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Electrochemical chlorination of some 5-unsaturated steroids*

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Abstract: Five 5-unsaturated steroids were subjected to constant current electrolysis (50 mA) in a dichloromethane solution of tetraethylammonium chloride in an undivided electrolytic cell at room temperature, using a graphite stick as the anode and a cooper spiral as the cathode. The addition of electrochemically generated elemental chlorine onto the double bond of cholesterol derivatives (5-cholestene, cholesteryl acetate, cholesteryl benzoate and 3-chloro-5-cholstene) gave the corresponding 5α,6β-dichlorosteroids, in good yields (70–73 %). The obtained compounds (5α,6β-dichlorocholestane, 5α,6β-dichlorocholestane-3β-yl acetate, 5α,6β-dichlorocholestane-3β-yl benzoate and 3β,5α,6β-trichlorocholestane) were characterized by physical and spectral data (IR, ^{1}H–NMR and ^{13}C–NMR). However, under the same reaction conditions, cholesterol produced a mixture of products from which the expected dichloro derivative (3β-hydroxy-5α,6β-dichlorocholestane) could not be isolated. This compound was prepared by alkaline hydrolysis of 5α,6β-dichlorocholestan-3β-yl acetate and 5α,6β-dichlorocholestan-3β-yl benzoate in methanol.

Keywords: electrolysis, electrochemical chlorination, 5-unsaturated steroids, 5α,6β-dichlorosteroids.

INTRODUCTION

There are only few groups of organic compounds that have captured the attention of chemists so intensively as the steroids. Among the many transformations of these compounds, one of the most important reactions is the protection of the double bond in the 5,6 position. The best way to prevent an undesirable participation of the double bond of a steroid in a certain reaction is to convert it into the dihalide.[1,2] Subsequent deprotection of the double bond can be achieved with several reagents, such as zinc dust in boiling acetic acid,[2] sodium iodide,[3] ferrous chloride,[4] and chromous chloride.[5]

Although 5,6-dibromo steroids can be prepared more easily than the corresponding dichlorides, there is a wide interest in the synthesis of the latter, particu-

* Dedicated to Professor Živorad Čeković on the occasion of his 70th birthday.

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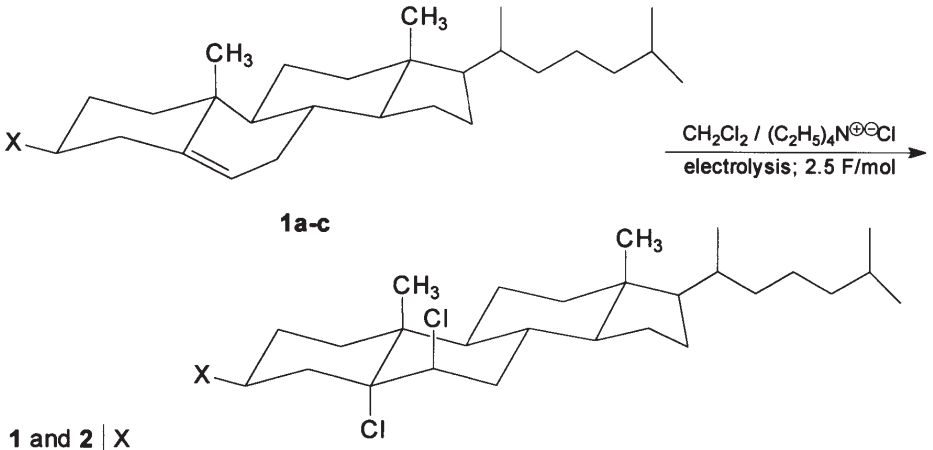
larly due to their higher stability. Thus, Mauthner and Suida reported on the addition of free chlorine to cholesterol and its esters resulting in the formation of the corresponding 5,6-dichloro products.[6] Since chlorine reacts non-selectively with vairous regions of the steroid molecule, direct chlorination of unsaturated steroids with free chlorine seems to be unsuitable for protection of the double bond, as the obtained mixtures are difficult to separate. Depending on the solvent used, many products, such as chlorohydrins, 5,6-diols, epoxides, and even some dimeric molecules have been detected besides the desired derivative.[7–9] Much better reslts could be achieved if 5-unsaturated steroids were reacted with: a) chlorine at –20 ºC in the presence of antimony trichloride;[10] b) chlorides of trivalent iodine;[10–12] c) chlorine generated *in situ* from acetyl chloride and MnO_2;[13] or d) by gas-solid addition of chlorine.[14] Recently, a group of Japanese chemists reported on an electrochemical method for the chlorination of cholesterol under constant current electrolysis at –2.0 ≈ –2.4 V *vs.* SCE (saturated calomel electrode), using the mixed solvent system (CH_2Cl_2–CH_3CH–H_2O, 2:2:1).[15] The transformation involved the use of $(C_4H_9)_4NBF_4$ as te electrolyte, in the presence of ferric chloride, hematoporphyrin and geseous oxygen. Three products, namely 5α,6β-dichlorocholestane-3β-ol, 6α-chloro-3β,5β-cholestanediol and the corresponding β-5,6-epoxiderivative, were obtained in 40–68 % overall yield. The product ratio depended on the reaction conditions. In continuation of our earlier studies on the electrochemical generation of electrophilic species,[16,17] we also reported, at the same time, on the chlorination of some steroids by simple constant current electrolysis under an uncontrolled electrode potential, resulting in the formation of the corresponding 5α,6β-dichloro derivatives.[18] In this paper, a full account of this work, including experimental details and spectral data of the obtained compounds, is given.

