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MODIFIED COUMARINS. 32. SYNTHESIS OF AMINO-ACID DERIVATIVES OF DIHYDROPYRANOCOUMARINS

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Linear dihydropyranocoumarins containing natural and synthetic amino acids were synthesized using activated esters.

Key words: coumarins, pyranocoumarins, amino-acid derivatives, activated esters, synthesis.

Benzopyran-2-one is a structural component of many important natural secondary metabolites [1] and highly active pharmacological compounds [2]. Pyranocoumarins are widely distributed in nature and contain a 2,2-dimethylpyran ring annelated to the benzopyran-2-one moiety [1]. Most natural pyranocoumarins are derivatives of the linear pyranone xanthyletin. Pyranocoumarins also include coumarin derivatives with an annelated 2,2-dimethyldihydropyran ring. Typical representatives are the dihydropyranocoumarins dihydroxanthyletin, which is produced by the plants *Cassia pumila* Lam. [3] and *Ammi majus* [4], and 5-methoxydihydroxanthyletin, which was isolated from *Glycyrrhiza uralensis* [5].

The important role of amino acids in vital functions has for a long time stimulated the search for new biologically active compounds among natural amino acids, their synthetic analogs, and various compounds containing amino acids. Therefore, introduction into the pyranocoumarin molecule of an amino-acid substituent is interesting to both theoretical organic synthesis and targeted synthesis of new biologically active compounds.

Herein we report the functionalization of the dihydropyranocoumarin moiety by introduction of additional pharmacophores, i.e., natural and synthetic amino acids.

7-Hydroxy-2,2-dimethylchroman-4-one (**1**) that was required for further transformations was prepared by Kabbe condensation of 2,4-dihydroxyacetophenone and acetone in the presence of pyrrolidine [6, 7]. Clemmensen reduction of **1** using zinc dust in HCl formed 2,2-dimethylchroman-7-one (**2**). Pechmann condensation of **2** and dimethylacetylsuccinate in the presence of conc. H_2SO_4 formed the methyl ester of (4,8,8-trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetic acid (**3**).

The PMR spectrum of **3** exhibited a simplified splitting pattern for the aromatic protons compared with the starting 2,2-dimethylchromane because of decoupling of H-6 of the dihydropyran ring. Protons H-5 and H-10 of the 8,8-dimethyl-7,8-dihydropyrano[3,2-*g*]chromen-2-one appeared as two 1H singlets at 7.56 and 6.65 ppm, respectively. Furthermore, the PMR spectrum of **3** had resonances characteristic of a 2,2-dimethyldihydropyran ring (6H singlet at 1.31 ppm and two triplets at 1.82 and 2.81 ppm with SSCC 6.4 Hz) and an ester (two singlets at 3.60-3.65 ppm).

Alkaline hydrolysis of ester **3** produced dihydropyranocoumarinacetic acid **4**, amino-acid derivatives of which were synthesized using the method of activated esters that is widely employed in peptide synthesis because it had a free carboxylic acid [8]. The *N*-hydroxysuccinimide ester was used to activate the carboxylic acid because it is typically highly reactive, does not racemize the products [9], and has been used successfully to synthesize similar compounds [10-12]. The activated ester was prepared by reacting starting acid **4** with *N*-hydroxysuccinimide (SuOH) in anhydrous dioxane using diisopropylcarbodiimide (DIC) as the condensing agent. The reaction of the activated ester and sodium salts of amino acids in dioxane:water at room temperature with subsequent acidolysis of the resulting salts afforded in 64-86% yields amino-acid derivatives of dihydropyranocoumarin **5**-**17** with free carboxylic acids.

