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SOLVOLYSIS OF STEROL TOSYLATES IN AQUEOUS DIMETHYLFORMAMIDE

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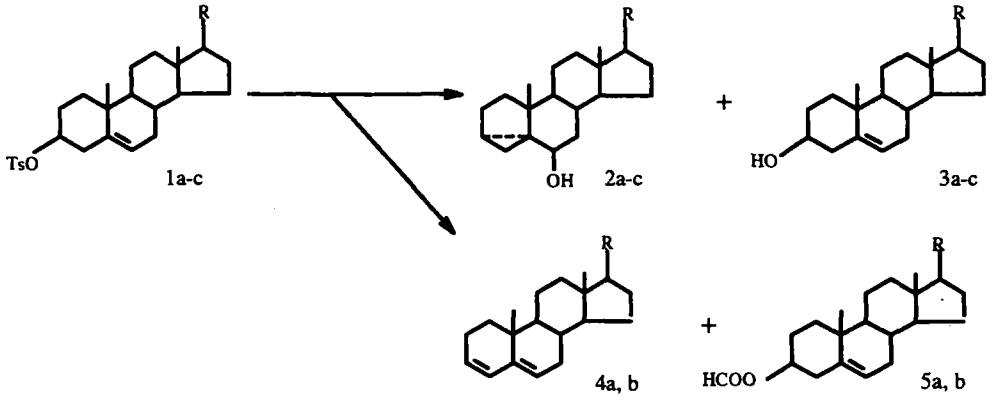
*It has been established that the heating of the sterol tosylates (**1a—c**) in aqueous dimethylformamide in the presence of sodium acetate leads to the formation of the 3α,5-cyclo-6β-alcohols (**2**), the sterols (**3**), the 3,5-dienes (**4**), and the sterol formates (**5**).*

The rearrangement of sterol tosylates (or mesylates) of type (**1**) in aqueous acetone in the presence of weak bases such as potassium acetate or potassium bicarbonate with the formation of the 6-alcohols (**2**) is one of the most important methods of synthesizing sterols oxidized at C-6 [1]. This reaction is used most widely for the introduction of 6-keto groups in the synthesis of ecdysteroids [2, 3] and brassinosteroids [4, 5]. However, in spite of its wide use, this method of synthesizing 3α,5-cyclo-6β-alcohols (**2**) possesses a number of drawbacks, to which we may assign above all the slow rate of solvolysis [6] and the low solubility in a mixture of acetone and water of both the tosylate (or mesylate) and inorganic salts. The use of other solvents, such as methyl ethyl ketone [7] or dimethyl sulfoxide [8], does not solve the problem.

In order to develop a new method of synthesizing 3α,5-cyclo-6β-alcohols, we have studied for the first time the solvolysis of sterol tosylates (**1a—c**) in aqueous dimethylformamide. The choice of dimethylformamide was due to its good dissolving capacity and its high boiling point. The latter circumstance made it possible to conduct solvolysis at an elevated temperature and thereby to shorten the reaction time considerably. We found that when a solution of cholesterol tosylate (**1a**) in aqueous dimethylformamide was heated in the presence of sodium acetate a minimum of four products was formed. As expected, the main one was the 3α,5-cyclo-6β-alcohol (**2a**), isolated with a yield of about 50%. We showed the structure of compound (**2a**) with the aid of spectra. In particular, the presence of a hydroxy group in its molecule was confirmed by the appearance in its IR spectrum of bands of the stretching vibrations of this group at 3620 cm^{-1}.



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In the ^{1}H NMR spectrum of the substance under discussion there were no signals of any vinyl protons whatever, which showed the absence of a 5-double bond from its structure. At the same time, at 3.26 ppm there was the signal of an H-6 proton geminal to a 6-hydroxy group. From the half-width of this signal (W/2 = 5 Hz) it was possible to deduce the axial (i.e., β-) orientation of the 6-hydroxy group. The presence of an additional three-membered ring in the molecule of compound (**2a**) was confirmed by proton signals in the strong-field region of the spectrum at 0.30 and 0.52 ppm. It must also be mentioned that the parameters of the ^{1}H NMR spectrum of the 3α,5-cyclo-6β-alcohol (**2a**) that we had obtained were very close to those described for this substance in the literature [9].

The second substance isolated from the products of this reaction with a yield of more than 10% was cholesterol (**3a**). Proof of the structure of sterol (**3a**) caused no difficulties, since it was found to be identical in all respects with the cholesterol that we had used as the starting material for synthesizing the tosylate (**1a**). It must be mentioned that the formation of cholesterol on the solvolysis of tosylate(**1a**) has been observed previously [10].