RESULTS AND DISCUSSION

For the investigations, five 5-unsaturated steroids were chosen as substrates, namely 5-cholestene (**1a**), cholesterol (**1b**), chlolesteryl acetate (**1c**), cholesteryl benzoate (**1d**) and 3β-chloro-5-cholestene (**1e**). Elemental chlorine was generated by simple constant current electrolysis (50 mA) of a dichloromethane solution of tetraethylammonium chloride in the presence of **1a** (Scheme 1). The electrolysis was performed at room temperature in an undivided electrolytic cell, using dichloromethane as the solvent, tetraethylammonium chloride as the electrolyte, a graphite stick as the anode and a copper spiral as the cathode. In view of the fact that chlorine and the substrate react in a 1:1 mole ratio, the electrolysis time was estimated to provide a 2 F/mol charge consumption. Thin layer chromatography (SiO_2/petroleum ether–acetone 95:5) of the reaction mixture showed two reaction products with very similar R_f values, along with some unchanged 5-cholestene. After column chromatography (Al_2O_3/petroleum ether), only one of the two products (the strongly predominant one) was isolated as a pure compound. Comparing

its ^{1}H-NMR data (δ 1.33, *s*, 19-H_3, and δ 4.34–4.37, *m*, 6α-H), melting point (118–120.5 °C) and $[\alpha]_D$ (–27.5°) to those given in the literature (δ 1.33, *s*, 19-H_3, and δ 4.42, *m*, 6α-H; 120–122 °C; –28°),[19] and analyzing the ^{13}C-NMR spectral data (which could not be found elsewhere), this compound was identified as 5α,6β-dichlorocholestane (**2a**, Scheme 1).



1 and 2	X
a	H
b	OH
c	OAc
d	OCOPh
e	Cl

2a (72%)
2b –
2c (70%)
2d (73%)
2e (71%)

Scheme 1.

Although the isolated yield of the compound **2a** was satisfactory (65 %), the fact that some amount of the substrate remained unchanged prompted us to perform several experiments in which more than 2 F/mol charge was consumed. The amount of unchanged substrate in the reaction mixture decreased to trace amounts by simple prolongation of the electrolysis time. Thus, the consumption of 2.5 F/mol charge gave the product in 72 % yield. Further prolongation of the electrolysis time, however, did not result in an enhancement of the yield. Instead, several new side products, which could not be separated and identified, appeared. Also additional experiments were carried out with an increased current (up to 200 mA), in order to shorten the electrolysis time. However, increased amounts of unknown side products were obtained.

