IMPROVED METHODS FOR OBTAINING IMMONIUM PERCHLORATES AND ENAMINES OF SOLANIDINE TYPE STEROIDAL ALKALOIDS

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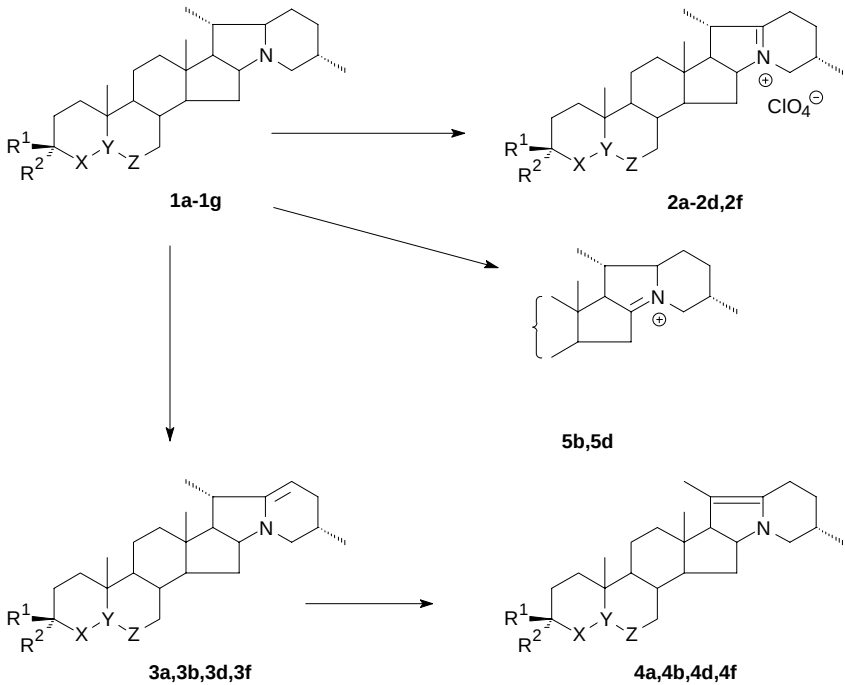
Oxidation of solanidine and some of its derivatives with mercury(II) acetate in acetone afforded corresponding *N*-22 immonium perchlorates or 22(23)-enamines. It has been found that the effect of solvents on regioselectivity e.g. formation *N*-22 and *N*-16 immonium salts, was remarkable. The isomerisation of 22(23)-enamines into corresponding 20(22)-enamines, potentialy important intermediates in planned chemical degradation of solanidine to steroidal hormones, was performed in 0.1% acetic acid in ether, or in dichloromethane (chloroform).
Key words: Steroidal alkaloids; Solanidine; *N*-22 Immonium perchlorates; Enamines.

Study of a possible chemical degradation of the indolizidine system of solanidine (**1a**), directed towards synthesis of progesterone, was based on earlier discovered conversion[1] of the indolizidine system in solanidine type alkaloids into the corresponding *N*-22 immonium perchlorates. Thus, by applying the reaction conditions given in the mentioned literature[1] (procedure *A*, see Scheme 1) upon compound **1d**, the desired immonium salt **2d** was obtained[2] in a small yield (6%). The side-product **5d** which was not earlier described[1] was obtained[2] in a yield of 39%. On the other hand, the oxidation of 5α-chloro derivative of solanidine **1f** under reaction condition *A* led to a simultaneous regeneration of 5,6-double bond, i.e., to the formation[2] of **2b** and **5b**. Since procedure *A* was not completely convenient, a novel electrochemical procedure for the oxidation of **1b**, **1d** and **1f** into corresponding *N*-22 and *N*-16 immonium perchlorates was worked out[3]. In the present work we have worked out two new chemical procedures (*B* and *C*) for preparation of the solely desired *N*-22 immonium salts of solanidine (**1a**) and some of its derivatives **1d–1g** (Scheme 1). On the other hand, according to our knowledge, there is only one described method[1,4] for conversion of the indolizidine system in solanidine type alkaloids into the corresponding 20(22)-enamines (via *N*-22 immonium salts and 22(23)-enamines). The present paper describes a method for preparation of 22(23)-enamines directly from solanidine type steroidal alkaloids with out

N-22 immonium salts isolation, and some methods for isomerisation of 22(23)-enamines to corresponding 20(22)-enamines important intermediates in a planned degradation of solanidine to steroidal hormones.



