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Some observations on solasodine reactivity

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ABSTRACT

This article presents new transformations of solasodine – a representative steroid alkaloid sapogenin from the *Solanum* family. Oxidation of *N,O*-diacetylated solasodine with either $NaNO_2/BF_3.Et_2O$ or *t*-BuONO/$BF_3.Et_2O$ resulted in partial degradation of the side chain to (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone (vespertilin acetate). The same starting compound when treated with TMSOTf afforded the corresponding pseudosapogenin after aqueous work-up. However, when the crude reaction mixture was directly subjected to purification on a silica gel column, efficient autoxidation to pregna-5,16-dien-3β-ol-20-one acetate was observed. One-step synthesis of this important drug intermediate from spirosolan alkaloids may be potentially exploited for large-scale production of steroid hormones.

1. Introduction

Steroidal alkaloid glycosides (SAGs) are natural products showing diverse biological activity [1,2]. The largest source of SAGs is the *Solanaceae* family, which includes economically important genera such as the potato, tomato, eggplant, and capsicum. Upon hydrolysis, steroidal alkaloid glycosides yield sugars and steroidal alkaloid sapogenins (SASs). Solanum alkaloids are in fact the nitrogen-analogs of steroidal sapogenins (Fig. 1).

SASs containing oxa-aza spiro (spirosolan) structures may have either an *R* or *S* configuration at the spiro carbon atom (C-22), which is very rare for their oxygen counterparts. The C27 methyl group in spirosolans is always in equatorial position, whereas spirostanes show various orientation of this methyl group. The 21-methyl group is α-oriented (20*S*) in both spirostanes and spirosolans.

The chemistry of steroidal sapogenins has been extensively explored since the 1950s [3,4]. In contrast, knowledge regarding the chemistry of SASs is rather limited [5,6]. In this paper we present the results of a study on selected reactions of the representative steroid alkaloid sapogenin – solasodine.

2. Methods and materials

2.1. Chemistry

2.1.1. General methods

Reagent-grade chemicals were purchased and used as received. Methylene chloride was freshly distilled. Flash column chromatography and dry flash chromatography were performed with silica gel, pore size 40 Å (70–230 mesh), unless otherwise stated. All reactions were monitored by TLC on silica gel plates 60 F254. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra for all compounds were recorded at ambient temperature and were referenced to TMS (0.0 ppm) and $CDCl_3$ (77.0 ppm), respectively, unless otherwise noted. NMR resonance multiplicities were reported using the following abbreviations: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet; coupling constants *J* were reported in Hz. IR spectra were obtained in a $CHCl_3$ solution with an FT-IR spectrometer, and data are reported in cm^{-1}. Melting points were determined by a Kofler bench (Boetius type) apparatus and are uncorrected.

2.1.1.1. Acetylation of solasodine acetate. Solasodine acetate (750 mg; 1.6 mmol) was dissolved in pyridine (25 ml) and acetic anhydride (5 ml) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into aqueous HCl and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. Silica gel column chromatography with ethyl acetate/hexane 18:82 elution afforded *N,O*-diacetylosolasodine in 80% yield (**1**, 655 mg). Compound **1** proved identical in all respects with the same compound described in the literature [7]. M.p. (DCM/hexane) 161–163 °C (lit. [7] 162–164 °C); ^{1}H NMR: δ 5.31 (m, 1H), 4.54 (m, 1H), 4. 13 (q, *J* = 7.1 Hz, 1H), 3.95 (bd, *J* = 11.5 Hz, 1H), 3.05 (m, 1H), 2.80 (dd, *J* = 13.0, 6.6 Hz, 1H), 2.14 (s, 3H), 1.98 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR: δ 170.7 (C), 170.3 (C), 139.6 (C), 122.1 (CH), 101.0 (C), 78.6

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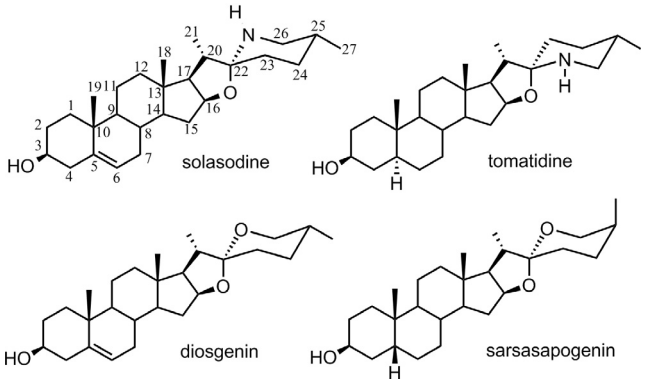


Fig. 1. Structures of steroid alkaloid sapogenins and spirostanes.