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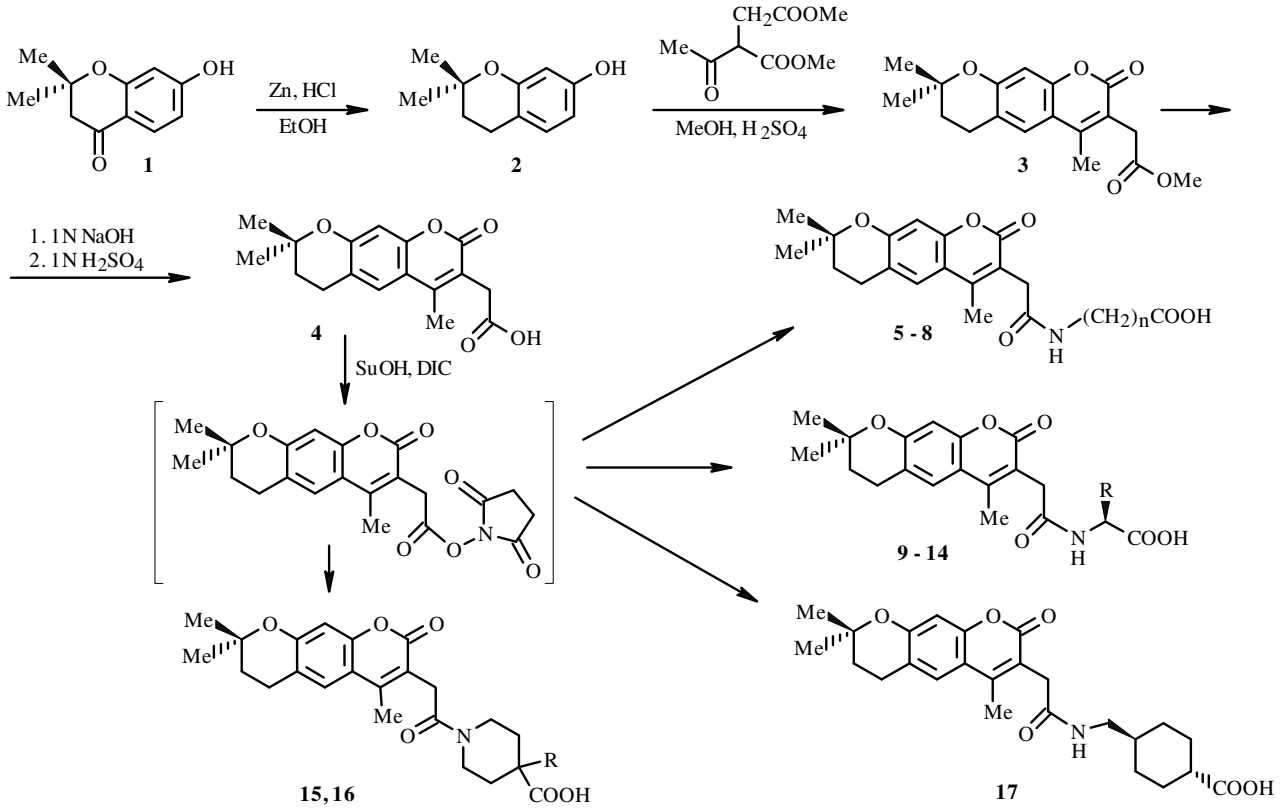
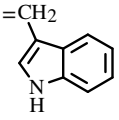


5: n = 1; **6:** n = 2; **7:** n = 3; **8:** n = 5; **9:** R = CH_3; **10:** R = CH_2CH_3; **11:** R = $CH(CH_3)_2$
12: R = Ph; **13:** R = CH_2Ph-4-Cl; **14:** R =  ; **15:** R = H; **16:** R = Ph

Derivatives of dihydropyranocoumarin with glycine (**5**), *β*-alanine (**6**), L-alanine (**9**), L-valine (**11**), L-phenylglycine (**12**), DL-4-chlorophenylalanine (**13**), L-tryptophan (**14**), DL-2-aminobutanoic (**10**), 4-aminobutanoic (**7**), 6-aminohexanoic (**8**), 4-piperidinecarboxylic (**15**), 4-phenylpiperidine-4-carboxylic (**16**), and *trans*-4-aminomethylcyclohexanecarboxylic (**17**) acids were synthesized.

PMR spectra of **5**-**17** contained resonances for the dihydropyranocoumarin ring, the amino-acid, the formed amide bond (7.78-8.72 ppm), and the free carboxylic acid (11.90-12.80 ppm).

EXPERIMENTAL

The course of reactions and purity of products were monitored using TLC on Merck 60 F_{254} plates with elution by $CHCl_3$:CH_3OH (9:1 and 95:5). Melting points were determined on a Kofler block. PMR spectra were measured on Varian VXR-300 and Mercury 400 spectrometers at 300 and 400 MHz, respectively, relative to TMS (internal standard). Elemental analyses of all compounds agreed with those calculated.