In formulae **1-5**

a, R^1 = OH; R^2 = H; X = CH_2; YZ = C=CH

b, R^1 = $OCOCH_3$; R^2 = H; X = CH_2; YZ = C=CH

c, R^1 = $OCOCCl_3$; R^2 = H; X - CH_2; YZ = C=CH

d, $R^1 + R^2$ = =O; XY = CH=C; Z = CH_2

e, R^1 = OH; R^2 = H; X = CH_2; YZ = CCl-CH_2

f, R^1 = $OCOCH_3$; R^2 = H; X = CH_2; YZ = CCl-CH_2

g, R^1 = $OCOCCl_3$; R^2 = H; X = CH_2; YZ = CCl-CH_2

SCHEME 1

EXPERIMENTAL

IR spectra (wave numbers in cm^{-1}) were recorded with a Perkin–Elmer 457 spectrometer in KBr pellets. The ^1H NMR spectra were recorded with a Brucker WP 250 SY in $CDCl_3$, $(CD_3)_2CO$ or C_6D_6, with tetramethylsilane as internal standard (unless stated otherwise). The chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz. The mass spectra were measured with a Varian CH-5 and Varian VG-7035 (the first number denotes the *m/z* value, and the ion abundances (in %) are given in parentheses). The melting points were determined with a Büchi SMP-20 apparatus and are not corrected.

3β-Acetoxy-5-solanidene (**1b**)

Solanidine (**1a**; 1.00 g, 2.5 mmol) was dissolved in the mixture of pyridine (55.4 ml) and acetic anhydride (24.6 ml) and the reaction mixture was left overnight at room temperature. The reaction is ceased by pouring the mixture into water. Upon treating with ammonia (pH 9) a white solid precipitates. This crude product was filtered, washed thoroughly with water and dried in air. The yield of the crude product was 97–100%. Chromatography on silica gel column (10 g; light petroleum–acetone, 10 : 1) and recrystallization from ethyl acetate–methanol mixture afforded the product **1b** (1.00 g, 90%; m.p. 208–210 °C). Literature[1] gives m.p. 208 °C.

3β-Trichloroacetoxy-5-solanidene (**1c**)

Solanidine (**1a**; 0.50 g, 1.25 mmol) was dissolved in absolute pyridine (20 ml). The obtained solution was cooled to –5 to 0 °C and trichloroacetic acid chloride (0.80 g, 4.46 mmol) was added. The reaction mixture was stirred for 1.5 h and diluted with water (ca 150 ml). After 4 h the crude compound **1c** (98.5%) was separated. Chromatography on a silica gel column (20 g; chloroform) and recrystallization from ethyl acetate afforded pure compound **1c** in a yield of 0.57 g (84%), m.p. 158–160 °C. IR spectrum: 1 760 (C=O from COOR), 1 245 (C–O from COOR), 985 (C–O), 860, 825, 680 (C–Cl from Cl_3CCOO). ^1H NMR spectrum ($CDCl_3$): 0.75 s, 3 H (3 × H-18); 0.80 d, 3 H, J = 6.3 (3 × H-27); 0.85 d, 3 H, J = 6.3 (3 × H-21); 1.00 s, 3 H (3 × H-19); 4.75 m, 1 H (H-3); 5.40 d, 1 H, J = 5.1 (H-6). Mass spectrum: 543 (M^+, 8), 528 (3), 381 (3), 204 (24), 150 (100). For $C_{29}H_{42}Cl_3NO_2$ (543.0) calculated: 64.14% C, 7.80% H; found: 64.35% C, 7.52% H.

3β-Hydroxy-5α-chlorosolanidane (**1e**)

Solanidine (**1a**; 3.00 g, 7.56 mmol) was dissolved in a mixture of chloroform (96 ml) and ethanol (24 ml). Through this solution, cooled at 0 °C, was bubbled dry gaseous HCl until saturation (3 h). The reaction mixture was kept for 4 days in refrigerator at 4 °C and then diluted with water (ca 300 ml), neutralized with $NaHCO_3$ and extracted with chloroform (10 × 50 ml). After the combined chloroform extract were dried with anhydrous Na_2SO_4 and chloroform was removed in vacuum, the crude product was obtained (3.04 g; 93%), m.p. 300–304 °C. After recrystallization from ethyl acetate the product **1e** (2.39 g, 73%; m.p. 317–323 °C) was obtained. IR spectrum: 3 240 (OH), 2 800–2 680 (CH next N), 1 045 (C–O). ^1H NMR spectrum ($CDCl_3$): 0.75 s, 3 H (3 × H-18); 0.80 d, 3 H, J = 6.3 (3 × H-27); 0.90 d, 3 H, J = 6.3 (3 × H-21); 1.05 s, 3 H (3 × H-19); 4.30 m, 1 H (H-3). Mass spectrum: 433 (M^+, 6), 397 (64), 382 (28), 204 (69), 150 (100). For $C_{27}H_{44}ClNO$ (434.1) calculated: 74.70% C, 10.22% H; found: 74.35% C, 10.52% H.

