylation of 7-hydroxy-3-(3-methoxyphenyl)-coumarin (**5a**) [19], 7-hydroxy-3-(2,4-dimethoxyphenyl)-coumarin (**5b**), and 7-hydroxy-3-(2,5-dimethoxyphenyl)-coumarin (**5c**) [20] using lupinylamine and formalin in propan-2-ol.



3a - d **4a - d**

3a, 4a: $R_1 = R_2 = H$, $R_3 = OMe$; **3b, 4b:** $R_1 = R_3 = H$, $R_2 = OMe$
3c, 4c: $R_1 = Me$, $R_2 = R_3 = H$; **3d, 4d:** $R_1 = Me$, $R_2 = OMe$, $R_3 = H$

a. **2**, CH_2O, *i*-PrOH, DMAP



5a - c **6a - c**

5a, 6a: $R_1 = R_2 = H$, $R_3 = OMe$
5b, 6b: $R_1 = R_2 = OMe$, $R_3 = H$
5c, 6c: $R_1 = R_3 = OMe$, $R_2 = H$

a. **2**, CH_2O, *i*-PrOH, DMAP

The structures of the synthesized derivatives were confirmed by NMR spectroscopy. Thus, NMR spectra lacked a resonance for the H-8 proton of the chromone ring and contained resonances for the CH_2-10 and CH_2-8 methylenes at 4.11–4.19 and 4.88–4.97 ppm, respectively, and for the lupinine protons.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC in Sorbfil UV-254 (Russia) and Merck (Germany) plates with elution by toluene:EtOH (9:1 and 95:5). NMR spectra were measured in $CDCl_3$ on the δ-scale relative to TMS (internal standard) on a Mercury 400 instrument (Varian, 400 MHz). Analytical data of all compounds agreed with those calculated.

1-Chloromethyl-(1*R*,9a*R*)-octahydro-2*H*-quinolizine Hydrochloride (1a). A solution of lupinine (30.0 g, 0.177 mol) in benzene (150 mL) was stirred, cooled, treated with $SOCl_2$ (30 mL, 0.414 mol), heated at 50–60°C for 3 h, and cooled. The benzene and excess of $SOCl_2$ were evaporated in vacuo. The residue was diluted with H_2O (25 mL), cooled, and treated with NaOH solution (50%) until strongly basic. The product was extracted by Et_2O (3 × 100 mL). The extract was dried over anhydrous Na_2SO_4. The solvent was distilled off. The product was distilled at reduced pressure. Yield 28.5 g (85.7%), $C_{10}H_{18}ClN$, bp 128–130°C (12 mm Hg). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.10–2.31, 2.77–3.72 (11H, 5H, 2m), 3.90–4.27 (2H, 2m, CH_2Cl).

2-[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-ylmethyl]-1*H*-isoindol-1,3(2*H*)-dione (1b). A solution of chloro-derivative **1a** (18.8 g, 0.1 mol) in anhydrous acetone (100 mL) was treated with potassium phthalimide (19.3 g, 0.104 mol), refluxed for 4 h, cooled, and treated with cold H_2O (400 mL). The resulting precipitate was filtered off, dried, and crystallized from EtOH. Yield 26.8 g (90%), $C_{18}H_{22}N_2O_2$, mp 164–165°C (petroleum ether). PMR spectrum (400 MHz, DMSO-d_6, δ, ppm): 1.09–

2.11 (14H, m, quinolizidine ring protons), 2.66–2.82 (2H, m, quinolizidine ring H-1 and H-9a), 3.58–3.70, 3.82–4.00 (2H, 2m, quinolizidine ring CH_2-1), 7.75–7.94 (4H, m, phthalimide protons).

[(1*R*,9a*R*)-Octahydro-2*H*-quinolizin-1-ylmethyl]amine (2). A solution of **1c** (12.1 g, 40.5 mmol) in EtOH (50 mL) was treated with hydrazine hydrate (2.2 mL, 45.3 mmol), refluxed for 2 h, cooled, and filtered. The filtrate was cooled, stirred, and purged with a stream of anhydrous HCl. The resulting precipitate of lupinylamine dihydrochloride was filtered off and washed with acetone. Yield 9.09 g (92.8%), $C_{10}H_{20}N_2 \cdot 2HCl$, mp >300°C (EtOH). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.12–2.13 (9H, m), 2.62–3.46 (9H, m), 8.31 (2H, br.s, NH_3^+), 10.95 (1H, br.s, NH^+).

The precipitate was dissolved in H_2O (100 mL), treated with KOH solution (4 g KOH in 10 mL H_2O), and extracted with Et_2O (3 × 50 mL). The extract was dried over Na_2SO_4. The Et_2O was distilled. Yield 5.1 g (80%). The product was used without further purification.

General Method for Synthesizing 4a–d and 6a–c. A hot solution of the appropriate 7-hydroxyisoflavone (**3a–d**, 2 mmol) or 7-hydroxy-3-arylcoumarin (**5a–c**, 2 mmol) in propan-2-ol (20 mL) was treated with lupinylamine (2.2 mmol), formalin (1.2 mL, 37%), and DMAP (5 mg). The mixture was refluxed for 3–5 h (end of reaction determined by TLC), cooled, and evaporated in vacuo. The solid was crystallized from a mixture of propan-2-ol and hexane.

