Reduction of glycyrrhizic acid

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The reduction of glycyrrhizic acid by $NaBH_4$ and $LiAlH_4$ was studied. The conditions for the selective reduction of the COOH groups of the carbohydrate chain and the C(11)=O group of aglycon were found.

Key words: glycyrrhizic acid, reduction, homoannular and heteroannular dienes.

Glycyrrhizic acid (GA) (**1**) is the main ingredient of the extract of licorice roots (*Glycyrrhiza glabra* and *Gl. uralensis*). Its derivatives possess high and diverse pharmacological activity (antiinflammatory, antiulcerous, antidote, immunostimulating, *etc.*).[1–3]

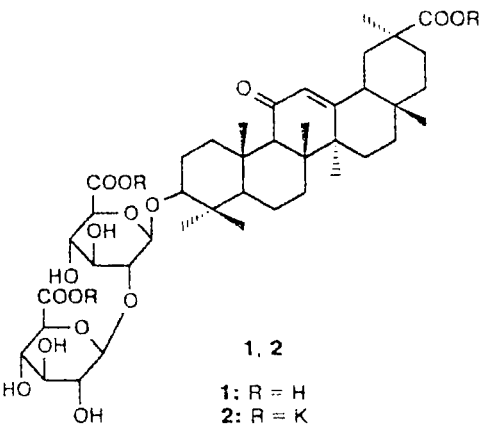
Aiming at the preparation of derivatives of this natural glycoside with the modified aglycon and/or carbohydrate part, we studied the reduction of GA by $NaBH_4$ and $LiAlH_4$ in THF under various conditions.

The reduction of GA potassium salt (**2**) by excess $NaBH_4$ in THF in the presence of 1 *M* KOH at 100 °C proceeds selectively at the COOH groups of the carbohydrate part and at the 11-keto group of the aglycon to form a homoannular diene (**3**) as the main product, which was isolated in the form of peracetate (**4**).

The structure of glycoside **4** was confirmed by spectral methods (IR, UV, and ^1H and ^{13}C NMR). Its UV spectrum contains maxima at 250, 260, and 280 nm, which are typical of glycosides of olean-9(11),12(13)-dien-3β-ols.[4] The ^1H NMR spectrum of glycoside **4** exhibits resonance signals of seven OAc groups and two olefinic protons in the region of δ 5.6 and 5.7. The ^{13}C NMR spectrum of peracetate **4** contains the signals of the olefinic C atoms at δ 154.62, 145.84, 121.52, and 115.63 and C atoms of the CH_2OAc groups of the carbohydrate part at δ 63.7 and 63.48. In the spectrum of glycoside **4**, the signal of C(30) carboxyl group of the aglycon is observed at δ 183.2.

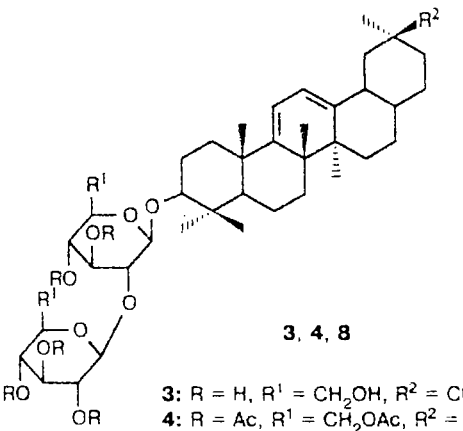
It is likely that the reduction of the C=O group of GA aglycon occurs *via* the formation of the 11-hydroxy derivative (**5**), which is easily dehydrated upon the treatment of the reaction mixture with hydrochloric acid.[5]

The reduction of GA (**1**) by excess $LiAlH_4$ in THF under mild conditions (20 °C) gave a mixture of glycosides, from which a heteroannular diene (**6**) characterized as acetate (**7**) was isolated in the individual state in 63% yield by column chromatography on silica gel.



1, **2**

1: R = H
2: R = K



3, **4**, **8**

3: R = H, $R^1 = CH_2OH$, R^2 = COOH
4: R = Ac, $R^1 = CH_2OAc$, R^2 = COOH
8: R = H, $R^1 = R^2 = CH_2OH$

The UV spectrum of **7** contains maxima at 242, 250, and 259 nm, which are usually detected in the spectra of heteroannular dienes.[4]