3β-Acetoxy-5α-chlorosolanidane (**1f**)

Solanidine (**1a**; 1.00 g, 2.5 mmol) was dissolved in a mixture of chloroform (30 ml) and glacial acetic acid (15 ml). Through this solution, cooled at 0 °C, dry gaseous HCl was bubbled until saturation (3 h). The reaction mixture was kept for 3 days at 4 °C and then diluted with water (ca 200 ml), neutralized with $NaHCO_3$ and extracted with chloroform. After the combined chloroform extract was dried with anhydrous Na_2SO_4 and chloroform was removed in vacuum, the crude product was obtained (1.7 g). Chromatography on an alumina column (35 g; dichloromethane) and recrystallization from ethyl acetate afforded pure compound **1f** in a yield of 1.5 g (88%), m.p. 304–307 °C. Literature[3] gives m.p. 304–307 °C. The spectroscopic data for **1f** were given in our previous paper[3].

3β-Trichloroacetoxy-5α-chlorosolanidane (**1g**)

3β-Hydroxy-5α-chlorosolanidane (**1e**; 2.36 g, 5.44 mmol) was dissolved in absolute pyridine (80 ml), followed by addition of trichloroacetic acid chloride (6.48 g, 35.6 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then diluted with water (ca 250 ml) and left at room temperature for 5 h. The separated crystals were collected and washed with water and dried. The crude compound **1g** (2.60 g, 82%) was purified by chromatography on a silica gel column (50 g; $CHCl_3$) and recrystallization from ethyl acetate, to afford pure compound **1g** (1.70 g, 54%; m.p. 219–221 °C). IR spectrum: 2 860–2 740 (CH next N), 1 760 (C=O from COOR), 1 240 (C–O from COOR), 1 000, 980 (C–O), 830, 680 (C–Cl from Cl_3CCOO). ^{1}H NMR spectrum ($CDCl_3$): 0.75 s, 3 H (3 × H-18); 0.80 d, 3 H, J = 6.3 (3 × H-27); 0.85 d, 3 H, J = 6.3 (3 × H-21); 1.10 s, 3 H (3 × H-19); 5.52 m, 1 H (H-3). Mass spectrum: 579 (M^+, 47), 543 (24), 204 (19), 150 (100). For $C_{29}H_{43}Cl_4NO_2$ (579.5) calculated: 60.10% C, 7.48% H; found: 60.23% C, 7.70% H.

General Procedure for Preparation of *N*-22 Immonium Perchlorates **2a–2d**

Method B: Solanidine (**1a**) or its derivatives **1b–1g**, (2 mmol) were dissolved in acetone (70 ml) on heating. Then the solution of EDTA disodium salt dihydrate (3.46 g, 9.3 mmol) and $Hg(OAc)_2$ (2.96 g, 9.3 mmol) in 2% acetic acid (30 ml) were added. Reaction mixture was heated with stirring in water bath for 1–2 h. The unreacted components were removed by filtration, the filtrate was first concentrated (3 ml), diluted with water (ca 100 ml), made alkaline (pH 12, 30% NaOH), and finally extracted with ether. After the combined ether extract was dried with anhydrous Na_2SO_4 and a mixture of 70% $HClO_4$ and methanol (1 : 1, pH 5) was added the *N*-22 immonium perchlorates **2a–2d** were recrystallized from acetone–ether mixture.

3β-Hydroxy-5,22(N)-solanidiene perchlorate (**2a**), 60% from **1a**, 50% from **1e**, 50% from **1g**, m.p. 277–278 °C, ref.[1] m.p. 286–291 °C. IR spectrum: 3 450 (OH); 1 660 (C=N$^+$), 1 090, 625 (ClO_4^-). ^{1}H NMR spectrum ($CDCl_3$): 0.75 s, 3 H (3 × H-18); 1.00 s, 3 H (3 × H-19); 1.10 d, 3 H, J = 6.4 (3 × H-27); 1.45 d, 3 H, J = 6.4 (3 × H-21); 3.50 m, 1 H (H-3); 5.10 m, 1 H (H-16); 5.30 d, 1 H, J = 5.1 (H-6). Mass spectrum: 397 ($M^+ - ClO_4^-$, 9), 396 (24), 395 (66), 378 (12), 204 (2), 162 (100), 150 (12). For $C_{27}H_{42}ClNO_5$ (495.5) calculated: 65.38% C, 8.47% H; found: 65.30% C, 8.74% H.