The syntheses of 2,2-dimethylchromanes **1** and **2** have been published [7].

Methyl-(4,8,8-trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetate (3). A cooled (0°C) solution of 2,2-dimethylchroman-7-one (17.8 g, 0.1 mol) and dimethylacetylsuccinate (16.2 mL, 0.1 mol) in CH_3OH (20 mL) was stirred vigorously, cooled, treated dropwise with conc. H_2SO_4 (50 mL), stirred for 8 h, left overnight at room temperature, and poured into icewater (500 mL). The resulting precipitate was filtered off and crystallized from aqueous methanol. Yield 23.41 g (74%), mp 172-173°C, $C_{18}H_{20}O_5$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.31 (6H, s, 2 × CH_3-8), 1.82 (2H, t, J = 6.4, CH_2-7), 2.31 (3H, s, CH_3-4), 2.81 (2H, t, J = 6.4, CH_2-6), 3.62 (2H, s, CH_2-3), 3.65 (3H, s, $COOCH_3$), 6.65 (1H, s, H-10), 7.56 (1H, s, H-5).

(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetic Acid (4). A solution of **3** (22.15 g, 70 mmol) in propanol-2 (50 mL) was treated with NaOH solution (150 mL, 150 mmol, 1 M), and heated and stirred vigorously for 1 h (course of reaction monitored using TLC). When the reaction was finished the mixture was cooled, poured into water (500 mL), and acidified to pH 5-6. The resulting precipitate was filtered off and crystallized from aqueous propanol-2. Yield 18.62 g (88%), mp 181-182°C, $C_{17}H_{18}O_5$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.30 (6H, s, 2 × CH_3-8), 1.81 (2H, t, J = 6.4, CH_2-7), 2.32 (3H, s, CH_3-4), 2.81 (2H, t, J = 6.4, CH_2-6), 3.54 (2H, s, CH_2-3), 3.65 (3H, s, $COCH_3$), 6.67 (1H, s, H-10), 7.54 (1H, s, H-5), 12.10 (1H, br.s, COOH).

General Method for Synthesizing *N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]amino Acids 5-17. A solution of **4** (0.91 g, 3 mmol) and *N*-hydroxysuccinimide (0.38 g, 3.3 mmol) in anhydrous dioxane (20 mL) was stirred vigorously, treated with diisopropylcarbodiimide (0.52 mL, 3.3 mmol), and stirred for 2 h (course of reaction monitored by TLC). The resulting activated ester was treated with the appropriate amino acid (3.3 mmol) and $NaHCO_3$ (0.28 g, 3.3 mmol) in water (20 mL) and stirred vigorously for 2-4 h (course of reaction monitored by TLC). When the reaction was finished the precipitate of diisopropylurea was filtered off. The filtrate was diluted with water (200 mL) and acidified to pH 5-6. The resulting precipitate was filtered off and crystallized from aqueous propanol-2.