(CH), 73.6 (CH), 61.9 (CH), 55.6 (CH), 49.9 (CH), 48.9 (CH_2), 40.8 (C), 39.9 (CH_2), 38.0 (CH), 37.9 (CH_2), 36.8 (CH_2), 36.6 (C), 31.9 (CH_2 × 2), 30.9 (CH), 27.8 (CH), 27.6 (CH_2), 25.1 (CH_3), 24.1 (CH_2), 23.8 (CH_2), 21.2 (CH_3), 20.7 (CH_2), 19.1 (CH_3), 18.4 (CH_3), 16.2 (CH_3), 16.0 (CH_3).

2.1.1.2. Oxidation of 1 with $NaNO_2/BF_3Et_2O$. *N,O*-Diacetylsolasodine **1** (75 mg; 0.14 mmol) was dissolved in glacial AcOH (10 ml). Then $BF_3.Et_2O$ (0.005 ml; 6 equiv) was added. Sodium nitrite (30 mg; 3 equiv) was added portion-wise for 30 min. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water and pH was adjusted to 8–9 by adding $NaHCO_3$. The product was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and evaporated *in vacuo*. Silica gel column chromatography with ethyl acetate/hexane 15:85 elution afforded (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone in 80% yield (**2**, 46 mg). Compound **2** proved identical in all respects with the same compound described in the literature [8]. M.p. (DCM/hexane) 216–220 °C (lit. [8] 210–212 °C; [9] 216–220 °C); ^{1}H NMR: δ 5.38 (m, 1H), 4.96 (m, 1H), 4.61 (m, 1H), 2.60 (q, *J* = 7.6 Hz, 1H), 2.04 (s, 3H), 1.33 (d, *J* = 7.6 Hz, 3H), 1.05 (s, 3H), 0.78 (s, 3H); ^{13}C NMR: δ 181.3 (C), 170.5 (C), 139.8 (C), 121.9 (CH), 82.7 (CH), 73.7 (CH), 58.9 (CH), 54.7 (CH), 49.9 (CH), 41.4 (C), 38.1 (CH_2), 38.0 (CH_2), 36.9 (CH_2), 36.6 (C), 36.0 (CH), 33.1 (CH_2), 31.8 (CH_2), 31.2 (CH), 27.7 (CH_2), 21.4 (CH_3), 20.3 (CH_2), 19.3 (CH_3), 18.0 (CH_3), 13.7 (CH_3).

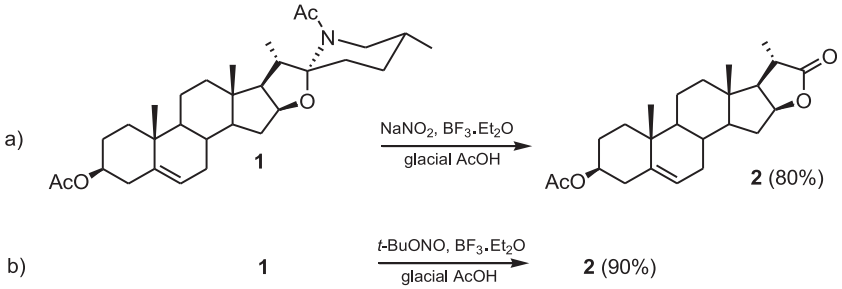
2.1.1.3. Oxidation of 1 with t-BuONO/BF_3Et_2O. *N,O*-Diacetylsolasodine **1** (250 mg; 0.5 mmol) was dissolved in glacial AcOH (10 ml). Then $BF_3.Et_2O$ (0.03 ml; 0.5 equiv) was added followed by *tert*-butyl nitrite (0.3 ml; 5 equiv). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water and pH was adjusted to 8–9 by adding $NaHCO_3$. The product was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and evaporated *in vacuo*. Silica gel column chromatography with ethyl acetate/hexane 15:85 elution afforded (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone in 90% yield (**2**, 175 mg). Compound **2** proved identical in all respects with the same compound described in the literature.