In addition to the alcohols (**2a**) and (**3a**), we isolated cholesterol formate (**5a**) from the reaction mixture with a yield of 25%. The IR spectrum of this substance had an absorption band at 1735 cm^{-1}, characteristic for an ester function. In its turn, in the ^{1}H NMR spectrum at δ 8.40 ppm there was a singlet of the proton of a formate group. Also characteristic was the position of a multiplet of the H-3 methine proton with δ 4.73 ppm. The half-width of this signal (W/2 = 29 Hz) showed the β-orientation of the 3-formate group. Since the spectrum included the signal of an H-6 vinyl proton (δ 5.40 ppm) it was possible to deduce the presence of a 5-double bond in the structure of compound (**5a**). It must be mentioned that, for us, the production of the formate (**5a**) in this reaction was completely unexpected. Its formation can apparently be explained by the existence of nucleophilic properties in dimethylformamide.

A minor product, isolated from the reaction mixture in very low yield was the 3,5-diene (**4a**), formed by a tosylate elimination reaction. Characteristic for the ^{1}H NMR spectrum of this compound was the absence of any signals whatever of protons geminal to hydroxy groups or ester functions. At the same time, it contained the signals of three vinyl protons, at 5.37, 5.59, and 5.92 ppm. A definitive confirmation of the structure of the compound under discussion was the identity of its ^{1}H NMR spectrum and that of the cholesta-3,5-diene (**4a**) that we obtained in the usual way by the dehydrochlorination of cholesteryl chloride. We may also mention that the parameters of the ^{1}H NMR spectrum of the substance that we had obtained agreed well with those for cholest-3,5-diene described in the literature [11].

We have also studied yet another variant of the solvolysis of tosylate (**1a**). In it we used unpurified tosylate obtained immediately before by the interaction of cholesterol with *p*-toluenesulfonyl chloride in pyridine. It was found that in this case the main reaction products were compounds (**2—5a**).

We also investigated the solvolysis of β-sitosterol tosylate (**1b**). As in the first case, the solvolysis of tosylate (**1b**) formed mainly the 3α,5-cyclo-6β-alcohol (**2b**). Since we used technical β-sitosterol for the reaction, the yield of this substance was considerably lower than that of (**2a**). Its structure followed unambiguously from its IR and ^{1}H NMR spectra, the main characteristics of which agreed well with those described in the literature [12]. Minor products of the solvolysis of β-sitosterol tosylate (**1b**) were the 3,5-diene (**4b**) and the 3-formate (**5b**). Their structures were shown by comparing their IR and ^{1}H NMR spectra with those of compounds (**4a**) and (**5a**).

We have also studied the solvolysis of stigmasterol tosylate (**1c**) under conditions analogous to those described above. It was established that this reaction formed the 3α,5-cyclo-6β-alcohol (**2c**), stigmasterol (**3c**), and stigmasterol formate (**5c**), isolated from the reaction mixture with yields of 41.3, 19.4, and 32.6%, respectively. The structures of compounds (**2c**), (**3c**), and (**5c**) followed unambiguously from their spectra.

Thus, as a result of the investigation performed, we have shown that the main products in the solvolysis of sterol tosylates are 3α,5-cyclo-6β-alcohols. However, by-products formed at the same time are 3,5-dienes and the initial sterols and their formates, which considerably lowers the value of this variant of the reaction as a synthetic method.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were recorded on a UR-20 instrument in the 700—3600 cm^{-1} interval in films and in KBr tablets. The ^{1}H NMR spectra of solutions in deuterochloroform were obtained on Bruker WM-360 and AC-200 NMR spectrometers with working frequencies of 360 and 200 MHz, respectively. Chemical shifts are given relative to TMS as internal standard. For column chromatography we used silica gel of type L 40/100

(Lachema, Czech Republic). The course of the reaction was monitored and the purity of the products obtained was checked by means of TLC on Silufol plates (Kavalier, Czech Republic).