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]glycine (5).** Yield 0.73 g (68%), mp 216-217°C, $C_{19}H_{21}NO_6$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.30 (6H, s, 2 × CH_3-8′), 1.81 (2H, t, J = 6.4, CH_2-7′), 2.31 (3H, s, CH_3-4′), 2.81 (2H, t, J = 6.4, CH_2-6′), 3.50 (2H, s, CH_2-3′), 3.72 (2H, d, J = 6.0, CH_2-2), 6.67 (1H, s, H-10′), 7.54 (1H, s, H-5′), 8.19 (1H, t, J = 5.6, CONH), 12.50 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-*β*-alanine (6).** Yield 0.82 g (73%), mp 184-185°C, $C_{20}H_{23}NO_6$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.33 (6H, s, 2 × CH_3-8′), 1.83 (2H, t, J = 6.4, CH_2-7′), 2.31 (3H, s, CH_3-4′), 2.38 (2H, t, J = 6.8, CH_2-2), 2.84 (2H, t, J = 6.4, CH_2-6′), 3.25 (2H, q, J = 6.8, CH_2-3), 3.44 (2H, s, CH_2-3′), 6.69 (1H, s, H-10′), 7.56 (1H, s, H-5′), 7.97 (1H, t, J = 5.6, CONH), 12.30 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-4-aminobutanoic Acid (7).** Yield 0.91 g (78%), mp 172-173°C, $C_{21}H_{25}NO_6$.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.33 (6H, s, 2 × CH_3-8′), 1.65 (2H, m, CH_2-3), 1.83 (2H, t, J = 6.6, CH_2-7′), 2.19 (2H, t, J = 7.2, CH_2-2), 2.32 (3H, s, CH_3-4′), 2.84 (2H, t, J = 6.6, CH_2-6′), 3.04 (2H, q, J = 6.6, CH_2-4), 3.40 (2H, s, CH_2-3′), 6.60 (1H, s, H-10′), 7.48 (1H, s, H-5′), 7.85 (1H, t, J = 5.4, CONH), 11.92 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-6-aminohexanoic Acid (8).** Yield 0.80 g (64%), mp 168-169°C, $C_{23}H_{29}NO_6$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.25 (2H, m, CH_2-4), 1.33 (6H, s, 2 × CH_3-8′), 1.37 (2H, m, CH_2-3), 1.48 (2H, m, CH_2-5), 1.83 (2H, t, J = 6.6, CH_2-7′), 2.32 (3H, s, CH_3-4′), 2.84 (2H, t, J = 6.6, CH_2-6′), 3.02 (2H, q, J = 6.8, CH_2-6), 3.43 (2H, s, CH_2-3′), 6.69 (1H, s, H-10′), 7.55 (1H, s, H-5′), 7.84 (1H, t, J = 5.6, CONH), 11.98 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-L-alanine (9).** Yield 0.96 g (86%), mp 221-222°C, $C_{20}H_{23}NO_6$.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.31 (3H, d, J = 7.2, CH_3-2), 1.33 (6H, s, 2 × CH_3-8′), 1.83 (2H, t, J = 6.9, CH_2-7′), 2.30 (3H, s, CH_3-4′), 2.83 (2H, t, J = 6.9, CH_2-6′), 3.48 (2H, s, CH_2-3′), 4.20 (1H, m, H-2), 6.59 (1H, s, H-10′), 7.47 (1H, s, H-5′), 8.12 (1H, d, J = 7.2, CONH), 12.10 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-DL-2-aminobutanoic Acid (10).** Yield 0.92 g (79%), mp 216-217°C, $C_{21}H_{25}NO_6$.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.91 (3H, t, J = 7.5, CH_3-4), 1.33 (6H, s, 2 × CH_3-8′), 1.60-1.80 (2H, m, CH_2), 1.83 (2H, t, J = 6.9, CH_2-7′), 2.31 (3H, s, CH_3-4′), 2.83 (2H, t, J = 6.9, CH_2-6′), 3.51 (2H, s, CH_2-3′), 4.12 (1H, m, H-2), 6.59 (1H, s, H-10′), 7.46 (1H, s, H-5′), 8.05 (1H, d, J = 7.2, CONH), 11.95 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-L-valine (11).** Yield 0.79 g (66%), mp 198-199°C, $C_{22}H_{27}NO_6$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.82 (6H, d, J = 6.0, 2 × CH_3-3), 1.24 (6H, s, 2 × CH_3-8′), 1.74 (2H, t, J = 7.2, CH_2-7′), 1.95 (1H, m, H-3), 2.23 (3H, s, CH_3-4′), 2.75 (2H, t, J = 7.2, CH_2-6′), 3.48 (2H, s, CH_2-3′), 4.14 (1H, m, H-2), 6.60 (1H, s, H-10′), 7.46 (1H, s, H-5′), 8.10 (1H, d, J = 8.4, CONH), 12.05 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-L-phenylglycine (12).