2.1.1.4. Reaction of 1 with TMSOTf without aqueous work-up. *N,O*-Diacetylsolasodine **1** (50 mg, 0.1 mmol) was dissolved in dry dichloromethane (15 ml). TMSOTf (1 equiv, 0.018 ml) was then added to the solution. The solution was placed on a silica gel column after a period of 10 min. The reaction mixture remained on the column for 72 h. Then pregna-5,16-dien-3β-ol-20-one acetate (21 mg, 60%) was eluted with an ethyl acetate/hexane 35:65 mixture. Compound **3** proved identical in all respects with the same compound described in the literature [10]. M.p. (DCM/hexane) 169–172 °C (lit. [10] 172–174 °C); ^{1}H NMR: δ 6.72 (m, 1H), 5.35 (d, *J* = 5.0 Hz, 1H), 4.62 (m, 1H), 2.27 (s, 3H), 2.04 (s, 3H), 1.07 (s, 3H), 0.93 (s, 3H); ^{13}C NMR: δ 196.8 (C), 170.5 (C), 155.4 (C), 144.4 (CH), 140.3 (C), 121.9 (CH), 73.8 (CH), 56.3 (CH), 50.4 (CH), 46.1 (C), 38.1 (CH_2), 36.8 (CH_2), 36.7 (C), 34.6 (CH_2), 32.2 (CH_2), 31.5 (CH_2), 30.1 (CH), 27.7 (CH_2), 27.1 (CH_3), 21.4 (CH_3), 20.6 (CH_2), 19.2 (CH_3), 15.7 (CH_3).

2.1.1.5. Reaction of 1 with TMSOTf followed by aqueous work-up. *N,O*-Diacetylsolasodine **1** (40 mg, 0.1 mmol) was dissolved in dry dichloromethane (15 ml). TMSOTf (0.044 ml, 2 equiv) was then added to the solution. After 24 h the reaction mixture was poured into water and extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and evaporated *in vacuo*. Silica gel chromatography with ethyl acetate/hexane 7:3 elution afforded *N*-acetylopseudosolasodine acetate (23 mg, 60%). Compound **4** proved identical in all respects with the same compound described in the literature [7]. M.p. (DCM/hexane) 134–137 °C (lit. [11] 134–136 °C); ^{1}H NMR: δ 5.58 (bs, 1H), 5.38 (d, *J* = 4.6 Hz, 1H), 4.75 (m, 1H), 4.62 (m, 1H), 3.714 (m, 1H), 2.27 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.04 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 1H), 0.69 (s, 3H); ^{13}C NMR: δ 170.5 (C), 170.0 (C), 151.3 (C), 139.7 (C), 122.3 (CH), 104.0 (C), 84.3 (CH), 73.8 (CH), 64.1 (CH), 54.9 (CH), 49.9 (CH), 45.3 (CH_2), 43.2 (C), 39.4 (CH_2), 38.1 (CH_2), 36.9 (CH_2), 36.7 (C), 34.1 (CH_2), 32.7 (CH), 32.1 (CH_2), 31.7 (CH_2), 31.2 (CH), 27.7 (CH_2), 23.4 (CH_3), 23.1 (CH_2), 21.4 (CH_3), 20.9 (CH_2), 19.3 (CH_2), 17.6 (CH_3), 13.9 (CH_3), 11.6 (CH_3).

3. Results and discussion

There are many examples of interesting reactions of 23-oxo functionalized steroidal sapogenins in the literature [3,12]. The first aim of this project was to elaborate a convenient route to 23-oxo-solasodine acetate in order to study processes similar to those of 23-oxo-spirostanes. Since direct functionalization of solasodine at C23 failed, the amino group was protected by acetylation with Ac_2O/Py. Then derivative **1** was subjected to oxidation with $NaNO_2/BF_3.Et_2O$ according to the procedure first described by Barton [13] and improved by Iglesias-Arteaga [14] (Scheme 1a). The structure of the obtained product (20*S*)-3β-acetoxypregn-5-ene-20,16β-carbolactone (**2**) (vespertilin acetate) was elucidated from its ^{1}H NMR, in which the characteristic F ring signals of 26-methylene protons and the 27-methyl group disappeared. Vespertilin is a naturally occurring lactone with a proven biological



Scheme 1. Oxidation of *N,O*-diacetylsolasodine **1**.