Solvolysis of Cholesterol Tosylate (1a). A. A solution of 0.323 g of cholesterol tosylate (**1a**) (obtained from cholesterol by the procedure of Thompson et al. [13]) in 10 ml of dimethylformamide and 1 ml of water was treated with 0.162 g of crystalline sodium acetate. The reaction mixture was heated on the boiling water bath and was kept at this temperature for 2 h. After cooling to room temperature, the mixture was diluted with water and the reaction product was extracted with benzene. The benzene extract was washed with water and evaporated in vacuum. The residue was chromatographed on a column of silica gel with elution by hexane—benzene (1:1). This gave 0.017 g (8.3%) of amorphous cholesta-3,5-diene (**4a**).

^{1}H NMR spectrum (δ, ppm): 0.70 (18-Me), s), 0.86 (26-Me, d, J=6.6 Hz), 0.865 (27-Me, d, J=6.6 Hz), 0.91 (21-Me, d, J=6.6 Hz), 0.94 (19-Me, s), 5.37 (H-6, m, W/2=10 Hz), 5.59 (H-3, m, W/2=19 Hz), 5.92 (H-4, br, d, J=9.6 Hz).

Further elution led to 0.063 g of amorphous cholesterol formate (**5a**). Yield 25.0%.

IR spectrum (ν, cm^{-1}): 1735 (C=O). ^{1}H NMR spectrum (δ, ppm): 0.68 (18-Me, s), 0.87 (26/27-Me, d, J=6 Hz), 4.73 (H-3α, m, W/2=29 Hz), 5.40 (H-6, br, d, J=4.5 Hz), 8.04 (H-COO, s).

Benzene eluted 0.111 g of 3α,5-cyclo-5α-cholestan-6β-ol (**2a**). Yield 48.3%. mp 62—68°C (hexane); lit.: mp 66.7—69.7°C [10].

IR spectrum (ν, cm^{-1}): 3620 (OH). ^{1}H NMR spectrum (δ, ppm): 0.30 (H-4α, dd, J_1=8 Hz, J_2= 4.5 Hz), 0.52 (H-3β, t, J=4.5 Hz), 0.72 (18-Me, s), 0.86 (26/27-Me, d, J=6 Hz), 0.91 (21-Me, d, J=6.5 Hz), 1.06 (19-Me, s), 3.26 (H-6α, m, W/2=5 Hz).

Further elution with benzene gave 0.026 g of cholesterol (**3a**). Yield 11.7%. mp 141—145°C (hexane); lit.: mp 149°C [1]. A specimen had IR and ^{1}H NMR spectra identical with those of the authentic substance.

B. A reaction mixture consisting of a solution of 1.00 g of cholesterol (**3a**) and 1.00 g of *p*-toluenesulfonyl chloride in 6.5 ml of pyridine was kept at room temperature for 19.5 h and was then diluted with water. The resulting precipitate was filtered off and washed on the filter with water. The moist cholesterol tosylate (**2a**) so obtained, weighing 2.618 g, was dissolved in 30 ml of dimethylformamide, and 2 ml of water and 0.695 g of crystalline sodium acetate were added. The reaction mixture was heated on the boiling water bath for 4 h and was then cooled to room temperature and diluted with water. The reaction products were extracted with benzene, and the benzene extract was washed with water and was then evaporated in vacuum. The residue was chromatographed on a column of silica gel with elution by benzene—hexane (1:1). This gave 0.060 g of amorphous cholesta-3,5-diene (**4a**). Yield 4.2%.

Further elution led to the isolation of 0.313 g of cholesterol formate (**5a**). Yield 29.6%.

Benzene eluted 0.477 g of 3α,5-cyclo-5α-cholestan-6β-ol (**2a**). Yield 47.9%. mp 62—68°C (hexane).

Further elution with benzene gave 0.166 g of cholesterol (**3a**). Yield 16.7%.

Solvolysis of β-Sitosterol Tosylate (1b). A solution of 1.0 g of technical β-sitosterol (**3b**) and 1.0 g of *p*-toluenesulfonyl chloride in 9 ml of pyridine was kept at room temperature for 20 h and was then diluted with water. The resulting precipitate was filtered off and was washed on the filter with water. The moist β-sitosterol tosylate obtained, weighing 1.843 g, was dissolved in 35 ml of dimethylformamide, and 3 ml of water and 0.753 g of crystalline sodium acetate were added to the solution. The reaction mixture was heated on the boiling water bath for 2 h and was then cooled to room temperature and diluted with water. The reaction products were extracted with benzene, and the benzene extract was washed with water and evaporated in vacuum. The residue was chromatographed on a column of silica gel, giving 0.332 g of a mixture of the 3,5-diene (**4b**) and the formate (**5b**).