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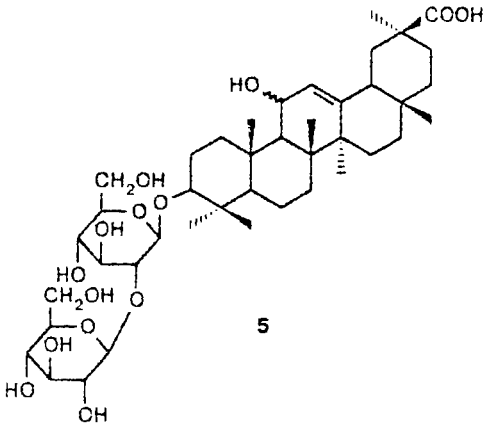
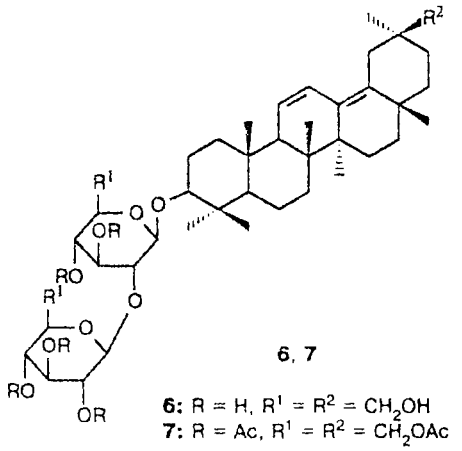


5



6, 7

6: R = H, $R^1 = R^2 = CH_2OH$
7: R = Ac, $R^1 = R^2 = CH_2OAc$

The ^{13}C NMR spectrum of peracetate **7** is characterized by signals of the olefinic C atoms of aglycon (δ 136.25, 134.59, 126.08, and 125.52) and CH_2OAc groups at δ ~62. In the low-field region, the resonance frequencies of eight C atoms of the ester carbonyl groups are observed. The ^1H NMR spectrum of glycoside **7** contains signals of the protons of eight MeCO groups in the region of δ ~2. The formation of heteroannular diene is also indicated by the negative value of the optical rotation.[4,5]

However, glycoside **6** is not the only product of the reduction of GA by $LiAlH_4$. The ^{13}C NMR spectrum of the crude product contains additional signals at δ 154.6, 145.8, 121.5, and 115.6 (~30%), which likely belong to the glycoside of a homoannular diene (**8**). The attempt to isolate this compound in the pure state was unsuccessful.

Experimental

IR spectra were recorded on UR-20 and Specord M-80 spectrophotometers (Nujol mulls). Electronic absorption spectra were recorded on a Specord UF-400 spectrometer in MeOH.

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer with working frequencies of 300 and 75.5 MHz, respectively, with broad-band and off-resonance proton decoupling in $CDCl_3$ and CD_3OD using $SiMe_4$ as the internal standard.

The optical activity was measured on a Perkin—Elmer 241 MC polarimeter. Melting points were determined on a Boetius instrument.

Column chromatography was performed on silica gel L (100/250 μm) (Chemapol, Czech Republic).

18β-Glycyrrhizic acid with the content of the main substance of ~95% obtained by a known procedure[6] was used.

3β-[*O*-(2,3,4-Tri-*O*-acetyl-β-D-glucopyranosyl)-(1→2)-(3,4-di-*O*-acetyl-β-D-glucopyranosyloxy)]-18β-olean-9(11),12(13)-dien-30-oic acid (4). A suspension of $NaBH_4$ (6 g) in THF (50 mL) was added portionwise at 0 °C to a solution of GA (2 g, 2.5 mmol) in a mixture of THF (50 mL) and 1 *M* KOH (50 mL). The mixture was stirred at 100 °C for 1 h. Excess $NaBH_4$ was decomposed with water, and the reaction mixture was acidified with 5% HCl to pH 2—3 and extracted with Bu^nOH (3×50 mL). The combined extracts were concentrated, and the residue was dissolved in MeOH and treated with a KU-2-8(H^+) cation-exchange resin. The resin was filtered off and washed with MeOH, and the filtrate was concentrated. The dry residue (3.0 g) was acetylated by a Py—Ac_2O (1 : 1) mixture (20 mL) according to a standard procedure. Crude product **4** (2.7 g) was obtained and recrystallized from aqueous MeOH. Yield 2.13 g (58%). M.p. 154—156 °C, $[\alpha]_D^{20}$ +48° (*c* 0.6, MeOH). Found (%): C, 62.22; H, 7.60. $C_{56}H_{80}O_{20}$. Calculated (%): C, 62.40; H, 7.51. IR, ν/cm^{-1}: 1760 (OAc). UV (MeOH), λ_{max}/nm (log ε): 250 (3.72), 260 (3.78), 280 (3.89). ^{13}C NMR ($CDCl_3$ + CD_3OD), δ: 183.21 (C(30)); 154.62 (C(11)); 145.84 (C(13)); 121.52 (C(12)); 115.63 (C(9)); 103.38 (C(1′)); 100.63 (C(1″)); 90.70 (C(3)); 63.48 (C(6′)); 63.70 (C(6″)). ^1H NMR ($CDCl_3$), δ: 0.8, 0.86, 0.9, 0.95, 1.04, 1.08, 1.15 (all s, 21 H, 7 Me); 1.90—2.10 (21 H, 7 OAc); 5.65 (d, 1 H, CH=, *J* = 5.8 Hz); 5.75 (d, 1 H, CH=, *J* = 6.2 Hz).

