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SYNTHESIS OF GLYCYRRHETIC ACID DERIVATIVES

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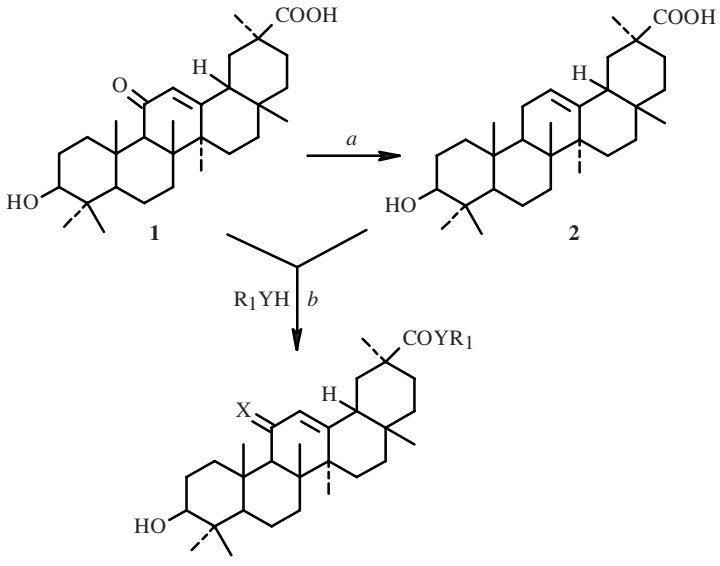
*11-Deoxyglycyrrhetinic acid (DGA) (**2**) was produced by Clemmensen reduction of the C-11 carbonyl of 18β-glycyrrhetic acid (GA) (**1**). Four derivatives of GA and DGA (**3a-3d**) were synthesized. Their structures were elucidated using spectral data (IR, mass, ^1H, ^{13}C NMR).*

Key words: synthesis, glycyrrhetic acid, 11-deoxyglycyrrhetinic acid, derivatives.

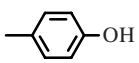
Glycyrrhetic acid (GA) (**1**) has been prepared from roots of *Glycyrrhiza glabra*. GA possesses anti-inflammatory, antiviral, antiallergic, antiulcer, antitumor, analgesic, and other properties [1-8]. Certain GA or 11-deoxyglycyrrhetinic acid (DGA) derivatives have been tested in the clinic. The disodium salt of 3-*O*-*β*-carboxypropionylglycyrrhetic acid was administered orally as an agent against stomach ulcer; ammonium glycyrrhinate in combination with L-cysteine and glycine, clinically for i.v. injections as an antiallergic agent. However, side effects were observed in patients who recieved high doses of glycyrrhizic acid or GA over long periods. One side effect was mineral-corticoid-like action that was noted as pseudoaldosteroidism occurring due to inhibition of metabolic clearance of endogenous corticoid with retention of sodium ions and water and elimination of potassium ions.

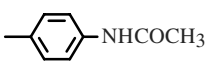


3a - 3d

3a: X = O, Y = NH, R_1 = 

3b: X = H_2, Y = NH, R_1 = 

3c: X = O, Y = NH, R_1 = 

3d: X = O, Y = O, R_1 = 

a) dioxane, Zn(Hg)/HCl, 0→20°C; *b*) THF, DCC/DMAP, 0→20°C.

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It was reported that DGA amide derivatives containing a piperazine ring are more effective than DA and decrease the incidence of ulcers in the duodenum. Furthermore, these derivatives have a lower or unimportant aldosteroid-like side effect [9].

Thus, the structures of GA and DGA must be modified in order to prepare derivatives with more significant biological activity.

Herein we report the preparation of **2** by Clemmensen reduction of the carbonyl on C-11 of GA and the synthesis of the four GA and DGA derivatives **3a**-**3d**, which were synthesized in the presence of DCC/DMAP in THF. The structures of the synthesized compounds were confirmed by IR, mass, PMR, and ^{13}C NMR spectral data.

EXPERIMENTAL

Melting points were determined on a Yanaco MP-300 melting-point apparatus equipped with a microscope and were not corrected. PMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Inova-400 spectrometer with TMS internal standard. ESI-mass spectra were obtained in an HP1100LC/MS instrument. 18-β-Glycyrrhetic acid (98% pure, HPLC) was purchased from Shuguang company for production of natural products (Shandun District, China); dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP), from Shanhai Reagent Company, China). Other commercially available reagents were used without further purification. THF was distilled over sodium and benzophenone before use. The course of reactions was monitored by TLC on Silufol GF 254 plates. Compounds were developed by phosphomolybdic acid solution (10%).

Reaction products were isolated by column chromatography over silica gel (200-300 mesh, reagent plant, Tsindao).

11-Deoxyglycyrrhetinic Acid (2). $HgCl_2$ (1.0 g) was placed in a one-necked round-bottomed flask (50 mL), treated with HCl (20 mL, 5%), and stirred until the solid dissolved. The reaction mixture was treated with zinc dust (5 g) and stirred for another 30 min. The solvent was distilled. The solid in the flask was washed three times with dioxane. 18-β-Glycyrrhetic acid (1 g) dissolved in dioxane (10 mL) was added with stirring to the solid in a cooling bath, treated dropwise over 30 min with conc. HCl (5 mL), and stirred for 30 min in an ice bath at room temperature. The course of the reaction was monitored by TLC. The Zn powder was filtered off. Dioxane was distilled at reduced pressure to produce DGA, which was recrystallized in acetic acid to afford pure **2** (0.75 g, 77%), which was obtained previously in the hydrolysis products of glycyrrhizic acid and its salts [10].

11-Deoxyglycyrrhetinic acid, white powder, mp 323-325°C (acetic acid).

