SYNTHESIS OF AMIDES OF 3-O-ACETYL-18-βH-GLYCYRRHETIC ACID

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Methods of preparing amides of 3-O-acetyl-18-βH-glycyrrhetic acid from certain amines are described. The structures of the prepared amides have been confirmed by chemical and spectral analyses.

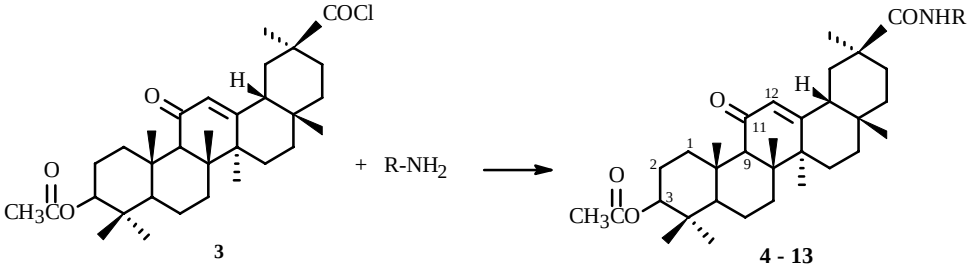
Key words: glycyrrhizic and glycyrrhetic acids, amides.

Licorice (*Glycyrrhiza glabra* L.) is one of the oldest medicinal plants. The active principle of licorice extract and its main component is a triterpene glycoside, glycyrrhizic acid.

Many derivatives have been synthesized from glycyrrhizic acid and its aglycone, glycyrrhetic acid. They typically have anti-inflammatory, antitumor, and anti-allergic activity [1-3]. Many derivatives of glycyrrhizic and glycyrrhetic acids are highly effective against the HIV virus [4, 5].

Considering this, we synthesized various amides in order to produce novel compounds.

Glycyrrhetic acid (**1**) was isolated from the thick extract of licorice root by the literature method [6]. Treatment of **1** with acetic anhydride in pyridine gave 3-O-acetyl-18-βH-glycyrrhetic acid (**2**) [7]. The acylchloride of **2** (**3**) was obtained as before [8]. Reaction of **3** with aromatic amines gave the corresponding amides **4-13**.



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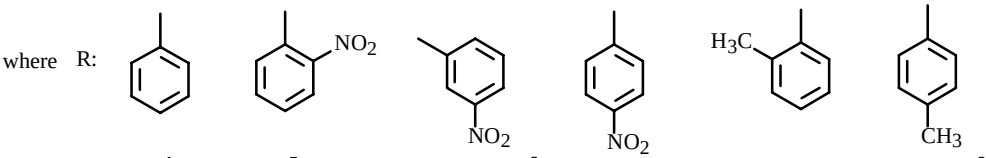
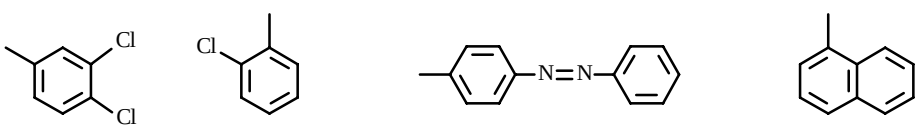


4 **5** **6** **7** **8** **9**



10 **11** **12** **13**

The following characteristic frequencies (ν, cm^{-1}) were observed in all IR spectra of amides of **2**: 1680 (11-C=O), 1735 (OAc), 1630-1680 (CO-30), 1510-1570 (CO–NH).

The structures of the synthesized compounds (**4-13**) were characterized by PMR spectra. The core of the amides is 3-O-acetyl-18-βH-glycyrrhetic acid (**2**), for which the assignment of certain signals is known from the literature [9, 10]. We present a more complete assignment for most of the characteristic signals.

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At weak field, the H-12 proton of the double bond resonates at 5.63 ppm; Ha-3, at 4.46 ppm with splitting by the neighboring vicinal protons on C-2. The deshielding effect of the carbonyl on C-11 shifts the signal of the equatorial He-1 proton from the methylene region to weak field (2.76 ppm), where it appears as an unsymmetrical doublet with spin—spin coupling constant (SSCC) J = 13.5 Hz.