3β-Acetoxy-5,22(N)-solanidiene perchlorate (**2b**), 60% from **1b**, 50% from **1f,** m.p. 270–271 °C, ref.[1] m.p. 270–278 °C. Spectroscopic data was given in our previous paper[3].

3β-Trichloroacetoxy-5,22(N)-solanidiene perchlorate (**2c**), 60%, m.p. 243–244 °C. IR spectrum: 1 760 (C=O from COOR); 1 670 (C=N$^+$), 1 255 (C–O from COOR), 1 090, 620 (ClO_4^-). ^{1}H NMR spectrum ($CDCl_3$): 0.65 s, 3 H (3 × H-18); 1.05 s, 3 H (3 × H-19); 1.15 d, 3 H, J = 6.4 (3 × H-27); 1.50 d, 3 H, J = 6.4 (3 × H-21); 4.75 m, 1 H (H-3); 5.00 m, 1 H (H-16); 5.45 d, 1 H, J = 5.1 (H-6). Mass spectrum: 524 ($M^+ - ClO_4^-$, 3), 381 (26), 380 (100), 379 (19), 378 (27), 377 (13), 376 (8), 375 (2). For $C_{29}H_{41}Cl_4NO_6$ (641.5) calculated: 54.30% C, 6.44% H; found: 53.97% C, 6.77% H.

4,22(N)-Solanidien-3-one perchlorate (**2d**), 50%, m.p. 272–275 °C, ref.[1] m.p. 283–287 °C. Spectroscopic data were given in our previous paper[3].

Method C: Solanidine (**1a**) or its derivatives (**1b–1g**, 1 mmol) were suspended in acetone (20 ml) and $Hg(OAc)_2$ (1.12 g, 3.5 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 h and then filtered. The obtained filtrate was concentrated at 3 ml, diluted with water (20 ml), heated at 40–50 °C and 15% NaOH was added (pH 12). After cooling at room temperature the obtained suspension was extracted with ether. Ether extract was acidified with $HClO_4$ in methanol (1 : 1, 0.4 ml), whereupon the *N*-22 immonium perchlorates: **2a**, 86% from **1a**, 65% from **1e**, 37% from **1g**, m.p. 277–278 °C; **2b**, 68%, m.p. 259–262 °C; **2c**, 43%, m.p. 243–244 °C; **2d**, 78%, m.p. 272–275 °C and 3β-acetoxy-5α-chloro-22(*N*)-solanidene perchlorate (**2f**), 39%, m.p. 165–168 °C were obtained. Spectroscopic data for **2f** were given in our previous paper[3].

General Procedure for the Synthesis of 22(23)-Enamines (Method *C'*)

Solanidine (**1a**) or its derivative (**1b–1f**, 1 mmol) was suspended in acetone (20 ml) and $Hg(OAc)_2$ (1.12 g, 3.5 mmol) was added. The obtained suspension was stirred at room temperature for 1.5 h and then filtered. The filtrate was concentrated at 3 ml, diluted with water (20 ml), heated at 40–50 °C and 15% NaOH was added (pH 12). The separated crystals of 22(23)-enamines **3a**, **3b**, **3d**, and **3f** were collected and washed with water and dried.

3β-Hydroxy-5,22(23)-solanidiene (**3a**), 87% from **1a**, 84% from **1e**, 38% from **1c**, m.p. 170 °C. IR spectrum: 3 350 (OH), 1 650 (C_{22}=C_{23}); 1 030 (C–O). ^{1}H NMR spectrum (CD_3COCD_3): 1.00 s, 3 H (3 × H-18); 1.02 s, 3 H (3 × H-19); 1.10 d, 3 H, *J* = 6.3 (3 × H-27), 1.17 d, 3 H, *J* = 6.3 (3 × H-21); 3.40 m, 1 H (H-3); 5.30 d, 1 H, *J* = 5.1 (H-6). Mass spectrum: 395 (M^+, 8), 204 (2), 162 (100), 150 (24), 148 (19).

