*Chemistry of Natural Compounds, Vol. 35, No. 2, 1999*

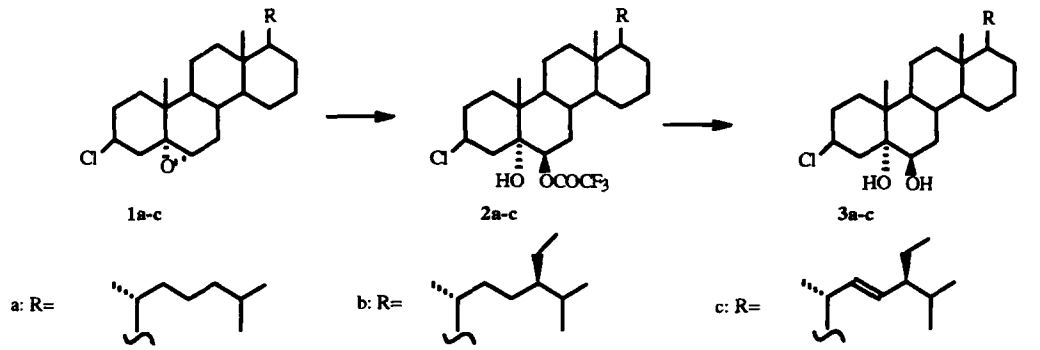
# REACTION OF 3β-CHLORO-5α,6α-EPOXYSTEROIDS WITH TRIFLUOROACETIC ACID

**N. V. Kovganko and S. K. Ananich**

UDC 547.92

*It has been established that on the interaction of the 5α,6α-epoxysteroids (**1a—c**) with trifluoroacetic acid in chloroform the 6-trifluoroacetates of the 5α,6β-diols (**2a—c**) are formed in high yield. The alkaline hydrolysis of the trifluoroacetates (**2a—c**) leads to the corresponding diols (**3a—c**).*

Earlier [1], during a study of the epoxidation of 3β-chloro-$\Delta^5$-steroids with trifluoroperacetic acid, we noted the formation not only of the epoxides (**1a,b**) but also of the 6-trifluoroacetates (**2a,b**). One of the most probable routes of formation of substances (**2a,b**) may consist in the opening of the 5α,6α-epoxide ring in steroids (**1a,b**) under the action of the trifluoroacetic acid, which is always present in the reaction mixture when working with trifluoroperacetic acid. We undertook the present investigation with the aim of confirming this possibility.




The initial 5α,6α-epoxides (**1a—c**) were obtained by procedures developed previously [1, 2] in which cholesterol, β-sitosterol, and stigmasterol, respectively, were treated with thionyl chloride and the resulting 3β-chloro-$\Delta^5$- derivatives were then epoxidized with *m*-chloroperbenzoic acid. We found that the sole products of the reactions of the 5α,6α-epoxysteroids (**1a—c**) with trifluoroacetic acid in chloroform were the 6-trifluoroacetates of the 5α,6β-diols (**2a—c**). Compounds (**2a—c**) were fairly stable thermally and were isolated from the reaction mixture in high yield. Their structure was shown unambiguously by their spectra. Thus, their IR spectra contained a band of the stretching vibrations of a carbonyl group that is characteristic for trifluoroacetates. In addition, in the 3550—3570 $cm^{-1}$ region there was a band corresponding to the stretching vibrations of a hydroxy group.

Characteristic for the $^1H$ NMR spectra of steroids (**2a—c**) was the presence of a signal of the H-6α methine proton geminal to the 6-trifluoroacetoxy grouping at δ 4.82 ppm. From the magnitude of the half-width of this signal (W/2 = 6 Hz) it is possible to deduce the axial orientation of the 6-trifluoroacetoxy group. Furthermore, in each of the spectra of compounds (**2a—c**) there was the signal of the H-3α methine proton geminal to a chlorine atom (δ 4.30 ppm). The half-width of this signal (W/2 = 24 Hz) showed its axial orientation. Thus, since the C-3 configuration did not change during the reaction, steroids (**2a—c**) had a *trans-A/B* linkage. The downfield shift of the H-3α signal as compared with its position in the spectra of the

Institute of Bioorganic Chemistry, Belarus' National Academy of Sciences, 220141, Belarus', Minsk, ul. Akad. Kuprevicha, 5/2. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 201—204, March-April, 1999. Original article submitted December 11, 1998.