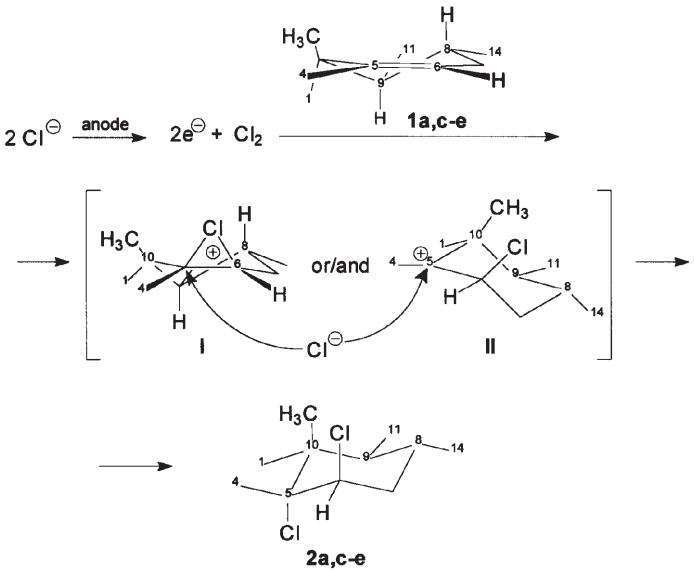
According to a literature report, low-temperature addition of chlorine onto unsaturated steroids affords higher yields of the corresponding dichlorides.[10] However, experiments with **1c** resulted in the same yields at both –10 and –5 °C (water–acetone–ice bath) and at room temperature.

Further investigations involved the electrolysis of cholesterol under the same experimental condition but, surprisingly, this compound gave a mixture which

probably contained neither 5α,6β- nor 5α,6α-dichlorocholestan-3β-ol. A reasonable explanation of such a dramatic influence of the hydroxyl group on the reaction could not be given without further investigations.

In order to examine whether other oxygen functionalities exhibit the same effect on this reaction, two additional substrates – esters **1c** and **1d** – were subjected to the same reaction conditions. Contrary to the free hydroxyl group, the ester function did not hamper the addition of chlorine, so the corresponding dichlorides **2c** and **2d** were isolated in 70 and 73 % yield, respectively, Dichloro acetates **2c** and **2d**, were then hydrolyzed with potassium hydroxide in methanol, to give 5α,6β-dichlorocholestan-3β-ol (**2b**) in almost quantitative yield. This compound was identified by its physical and spectral data, which were in good agreement with those from the literature.[19] Another steroid possessing a heteroatom in the 3β-position, chloride **3e**, was also employed as the substrate during those investigations. It reacted analogously to **1a**, **1c** and **1d**, affording a product which was identified as the trichloride **2e** on the basis of spectral data (71 %).

The mechanism of this reaction seems to be relatively simple. We believe that the reaction starts by the oxidation of chloride ions at the anode yielding free chlorine, followed by its addition onto the double bond of the substrate. The initial electrophilic attack to the double bond results in a tricentric chloronium ion or a free tertiary carbocation (**I** or **II**, Scheme 2), followed by anti-attack of the chloride anion to form the final product. The appearance of only 5α,6β-diastereoisomers as the products of this reaction may be explained by the Markovnikov rule and the initial apparoach of chlorine to the double bond from the β-side of the steroid molecule.



Scheme 2.

In conclusion, the results presented herein indicate a suitable and efficient method for vicinal dichlorination of 5-unsaturated steroids. The amount of the generated chlorine can be precisely controlled, eliminating the need to use chlorine cylinders or to generate the gas by polluting chemical reactions. The necessary equipment is simple, cheap and easily available.

EXPERIMENTAL

All the employed chemicals are commercially available and were used as received, except for the solvents which were purified by distillation. IR Measurements were carried out using a Perkin-Elmer 457 grating FT instrument. NMR spectra were recorded on a Varian Gemini (200 MHz) spectrometer, using $CDCl_3$ as the solvent. Chemical shifts are expressed in ppm using Me_4Si as the internal standard. Melting points were determined on a Kofler hot-plate apparatus. The $[\alpha]_D$ values were measured in a 1 dm tube at 20 ºC using a Perkin-Elmer SP polarimeter. A Uniwatt Beha Labor-Netzgerät (NG 394) was used as a direct current source for the electrolysis. A cylindrical glass vessel, equipped with a magnetic stirrer, a graphite stick (as the anode; Ø = 0.6 cm) and a copper spiral (as the cathode; Ø = 2.5 cm), was used as the undivided cell.