30-*O*-Acetyl-3-*O*-[*O*-(2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl)-(1→2)-(3,4-di-*O*-acetyl-β-D-glucopyranosyloxy)]-18β-olean-11(12),13(18)-diene-3β,30-diol (7). A solution of GA (2 g, 2.5 mmol) in THF (100 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (4 g) in anhydrous THF (100 mL). The mixture was stirred at 20 °C for 4 h. Excess $LiAlH_4$ was decomposed with water, and the residue was filtered off, triturated with 5% HCl, and extracted with $CHCl_3$ and then with Bu^nOH. The combined butanolic extracts were concentrated to give a crude glycoside (0.85 g). The product was dissolved in MeOH (20 mL) and treated with a KU-2-8(H^+) cation-exchange resin. The resin was filtered off and washed with MeOH. The filtrate was concentrated. The resulting mixture of glycosides (0.62 g) was chromatographed on a column with silica gel L (100/160 μm) using stepwise elution with a $CHCl_3$—EtOH (10 : 1→1 : 1) mixture. Glycoside **6** (0.2 g, 63%) was eluted with a $CHCl_3$—EtOH (5 : 1→2 : 1) mixture. This glycoside (0.11 g) was acetylated by a Ac_2O—Py (1 : 1) mixture according to a standard procedure. After triple recrystallization from aqueous methanol, peracetate **7** (0.25 g) was obtained. M.p. 210—212 °C, $[\alpha]_D^{20}$ −45° (*c* 0.04, EtOH). Found (%): C, 62.95; H, 8.22. $C_{58}H_{84}O_{20}$. Calculated (%): C, 63.25; H, 7.69. IR, ν/cm^{-1}: 1760 (OAc); 1650 (C=C—C=C). UV (MeOH), λ_{max}/nm (log ε): 242 (4.12), 250 (4.18), 259 (4.03). ^1H NMR ($CDCl_3$), δ: 0.7, 0.8, 0.88, 0.96, 1.09, 1.15, 1.30 (21 H, 7 Me); 1.98—2.12 (24 H, 8 OAc); 6.34 (d, 1 H, CH=, *J* = 9.5 Hz); 5.55 (d, 1 H, CH=,

J = 4.6 Hz). ^{13}C NMR ($CDCl_3$ + CD_3OD), δ: 136.25 (C(11)); 134.59 (C(13)); 126.08 (C(12)); 125.52 (C(18)); 62.47 (C(30)); 62.08 (C(6′)); C(6″)).

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New electrophilic iodochlorinating systems based on iodine(+1)

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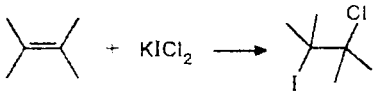
Two new convenient systems for electrophilic iodochlorination of olefins are proposed: KIO_3 + I_2 + HCl (in aqueous solutions) and $KICl_4$ + I_2 (in organic solvents).

Key words: electrophilic addition, iodination, organic iodides.

Previously, we proposed that potassium dichloroiodate(I) would be a convenient reagent for iodochlorination of multiple bonds.[1]

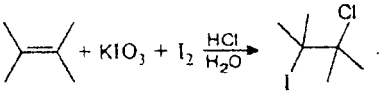


The present work describes two new iodinating systems based on monovalent iodine. Potassium dichloroiodate(I) can be obtained by a three-stage synthesis.[2] The systems proposed make the synthesis simpler because compounds of monovalent iodine are formed *in situ*.

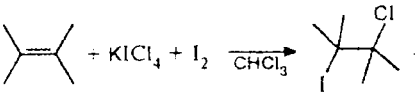
The first system based on KIO_3 + I_2 replaces $KICl_2$ in reactions conducted in aqueous media. It is known that in the presence of HCl the equilibrium

$$IO_3^- + 2I_2 + 6H^+ + 10Cl^- \rightleftharpoons 5ICl_2^- + 3H_2O$$

is shifted to the right.[3] This allows one to obtain acidified $KICl_2$ solutions and to use them as an iodinating system:



When an organic solvent is used as the medium, a system based on potassium tetrachloroiodate(III) (obtained in one step by chlorination of an aqueous KI solution)[2] and iodine is effective



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