3β-Acetoxy-5,22(23)-solanidiene (**3b**), 94%, m.p. 175–177 °C. IR spectrum: 1 715 (C=O from COOR); 1 650 (C_{22}=C_{23}); 1 230 (C–O from COOR); 1 015 (C–O). ^{1}H NMR spectrum (C_6D_6): 0.83 s, 3 H (3 × H-18); 0.85 s, 3 H (3 × H-19); 0.90 d, 3 H, *J* = 6.3 (3 × H-27); 1.15 d, 3 H, *J* = 6.3 (3 × H-21); 1.70 s, 3 H (OAc); 4.82 m, 1 H (H-3); 5.35 d, 1 H, *J* = 5.1 (H-6). Mass spectrum: 437 (M^+, 6), 162 (53), 148 (22), 91 (40), 79 (45), 67 (50), 55 (72), 43 (100).

4,22(23)-Solanidien-3-one (**3d**), 87%, m.p. 205–208 °C. IR spectrum: 1 675 (C=O); 1 660 (C_{22}=C_{23}); 1 620 (C_4=C_5); 1 330, 870. ^{1}H NMR spectrum (CD_3COCD_3): 0.85 s, 3 H (3 × H-18); 0.90 d, 3 H, *J* = 6.2 (3 × H-27); 1.00 d, 3 H, *J* = 6.2 (3 × H-21); 1.22 s, 3 H (3 × H-19); 5.61 s, 1 H (H-4). Mass spectrum: 393 (M^+,34), 378 (6), 162 (100), 148 (15). For $C_{27}H_{39}NO$. 2 H_2O (429.6) calculated: 75.48% C, 10.09% H; found: 75.76% C, 9.94% H.

3β-Acetoxy-5α-chloro-22(23)-solanidene (**3f**), 94%, m.p. 148–150 °C. IR spectrum: 1 745 (C=O from COOR); 1 670 (C_{22}=C_{23}); 1 250 (C–O from COOR); 1 030 (C_3–O). ^{1}H NMR spectrum (CD_3COCD_3): 0.78 s, 3 H (3 × H-18); 0.90 d, 3 H, *J* = 6.3 (3 × H-27); 1.00 d, 3 H, *J* = 6.3 (3 × H-21); 1.15 s, 3 H (3 × H-19); 1.95 s, 3 H (OAc); 5.30 m, 1 H (H-3). Mass spectrum: 473 (M^+, 34), 438 (4), 437 (14), 162 (100).

General Procedures for Preparation of 20(22)-Enamines

Method D: 22(23)-Enamines (**3a**, **3b**, **3d**, and **3f**; 1 mmol) were dissolved in 0.1% acetic acid in ether (15 ml) and the reaction mixture was intensively stirred in an atmosphere of nitrogen, at room temperature, for 30 min, protected from light. The reaction mixture was diluted with water, neutralized with $NaHCO_3$ and extracted with ether. Combined extracts are dried with Na_2SO_4 and drying agent and solvent are later removed. The 20(22)-enamines **4a**, **4b**, **4d**, and **4f** were obtained.

3β-Hydroxy-5,20(22)-solanidiene (**4a**), 90%, m.p. 148 °C. IR spectrum: 3 450 (OH); 1 670 (C_{20}=C_{22}); 1 050 (C–O). ^{1}H NMR spectrum ($CDCl_3$): 0.60 s, 3 H (3 × H-21); 0.85 d, 3 H, *J* = 6.3

(3 x H-27); 1.02 s, 3 H (3 × H-19); 1.60 s, 3 H (3 × H-18); 3.50 m, 1 H (H-3); 5.40 d, 1 H, J = 5.1 (H-6). Mass spectrum: 395 (M^+, 38), 204 (9), 162 (100), 150 (35).

3β-Acetoxy-5,20(22)-solanidiene (**4b**), 87%, m.p. 147–151 °C, ref.[3] m.p. 147–151 °C. Spectroscopic data were given in our previous paper[3].

4,20(22)-Solanidien-3-one (**4d**), 85%, m.p. 153 °C, ref.[3] m.p. 158–159 °C. Spectroscopic data were given in our previous paper[3].

3β-Acetoxy-5α-chloro-20(22)-solanidene (**4f**), 98%, m.p. 149 °C. IR spectrum: 1 745 (C=O from COOR); 1 670 (C_{20}=C_{22}); 1 250 (C–O from COOR); 1 035 (C–O). ^{1}H NMR spectrum ($CDCl_3$): 0.55 s, 3 H (3 × H-21); 0.80 d, 3 H, J = 6.3 (3 × H-27); 1.00 s, 3 H (3 × H-19); 1.50 s, 3 H (3 × H-18); 1.95 s, 3 H (OAc); 5.25 m, 1 H (H-3). Mass spectrum: 473 (M^+, 26), 438 (12), 437 (32), 162 (100), 148 (13), 97 (16).