General procedure for electrochemical chlorination

100 mg of the required substrate (about 0.25 mmol) and 250 mg of tetraethylammonium chloride were dissolved in 15 mL of dichloromethane. The solution was transferred into the electrolytic cell, vigorously stirred at room temperature, and electrolyzed at a constant current (50 mA). The electrolysis was stopped after about 20 min (exactly calculated to provide 2.5 F/mol charge). The solvent was removed by rotary evaporation, H_2O (15 mL) was added to the residue, and the mixture was extracted with three portions of diethyl ether (3×15 mL). The organic layers were collected and washed with a solution of $NaHSO_3$ (10 %, 40 mL) in order to remove any free chlorine, then with brine (40 mL) and H_2O (40 mL). After drying with anhydrous Na_2SO_4 overnight, the solvent was evaporated and the crude reaction mixture was subjected to column chromatography using 20 g of alumina or SiO_2. The elution was monitored by TLC (silica gel 60 on Al plates, layer thickness 0.2 mm, Merck). The physical and spectral data follow.

Physical data

5α,6β-Dichlorocholestane (**2a**). Chromatography (alumina/petroleum ether) gave 85.8 mg (72 %) of **2a** as colorless crystals: m.p. 118–120.5 ºC (lit.,[19] 120–122 ºC); $[\alpha]_D^{20}$ –27.5º ($CHCl_3$ *c*, 4.0 mg/mL; lit.,[19] –28º); IR (KBr): characteristic band at 657 cm^{-1} (lit.,[19] 660 cm^{-1}); characteristic ^{1}H-NMR signals (200 MHz, $CDCl_3$): δ 1.33 (*s*, 19-CH_3) and δ 4.34–4.37 (*m*, 6*α*-H) (lit.,[19] δ 1.33, *s*, and δ 4.42, *m*, respectively) and ^{13}C-NMR signals ($CDCl_3$): δ 12.2, 18.7, 19.4, 20.2, 20.8, 21.6, 22.6, 22.8, 23.8, 24.0, 28.9, 28.2, 30.2, 34.2, 35.0, 35.8, 36.1, 36.1, 39.5, 39.8, 41.2, 42.7, 46.3, 55.4, 56.1, 64.5, 86.4;

*5α,6β-Dichlorocholestan-3*β*-yl acetate* (**2c**). Chromatography (SiO_2/petroleum ether–acetone 95:5) gave 81.6 mg (70 %) of **2c** as a white solid: m.p. 87.5:–89.4 ºC (lit.,[10] 89–90 ºC); $[\alpha]_D^{20}$ –28.7º ($CHCl_3$, *c* 4.0 mg/mL; lit.,[10] –29º); IR (KBr): characteristic bands at 1739, 1238 and 651 cm^{-1}; characteristic ^{1}H-NMR signals (200 MHz, $CDCl_3$) signals: δ 1.36 (*s*, 19-CH_3), 2.01 (*s*, CH_3CO), 4.32–4.35 (*m*, 6α-H) and 5.25–5.42 (*m*, 3α-H) and ^{13}C-NMR signals ($CDCl_3$): δ 12.1, 18.6, 19.5, 21.1, 21.3, 22.5, 22.8, 23.8, 24.0, 26.2, 28.0, 28.1, 30.2, 34.2, 35.4, 35.7, 36.1, 39.2, 39.5, 39.6, 40.7, 42.7, 45.8, 55.2, 56.1, 63.6, 70.8, 84.4, 170.3;

*5α,6β-Dichlorocholestan-3*β*-yl benzoate* (**2d**). Chromatography (SiO_2/petroleum ethe–acetone (95:5) gave 83.5 mg (73 %) of **2c** as colorless crystals: m.p. 127–129 ºC (lit.,[10] 130–131 ºC); $[\alpha]_D^{20}$ –22.4º ($CHCl_3$, *c* 5.8 mg/mL; lit.,[10] –20º); IR (KBr): characteristic bands at 1723, 1273 and 655 cm^{-1}; characteristic ^{1}H-NMR signals (200 MHz, $CDCl_3$): δ 1.44 (*s*, 19-CH_3), 4.39 (*m*, 6α-H)

and 5.63 (*m*, 3α-H) and ^{13}C-NMR signals ($CDCl_3$): δ 12.2, 18.6, 19.6, 21.2, 22.6, 22.8, 23.8, 24.0, 26.3, 28.0, 28.2, 30.2, 34.2, 35.4, 35.7, 36.1, 39.3, 39.5, 39.5, 40.8, 42.7, 45.8, 55.2, 56.1, 63.7, 71.4, 84.4, 128.2, 129.6, 130.5, 132.8, 165.8;