** Yield 1.10 g (84%), mp 242-243°C, $C_{25}H_{25}NO_6$.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.32 (6H, s, 2 × CH_3-8′), 1.82 (2H, t, J = 6.8, CH_2-7′), 2.30 (3H, s, CH_3-4′), 2.83 (2H, t, J = 6.8, CH_2-6′), 3.60 (2H, s, CH_2-3′), 5.33 (1H, d, J = 7.6, H-2), 6.68 (1H, s, H-10′), 7.33-7.45 (5H, m, Ph-2), 7.55 (1H, s, H-5′), 8.72 (1H, d, J = 7.6, CONH), 12.60 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-DL-4-chlorophenylalanine (13).** Yield 1.29 g (89%), mp 239-240°C, $C_{26}H_{26}ClNO_6$.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.32 (6H, s, 2 × CH_3-8′), 1.83 (2H, t, J = 6.6, CH_2-7′), 2.13 (3H, s, CH_3-4′), 2.80-2.95 (3H, m, CH_2-3α, CH_2-6′), 3.04 (1H, dd, J = 4.5, 13.5, CH_2-3β), 3.42 (2H, s, CH_2-3′), 4.42 (1H, m, H-2), 6.60 (1H, s, H-10′), 7.19 (4H, s, H-2″, H-3″, H-5″, H-6″), 7.43 (1H, s, H-5′), 8.05 (1H, d, J = 8.1, CONH), 12.20 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-L-tryptophan (14).** Yield 1.19 g (81%), mp 226-227°C, $C_{28}H_{28}N_2O_6$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.32 (6H, s, 2 × CH_3-8′), 1.84 (2H, t, J = 6.6, CH_2-7′), 2.18 (3H, s, CH_3-4′), 2.85 (2H, t, J = 6.8, CH_2-6′), 3.00-3.18 (1H, m, CH_2-3), 3.42 and 3.48 (2H, 2d, J = 14.4, CH_2-3′), 4.48 (1H, m, H-2), 6.68 (1H, s, H-10′), 6.98 (1H, t, J = 7.2, H-6″), 7.06 (1H, t, J = 7.2, H-5″), 7.15 (1H, s, H-2″), 7.33 (1H, d, J = 8.0, H-7″), 7.50 (1H, s, H-5′), 7.52 (1H, d, J = 8.0, H-4″), 8.12 (1H, m, CONH), 10.86 (1H, s, NH-1″), 12.35 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-4-piperidinecarboxylic Acid (15).** Yield 1.03 g (83%), mp 193-194°C, $C_{23}H_{27}NO_6$.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.33 (6H, s, 2 × CH_3-8′), 1.35-1.95 (4H, m, CH_2-3, CH_2-5), 1.84 (2H, t, J = 6.6, CH_2-7′), 2.32 (3H, s, CH_3-4′), 2.80 (1H, m, H-4), 2.85 (2H, t, J = 6.6, CH_2-6′), 3.65 (2H, s, CH_2-3′), 4.05 and 4.17 (4H, 2m, CH_2-2, CH_2-6), 6.60 (1H, s, H-10′), 7.47 (1H, s, H-5′), 12.16 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-4-phenylpiperidine-4-carboxylic Acid (16).** Yield 1.10 g (75%), mp 239-240°C, $C_{29}H_{31}NO_6$.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.32 (6H, s, 2 × CH_3-8′), 1.70-1.95 (4H, m, CH_2-3, CH_2-5), 1.84 (2H, t, J = 6.8, CH_2-7′), 2.29 (3H, s, CH_3-4′), 2.85 (2H, t, J = 6.8, CH_2-6′), 3.68 (2H, s, CH_2-3′), 4.02 and 4.19 (4H, 2m, CH_2-2, CH_2-6), 6.69 (1H, s, H-10′), 7.29-7.44 (5H, m, Ph-4), 7.55 (1H, s, H-5′), 12.80 (1H, br.s, COOH).

***N*-[(4,8,8-Trimethyl-2-oxo-7,8-dihydropyrano[3,2-*g*]chromen-3-yl)acetyl]-*trans*-4-aminomethyl-cyclohexane-carboxylic Acid (17).** Yield 1.14 g (86%), mp 217-218°C, $C_{25}H_{31}NO_6$.

PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.92-1.35 (5H, m, CH_2-3, H-4, CH_2-5), 1.33 (6H, s, 2 × CH_3-8′), 1.65-1.95 (6H, m, CH_2-2, CH_2-6, CH_2-7′), 2.07 (1H, m, H-1), 2.77-2.90 (4H, m, CH_2-4, CH_2-6′), 3.41 (2H, s, CH_2-3′), 6.60 (1H, s, H-10′), 7.48 (1H, s, H-5′), 7.78 (1H, t, J = 7.2, CONH), 12.50 (1H, br.s, COOH).

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