A single peak at 2.33 ppm belongs to H-9, which has no close spin—spin couplings according to the structure. A 3H singlet at 2.01 ppm belongs undoubtedly to the acetyl methyl on C-3.

At strong field, signals characteristic of seven quaternary methyls appear. They were assigned by consulting the literature [9]. The CH_3-26 group resonates at 1.36 ppm; CH_3-29, at 1.20 ppm.

The CH_3-25 and CH_3-27 methyls give signals at 1.14 and 1.12 ppm, respectively. The chemical shifts of the CH_3-23, CH_3-24, and CH_3-28 methyls are very close (0.82-0.86 ppm).

The PMR spectra for most of **4-13** showed slight changes in the values of the above signals.

The signal for CH_3-29 is shifted to weak field up to 1.30 ppm, the position of which varies in the range 1.24-1.30 ppm depending on the bound radical. As a rule, the signals for CH_3-25 and CH_3-27 and CH_3-23, CH_3-24, and CH_3-28 appear as poorly resolved 6H and 9H signals at 1.13 and 0.85 ppm, respectively.

The position of the signal for the amide proton varies from 7.8 to 10.3 ppm depending on the structure and concentration. The aromatic region contains signals characteristic of the bound radicals. Qualitative and quantitative analyses of the signals (see Experimental) indicate that they are consistent with the proposed structures.

EXPERIMENTAL

TLC used Silufol UV-254 plates (Chemapol) and $CHCl_3$—CH_3OH (10:1) with development by I_2 vapor. IR spectra were recorded on a Specord 71 IR spectrophotometer in mineral oil; PMR spectra, on a Varian XL-100 instrument (USA) in $CDCl_3$ and CCl_4 with TMS internal standard. Compounds **1**, **2**, and **3** were prepared by the literature methods [6-9]. Analytical data for **4-13** correspond to those calculated.

Preparation of N-Phenyl-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (4). A solution of freshly prepared aniline (0.186 g, 0.002 mole) and triethylamine (0.28 mL, 0.002 mole) in absolute benzene (15 mL) was stirred and treated slowly with a solution of 3-O-acetyl-18-βH-glycyrrhetyl chloride (1.06 g, 0.002 mole) in absolute benzene (15 mL). The mixture was boiled for 3 h on a water bath. The course of the reaction was monitored using TLC.

The precipitate of triethylamine hydrochloride was filtered off and washed three times with absolute benzene. The solvent was distilled off. The solid was reprecipitated from $CHCl_3$—CH_3OH (10:1). Yield 0.95 g (81.2%), mp 165-167°C, R_f 0.76, $C_{38}H_{53}O_4N$. PMR (δ, ppm, J/Hz): 1.24 (3H, s, CH_3-29), 2.28 (1H, s, H-9), 2.77 (1H, br. d, J = 13.6, He-1), 4.40 (1H, m, H-3), 5.50 (1H, s, H-12), 7.21-7.35 (5H, m, Ar), 9.93 (1H, br. s, NH).

Compounds **5-13** were prepared analogously.

N-(*o*-Nitrophenyl)-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (5). Yield 64.2%, mp 280-282°C, R_f 0.74, $C_{38}H_{56}O_6N_2$.

PMR (δ, ppm, J/Hz): 1.28 (3H, s, CH_3-29), 2.27 (1H, s, H-9), 2.79 (1H, br. d, J = 13.5, He-1), 4.36 (1H, m, H-3), 5.52 (1H, s, H-12), 7.22-7.79 (4H, m, Ar), 10.31 (1H, br. s, NH).

N-(*m*-Nitrophenyl)-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (6). Yield 68.5%, mp 230-232°C, R_f 0.73, $C_{38}H_{56}O_6N_2$.

PMR (δ, ppm, J/Hz): 1.28 (3H, s, CH_3-29), 2.36 (1H, s, H-9), 2.73 (1H, br. d, J = 13.5, He-1), 4.41 (1H, m, H-3), 5.62 (1H, s, H-12), 7.69-8.61 (4H, m, Ar), 10.11 (1H, br. s, NH).