IR spectrum (ν_{max}, cm^{-1}): 3245, 2933, 1703, 1386, 1363, 1326, 1280, 1255.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.67 (3H, s, CH_3), 0.74 (3H, s, CH_3), 0.82 (3H, s, CH_3), 0.88 (6H, s, 2 × CH_3), 1.06 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.26-2.51 (m, 23H), 3.00 (1H, br.s, OH), 4.30 (1H, m, H-3), 5.17 (1H, t, J = 3.44, H-12), 12.01 (1H, s, COOH).

^{13}C NMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 181.1, 145.2, 125.1, 68.3, 64.6, 56.9, 47.4, 45.3, 45.2, 43.9, 43.5, 42.5, 39.8, 38.3, 36.3, 33.7, 32.8, 32.2, 28.8, 28.4, 28.0, 27.8, 27.7, 25.3, 24.8, 20.0, 18.8, 16.9, 15.8, 15.4.

Mass spectrum (*m*/*z*, %): 497 (100) $[M + Na]^+$, 413 (53), 381 (31), 148 (22); HRMS (*m*/*z*): 456.3605 (calc. for $C_{30}H_{48}O_3$, 456.3603).

General Method for Synthesis 3a-3d [9]. GA or DGA (0.5 mmol) and DCC (0.11 g, 0.55 mmol) were placed in a one-necked round-bottomed flask (25 mL) with THF (5 mL), stirred on an ice bath for 10 min, treated with DMAP (0.07 g, 0.55 mmol) and R_1 Y-H (0.55 mmol) in THF (5 mL), stirred in an ice bath for 30 min, and stirred at room temperature for 8 h. The completion of the reaction was monitored by TLC. Solvent was removed in vacuo. Reaction products were isolated by column chromatography [elution by petroleum ether:ethylacetate (5:1→2:1)] to afford **3a**-**3d**. Identical fractions were combined based on TLC results. Compounds **3a**-**3d** were isolated from petroleum ether:ethylacetate.

(*N*-Cyclohexyl)glycyrrhetinic acid amide (3a), white powder, yield 58.4%, mp 150-151°C (petroleum ether:ethylacetate).

IR spectrum (ν_{max}, cm^{-1}): 3446 (NH), 3385 (OH), 2950, 1652 (C=O), 1646 (HN–C=O), 1386, 1363, 1326, 1280, 1255, 1326, 1280, 1255.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.81 (3H, s, CH_3), 0.86 (3H, s, CH_3), 0.88 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.14 (6H, s, 2 × CH_3), 1.33 (3H, s, CH_3), 1.37-2.77 (m, 32H), 3.21-3.25 (1H, m, OH), 3.18 (1H, m, H-3), 5.44 (1H, d, J = 8.1, NH–), 5.63 (1H, s, H-12).

Mass spectrum (*m/z*, %): 552.7 (78) $[M + 1]^+$, 569.7 (100) $[M + 18]^+$, 574.7 (10) $[M + 23]^+$.

(*N*-Cyclohexyl)-11-deoxyglycyrrhetinic acid amide (3b), white powder, yield 61.3%, mp 79-82°C.

IR spectrum (ν_{max}, cm^{-1}): 3434 (NH), 3358 (OH), 2928, 1637 (HN–C=O), 1386, 1363, 1326, 1280, 1255.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.77 (3H, s, CH_3), 0.81 (3H, s, CH_3), 0.89 (3H, s, CH_3), 0.93 (3H, s, CH_3), 0.97 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.16-2.73 (m, 34H), 3.22 (1H, m, OH), 3.85 (1H, m, H-3), 5.21 (1H, s, H-12), 5.46-5.48 (1H, d, J = 8.0, NH).

Mass spectrum (*m/z*, %): 538.8 (85) $[M + 1]^+$, 555.8 (100) $[M + 18]^+$, 560.8 (18) $[M + 23]^+$.

(*N*-*p*-Hydroxyphenyl)glycyrrhetinic acid amide (3c), light-yellow solid, yield 48.4%, mp 208-211°C.

IR spectrum (ν_{max}, cm^{-1}): 3420 (NH), 3383 (OH), 2928, 1647 (C=O), 1637 (HN–C=O), 1513, 1386, 1363, 1326, 1280, 1255, 830.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.71 (3H, s, CH_3), 1.00 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.38-2.79 (m, 23H), 3.21-3.26 (1H, br.s, OH), 4.09-4.16 (1H, m), 5.57 (1H, s, Ph–OH), 5.67 (1H, s), 6.76-6.78 (2H, d, J = 8, Ph–H), 7.73 (1H, s, Ph–NH).

Mass spectrum (*m/z*, %): 562.7 (96) $[M + 1]^+$, 579.7 (100) $[M + 18]^+$, 584.6 (48) $[M + 23]^+$.

(*N*-*p*-Acetaminophenyl)glycyrrhetinic acid amide (3d), light-yellow solid, yield 77.1%, mp 213-214°C.

IR spectrum (ν_{max}, cm^{-1}): 3236 (OH, NH), 2927, 2850, 1793, 1654, 1625 (NH–C=O), 1575, 1386, 1363, 1326, 1270, 1244, 750.

PMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 0.69 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.92 (3H, s, CH_3), 1.03 (6H, s, 2 × CH_3), 1.07 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.09-2.50 (m, 19H), 2.54 (3H, s, O=C–CH_3), 3.03 (1H, m, OH), 4.29 (1H, m, H-3), 5.57 (1H, s), 7.42-7.44 (2H, d, J = 8, Ph–H), 7.99 (1H, s, NH).

Mass spectrum (*m/z*, %): 604.5 (70) $[M + 1]^+$, 621.3 (100) $[M + 18]^+$, 626.6 (56) $[M + 23]^+$.

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