3β,5α,6β-Trichlorocholestan (**2e**). Chromatography (alumina/petroleum ether) gave 83.4 mg (71 %) of **2e** as colorless crystals: m.p. 122–123 ºC; $[\alpha]_D^{20}$ –32.8º; IR (KBr): characteristic band at 654 cm^{-1}; characteristic ^{1}H-NMR signals (200 MHz, $CDCl_3$): δ 1.39 (*s*, 19-CH_3), 4.34 (*m*, 6α-H) and 5.51 (*m*, 3α-H) and ^{13}C-NMR signals ($CDCl_3$): δ 12.2, 18.6, 19.6, 21.1, 22.6, 22.8, 23.8, 24.0, 28.0, 28.1, 30.2, 31.7, 34.2, 35.5, 35.7 (two carbons – one CH and one CH_2), 36.1, 39.5, 39.6, 40.6, 42.7, 44.1, 45.8, 55.2, 56.1 (two CH groups), 63.3, 85.2;

Hydrolysis of 5α,6β-dic hlorocholestan-3β-yl acetate (**2c**) *and benzoate* (**2d**). 100 mg of compound **2c** or **2d** and 250 mg of potassium hydroxide were dissolved in 10 mL of methanol and refluxed for two hours. The methanol was distilled off and the residue extracted with 30 ml of ether. After evaporation of the solvent, 71.5–72.5 mg (> 98 %) of *5α,6β-dichlorocholestan-3β-ol* (**2b**) as a white solid was obtained, which was pure enough for determination of physical and spectral data, that follow: m.p. 139.5–142.0 ºC (lit.,[19] 142–143 ºC); $[\alpha]_D^{20}$ –27.0º ($CHCl_3$, *c* 6.4 mg/mL; lit.,[19] –27º); IR (KBr): characteristic bands at 3413 and 655 cm^{-1} (lit.,[19] 3390 and 655 cm^{-1}); characteristic ^{1}H-NMR signals (200 MHz, $CDCl_3$): δ 1.36 (*s*, 19-CH_3), 4.20–4.40 (*m*, 3α-H and 6α-H) (lit.,[19] 1.35, 4.23 and 4.35, respectively) and ^{13}C-NMR signals ($CDCl_3$): δ 12.2, 18.6, 19.7, 21.2, 25.5, 22.8, 23.8, 24.0, 28.0, 28.2, 30.2 (two carbons - one CH and one CH_2), 34.5, 35.4, 35.7, 36.1, 39.4, 39.7, 40.7, 42.7, 42.9, 45.9, 55.2, 56.1, 63.8, 67.8, 85.4.

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ИЗВОД

ЕЛЕКТРОХЕМИЈСКО ХЛОРОВАЊЕ НЕКИХ 5-НЕЗАСИЋЕНИХ СТЕРОИДА

СМИЉКА МИЛИСАВЉЕВИЋ[а] И РАСТКО Д. ВУКИЋЕВИЋ[б]

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Пет 5-незасићених стероида подвргнуто је електролизи при константној јачини струје (50 mA) у раствору тетраетиламмонијум-хлорида у дихлорметану. Реакција је изведена на собној температуре у неподељеној електролитичкој ћелији, коришћењем графитног штапића као аноде и бакарне спирале као катоде. Адицијом електрохемијски генерисаног елементарног хлора на двоструку везу деривата холестерола (5-холестена, холестерил-ацетата, холестерил-бензоата и 3-хлор-5-холестена) добијени су одговарајући 5α,6β-дихлорстероиди у високом приносу (70–73 %). Добијена једињења (5α,6β-дихлорхолестан, 5α,6β-дихлорхолестан-3β-ил-ацетат, 5α,6β-дихлорхолестан-3β-ил бензоат и 3β,5α,6β-трихлорхолестан) окарактерисана су физичким и спектралним (IR, ^{1}H-NMR и ^{13}C-NMR) подацима. Међутим, под истим реакционим условима холестерол даје смесу производа, из које очекивани дихлор-дериват (3β-хидрокси-5α,6β-дихлорхолестан) није издвојен. Ово једињење добијено је алкалном хидролизом 5α,6β-дихлорхолестан-3β-ил-ацетата и 5α,6β-дихлорхолестан-3β-ил бензоата у метанолу.

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