N-(*p*-Nitrophenyl)-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (7). Yield 70.2%, mp 192-196°C, R_f 0.75, $C_{38}H_{56}O_6N_2$.

PMR (δ, ppm, J/Hz): 1.29 (3H, s, CH_3-29), 2.34 (1H, s, H-9), 2.76 (1H, br. d, J = 13.5, He-1), 4.41 (1H, m, H-3), 5.56 (1H, s, H-12), 7.63 (2H, m, H-2′ + H-6′), 8.08 (2H, m, H-3′ + H-5′), 7.78 (1H, br. s, NH).

N-(2-Methylphenyl)-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (8). Yield 70.9%, mp 256-258°C, R_f 0.70, $C_{39}H_{55}O_4N$.

PMR (δ, ppm, J/Hz): 1.27 (3H, s, CH_3-29), 2.31 (1H, s, H-9), 2.64 (3H, s, CH_3-Ar), 2.75 (1H, br. d, J = 13.5, He-1), 4.37 (1H, m, H-3), 5.52 (1H, s, H-12), 6.96-7.67 (4H, m, Ar), 10.1 (1H, br. s, NH).

N-(4-Methylphenyl)-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (9). Yield 75.8%, mp 180-182°C, R_f 0.65, $C_{39}H_{55}O_4N$.

PMR (δ, ppm, J/Hz): 1.24 (3H, s, CH_3-29), 2.26 (1H, s, H-9), 2.30 (3H, s, CH_3-Ar), 2.78 (1H, br. d, J = 13.5, He-1), 4.40 (1H, m, H-3), 5.52 (1H, s, H-12), 7.12 (2H, m, H-3 + H-5), 7.37 (2H, m, H-2 + H-6), 7.78 (1H, br. s, NH).

N-(3,4-Dichlorophenyl)-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (10). Yield 62.2%, mp 184-186°C, R_f 0.75, $C_{38}H_{51}O_4N$.

PMR (δ, ppm, J/Hz): 1.30 (3H, s, CH_3-29), 2.30 (1H, s, H-9), 2.76 (1H, br. d, J = 13.6, He-1), 4.41 (1H, m, H-3), 5.58 (1H, s, H-12), 7.34-8.01 (3H, m, Ar), 10.80 (1H, br. s, NH).

N-(2-Chlorophenyl)-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (11). Yield 83.4%, mp 279-281°C, R_f 0.81, $C_{38}H_{52}O_4N$.

PMR (δ, ppm, J/Hz): 1.24 (3H, s, CH_3-29), 2.31 (1H, s, H-9), 2.79 (1H, br. d, J = 13.6, He-1), 4.41 (1H, m, H-3), 5.55 (1H, s, H-12), 6.98-8.02 (4H, m, Ar), 8.78 (1H, br. s, NH).

N-(1,1-Azophen-4-yl)-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (12). Yield 80.2%, mp 268-270°C, R_f 0.78, $C_{44}H_{57}O_4N_3$.

PMR (δ, ppm, J/Hz): 1.26 (3H, s, CH_3-29), 2.34 (1H, s, H-9), 2.75 (1H, m. d, J = 13.5, He-1), 4.40 (1H, m, H-3), 5.54 (1H, s, H-12), 7.50-8.01 (9H, m, Ar), 9.97 (1H, br. s, NH).

N-(Naphthyl)-3-O-acetyl-11-ketoolean-12-en-18-βH-30-amide (13). Yield 82.1%, mp 214-216°C, R_f 0.71, $C_{44}H_{55}O_4N$.

PMR (δ, ppm, J/Hz): 1.25 (3H, s, CH_3-29), 2.34 (1H, s, H-9), 2.76 (1H, br. d, J = 13.5, He-1), 4.41 (1H, m, H-3), 5.59 (1H, s, H-12), 7.03-7.92 (7H, m, Ar), 9.34 (1H, br. s, NH).

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