Method E: 22(23)-Enamines **3a**, **3b**, **3d**, and **3f** (1 mmol) were dissolved in dichloromethane or chloroform (10 ml) and the reaction mixture was left at room temperature for 30–90 min. After removal of solvent the products were obtained in the yields of 85–90%.

RESULTS AND DISCUSSION

The starting solanidine derivatives **1b** and **1f** were synthesized from solanidine by using the modified methods[1–3] (see Experimental). The new derivatives of solanidine **1c**, **1e**, and **1g** were obtained from solanidine by acylation and/or addition of gaseous HCl to the 5,6-double bond.

N-22 Immonium perchlorates **2a**, **2c**, and **2d** were synthesized by oxidation of **1a**, **1c**, and **1d** with $Hg(OAc)_2$ in acetone–acetic acid–water mixture in the presence of EDTA disodium salt dihydrate (procedure *B*, Scheme 1), in a yield of 50–60%, higher than in procedure[2] *A* and electrochemical method[3]. However, oxidation of compounds **1e**, **1f**, and **1g** under reaction condition *B*, in addition to the formation of the corresponding *N*-22 immonium perchlorates, led to a simultaneous regeneration of the 5,6-double bond (catalyzed by $Hg(OAc)_2$).

In a further attempt to avoid elimination of HCl in 5α-chloro derivatives of solanidine (**1e**, **1f**, and **1g**), we developed the procedure *C* (oxidation with $Hg(OAc)_2$ in acetone). This method was very successful in the case of **1a**, **1b**, **1d**, and **1f** affording corresponding *N*-22 immonium salts **2a**, **2b**, **2d** and **2f**. But in the case of **1c**, **1e**, and **1g** the perchlorate of solanidine **2a** was obtained as a result of a elimination of HCl and/or hydrolysis of 3β-ester function.

Experimentally found preference for the formation of *N*-22 immonium perchlorates **2a–2d** and **2f** in oxidation of **1a–1g** with $Hg(OAc)_2$ by methods *B* and *C* can be explained by steric hindrance in the initially formed mercurated complex. Namely, in accordance with the described oxidation mechanism[5] involving $Hg(OAc)_2$ reagent, hydrogens on C_{16} and C_{22} satisfy all stereoelectronic requirements for elimination process in the initially formed mercurated complex. As we pointed out in our earlier paper[3] one can suppose that hydrogen on C_{22} is more sterically hindered than on C_{16}. In method *A* single base available for the proton abstraction is acetate anion. It can face considerable steric obstruction approaching C_{22} hydrogen, due to its voluminous proton accepting

region $[O–C–O]^-$. The obstruction of C_{16} hydrogen appears to be more feasible, and therefore a mixture of *N*-22 and *N*-16 immonium perchlorates was formed. However, in methods *B* and *C* acetone solvent itself can act as a base. Oxygen behaves as less vo luminous and very weak base (C=O) and preferentially takes of the C_{22} hydrogen, resulting in an exclusively formation of *N*-22 immonium salts.

Particular goal of this paper was finding a suitable method for preparing 22(23)- and 20(22)-enamines of solanidine and its derivatives **1b–1g**, as important intermediates in a planned degradation of solanidine to steroidal hormones. This goal was achieved by methods *C′*, *D* and *E* (Scheme 1). Namely, when solanidine (**1a**) and its derivatives **1b**, **1d**, and **1f** were oxidized with $Hg(OAc)_2$ in acetone, at 25 °C, during 1–1.5 h and reaction mixture worked out in alkaline conditions (procedure *C′*), the corresponding 22(23)-enamines **3a**, **3b**, **3d**, and **3f** were obtained in good yields (87–94%, see Scheme 1). But in the cases of derivatives **1c**, **1e**, and **1g** elimination of HCl and/or hydrolysis of 3β-ester function occurred and enamine **3a** was isolated as the main reaction product.

The isomerization of 22(23)-enamines **3a**, **3b**, **3d**, and **3f** to the corresponding 20,22-enamines **4a**, **4b**, **4d**, and **4f** was achieved with 0.1% acetic acid in ether (procedure *D*, Scheme 1), as well as in dichloromethane or chloroform (procedure *E*, Scheme 1).

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