3-(4-Methoxyphenyl)-9-[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-ylmethyl]-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (4a). $C_{28}H_{32}N_2O_4$, yield 72%, mp 170–171°C (propan-2-ol:hexane). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.08–2.15 (14H, m, quinolizidine ring), 2.71–3.07 (4H, m, quinolizidine ring H-1 and H-9a, N–CH_2-9), 3.80 (3H, s, 4′-OMe), 4.11 (2H, s, CH_2-10), 4.89, 4.93 (2H, 2d, ^2J = 10.0, CH_2-8), 6.84 (1H, d, ^3J = 9.0, H-6), 6.93 (2H, d, ^3J = 8.4, H-3′, H-5′), 7.45 (2H, d, ^3J = 8.4, H-2′, H-6′), 7.87 (1H, s, H-2), 8.05 (1H, d, ^3J = 9.0, H-5).

3-(2-Methoxyphenyl)-9-[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-ylmethyl]-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (4b). $C_{28}H_{32}N_2O_4$, yield 68%, mp 206–208°C (propan-2-ol:hexane). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.11–2.12 (14H, m, quinolizidine ring), 2.74–3.04 (4H, m, quinolizidine ring H-1 and H-9a, N–CH_2-9), 3.80 (3H, s, 2′-OMe), 4.12 (2H, s, CH_2-10), 4.88, 4.93 (2H, 2d, ^2J = 10.0, CH_2-8), 6.84 (1H, d, ^3J = 8.8, H-6), 6.93–7.02 (2H, m, H-3′, H-5′), 7.24–7.36 (2H, m, H-4′, H-6′), 7.85 (1H, s, H-2), 8.04 (1H, d, ^3J = 8.8, H-5).

2-Methyl-9-[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-ylmethyl]-3-phenyl-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (4c). $C_{28}H_{32}N_2O_3$, yield 53%, mp 130–132°C (propan-2-ol:hexane). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.14–2.16 (14H, m, quinolizidine ring), 2.29 (3H, s, CH_3-2), 2.75–3.04 (4H, m, quinolizidine ring H-1 and H-9a, N–CH_2-9), 4.11 (2H, s, CH_2-10), 4.88, 4.92 (2H, 2d, ^2J = 10.0, CH_2-8), 6.80 (1H, d, ^3J = 8.8, H-6), 7.20–7.46 (5H, m, Ph-3), 7.97 (1H, d, ^3J = 8.8, H-5).

2-Methyl-3-(2-methoxyphenyl)-9-[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-ylmethyl]-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (4d). $C_{29}H_{34}N_2O_4$, yield 48%, mp 145–146°C (propan-2-ol:hexane). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.14–2.16 (14H, m, quinolizidine ring), 2.21 (3H, s, CH_3-2), 2.79–3.03 (4H, m, quinolizidine ring H-1 and H-9a, N–CH_2-9), 3.78 (3H, s, 2′-OMe), 4.15 (2H, s, CH_2-10), 4.93 (2H, s, CH_2-8), 6.81 (1H, d, ^3J = 8.9, H-6), 6.95–7.05 (2H, m, H-3′, H-5′), 7.14–7.19 (1H, m, H-6′), 7.32–7.39 (1H, m, H-4′), 7.99 (1H, d, ^3J = 8.9, H-5).

3-(3-Methoxyphenyl)-9-[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-ylmethyl]-9,10-dihydro-2*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (6a). $C_{28}H_{32}N_2O_4$, yield 55%, mp 181–182°C (propan-2-ol:hexane). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.14–2.10 (14H, m, quinolizidine ring), 2.75–3.02 (4H, m, quinolizidine ring H-1 and H-9a, N–CH_2-9), 3.86 (3H, s, 3′-OMe), 4.13, 4.18 (2H, 2d, ^2J = 17.1, CH_2-10), 4.90, 4.96 (2H, 2d, ^2J = 9.5, CH_2-8), 6.76 (1H, d, ^3J = 8.8, H-6), 6.91–6.96 (1H, m, H-4′), 7.22–7.26 (2H, m, H-2′, H-6′), 7.29 (1H, d, ^3J = 8.8, H-5), 7.32–7.38 (1H, m, H-5′), 7.74 (1H, s, H-4).

3-(2,4-Dimethoxyphenyl)-9-[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-ylmethyl]-9,10-dihydro-2*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (6b). $C_{29}H_{34}N_2O_5$, yield 68%, mp 118–120°C (propan-2-ol:hexane). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.07–2.13 (14H, m, quinolizidine ring), 2.75–3.03 (4H, m, quinolizidine ring H-1 and H-9a, N–CH_2-9), 3.80, 3.84 (6H, 2s, 2′-OMe, 4′-OMe), 4.11, 4.17 (2H, 2d, ^2J = 17.1, CH_2-10), 4.88, 4.95 (2H, 2d, ^2J = 9.5, CH_2-8), 6.52–6.58 (2H, m, H-3′, H-5′), 6.72 (1H, d, ^3J = 8.1, H-6), 7.23 (1H, d, ^3J = 8.1, H-5), 7.26–7.31 (1H, m, H-3′), 7.62 (1H, s, H-4).

3-(2,5-Dimethoxyphenyl)-9-[(1*R*,9a*R*)-octahydro-2*H*-quinolizin-1-ylmethyl]-9,10-dihydro-2*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one (6c). $C_{29}H_{34}N_2O_5$, yield 57%, mp 135–136°C (propan-2-ol:hexane). PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.12–2.15 (14H, m, quinolizidine ring), 2.77–3.01 (4H, m, quinolizidine ring H-1 and H-9a, N–CH_2-9), 3.79, 3.80 (6H, 2s, 2′-OMe, 5′-OMe), 4.12, 4.19 (2H, 2d, ^2J = 17.6, CH_2-10), 4.90, 4.97 (2H, 2d, ^2J = 10.0, CH_2-8), 6.75 (1H, d, ^3J = 9.0, H-6), 6.60–6.96 (3H, m, H-3′, H-4′, H-6′), 7.23 (1H, d, ^3J = 9.0, H-5), 7.67 (1H, s, H-4).

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