On further elution, 0.278 g of (24R)-3α,5-cyclo-5α-stigmastan-6β-ol (**2b**) was isolated. Yield 27.9%. mp 71—76°C (hexane—benzene); lit.: mp 77°C [12], 78—79°C [14].

IR spectrum (ν, cm^{-1}): 3620 (OH). ^{1}H NMR spectrum (δ, ppm): 0.30 (H-4α, dd, J_1=9 Hz, J_2=5 Hz), 0.54 (H-3β, t, J=4.5 Hz), 0.72 (18-Me, s), 0.82 (26-Me, d, J=7 Hz), 0.83 (27-Me, d, J=7 Hz), 0.85 (29-Me, t, J=7 Hz), 0.92 (21-Me, d, J=6 Hz), 1.06 (19-Me, s), 3.27 (H-6α, m, W/2=7 Hz).

The mixture of the diene (**4b**) and the formate (**5b**) was rechromatographed on a column of silica gel with elution by benzene—hexane (1:1). This gave 0.07 g of amorphous (24R)-stigmasta-3,5-diene (**4b**). Yield 7.5%.

^{1}H NMR spectra (δ, ppm): 0.71 (18-Me, s), 0.93 (21-Me, d, J=7Hz), 0.96 (19-Me, s), 5.39 (H-6, m, W/2=9 Hz), 5.59 (H-3, m, W/2=19 Hz), 5.92 (H-4, br, d, J=9.6 Hz).

Further elution with hexane—benzene(1:1) gave 0.243 g of β-sitosterol formate (**5b**). Yield 22.9%. mp 62—81°C (hexane—benzene).

IR spectrum (ν, cm^{-1}): 1735 (C=0). ^{1}H NMR spectrum (δ, ppm): 0.68 (18-Me, s), 1.03 (19-Me, s), 4.72 (H-3α, m,

W/2=21 Hz), 5.40 (H-6, br.d, J=4.5 Hz), 8.04 (H-COO, s).

Solvolysis of Stigmasterol Tosylate (1c). A reaction mixture consisting of a solution of 0.503 g of stigmasterol (**3c**) and 0.501 g of *p*-toluenesulfonyl chloride in 6 ml of pyridine was kept at room temperature for 23 h. Then it was diluted with water, and the resulting precipitate was filtered off and was washed on the filter with water. The moist stigmasterol tosylate obtained, weighing 1.444 g, was dissolved in 20 ml of dimethylformamide, and 1.5 ml of water and 0.346 g of crystalline sodium acetate were added. The mixture was heated on the boiling water bath for 2 h and was then cooled to room temperature and diluted with water. The resulting emulsion was extracted with benzene, and the benzene extract was washed with water and evaporated in vacuum. The residue was chromatographed on a column of silica gel with elution by hexane—benzene (1:1). This gave 0.175 g of stigmasterol formate (**5b**). Yield 32.6%. mp 67—82°C (hexane).

IR spectrum (ν, cm^{-1}): 1730 (C=O). ^1H NMR spectrum (δ, ppm): 0.70 (18-Me, s), 1.02 (19-Me, s), 4.72 (H-3α, m, W/2=30 Hz), 5.00 (H-22, dd, J_1=14 Hz, J_2=8 Hz), 5.16 (H-23, dd, J_1=15 Hz, J_2=8 Hz), 5.40 (H-6, br. d, J=4.5 Hz), 8.04 (H-COO, s).

Subsequent elution with benzene led to the isolation of 0.208 g of (24S)-3α,5-cyclo-5α-stigmast-22-en-6β-ol (**2c**). Yield 41.3%. mp 80—86°C (hexane); lit.: mp 48—50°C [14].

IR spectrum (ν, cm^{-1}): 3260 (OH). ^1H NMR spectrum (δ, ppm): 0.30 (H-4α, dd, J_1=8 Hz, J_2=5 Hz), 0.53 (H-3β, t, J=4.5 Hz), 0.75 (18-Me, s), 1.02 (21-Me, d, J=7 Hz), 1.06 (19-Me, s), 3.27 (H-6α, m, W/2=7 Hz), 5.00 (H-22, dd, J_1=15 Hz, J_2=8 Hz), 5.16 (H-23, dd, J_1=15 Hz, J_2=8 Hz).

Further elution with benzene led to 0.098 g of stigmasterol (**3c**). Yield 19.4%, mp 165—170°C (hexane); lit.: mp 170°C [1]. A specimen had IR and ^1H NMR spectra identical with those of the authentic substance.

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