0009-3130/99/3502-0179$22.00 

initial 5α,6α-epoxides (δ 4.10 ppm) was caused by the presence of the 1,3-diaxially located 5α-hydroxy group.

Convincing proof of the structure of steroids (**2a—c**) was provided by the results of their hydrolysis under the action of a solution of caustic soda in a mixture of ethanol and tetrahydrofuran. This led to the 5α,6β-diols (**3a—c**).

Compounds (**3a,b**) proved to be completely identical with authentic specimens that we had synthesized previously [1]. The structure of diol (**3c**) was shown by its spectra. In particular, the IR spectra of this compound lacked the band at 1790 $cm^{-1}$ that is characteristic for trifluoroacetates. In the $^1H$ NMR spectrum of diol (**3c**) the signal of the H-3α methine proton had practically the same chemical shift as in the spectrum of the initial trifluoroacetate (**2c**). At the same time, the signal of the H-6α methine proton in the spectrum of steroid (**3c**) was shifted upfield, to δ 3.54 ppm, in comparison with its position in the spectrum of the trifluoroacetate (**2b**). Such a shift is extremely characteristic for the hydrolysis of esters to alcohols.

Thus, the results of the investigation performed permit the conclusion that the 6-trifluoroacetates obtained on the interaction of $\Delta^5$-steroids with trifluoroperacetic acid are most probably formed as a result of the opening of 5α,6α-epoxides by trifluoroacetic acid. It must be mentioned that the formation of steroid trifluoroacetates has been observed previously in the reaction of 5,6-epoxides with trifluoroacetic anhydride in pyridine [3]. However, the yields of these compounds by this method [3] are extremely moderate. Consequently, the method of synthesizing 6-trifluoroacetates that we have proposed undoubtedly has a number of advantages over that described previously.

## 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 KBr tablets. The $^1H$ NMR spectra of solutions in deuterochloroform were obtained on a Bruker AC-200 spectrometer with a working frequency of 200 MHz. Chemical shifts are given relative to TMS as standard.

**3β-Chloro-5α-cholestane-5,6β-diol 6-Trifluoroacetate (2a).** A solution of 0.344 g of 3β-chloro-5,6α-epoxy-5α-cholestane (**1a**) (obtained from cholesterol as in [1]) in 5 ml of chloroform was treated with 0.2 ml of trifluoroacetic acid. The reaction mixture was kept at room temperature for 19 h and was then treated with 10 ml of saturated sodium bicarbonate solution. The organic layer was separated from the aqueous layer and was washed with water and evaporated in vacuum. This gave 0.430 g of the amorphous trifluoroacetate (**2a**). Yield quantitative.

IR spectrum (ν, $cm^{-1}$): 3550 (OH), 1795 ($CF_3CO$). $^1H$ NMR spectrum (δ, ppm): 0.68(18-Me, s), 0.86 (26/27-Me, d, J=7.2 Hz), 0.90 (21-Me, d, J=7.2 Hz), 1.14 (19-Me, s), 4.30 (H-3α, m, W/2=24 Hz), 4.82 (H-6α, m, W/2=6 Hz).

**(24R)-3β-Chloro-5α-stigmastane-5,6β-diol 6-Trifluoroacetate (2b).** A solution of 1.056 g of (24R)-3β-chloro-5,6α-epoxy-5α-stigmastane (**1b**) (obtained from β-sitosterol as in [2]) in 10 ml of chloroform was treated with 0.5 ml of trifluoroacetic acid. The reaction mixture was kept at room temperature for 23 h and was then treated with 15 ml of saturated sodium bicarbonate solution. The organic layer was separated from the aqueous layer and was washed with water and evaporated in vacuum. This gave 1.229 g of the amorphous trifluoroacetate (**2b**). Yield 93%.

IR spectrum (ν, $cm^{-1}$): 3560 (OH), 1790 ($CF_3CO$). $^1H$ NMR spectrum (δ, ppm): 0.68(18-Me, s), 0.80 (26-Me, d, J=7.0 Hz), 0.83 (27-Me, d, J=7.0 Hz), 0.84 (29-Me, t, J=8.0 Hz), 0.90 (21-Me, d, J=6.0 Hz), 1.16 (19-Me, s), 4.30 (H-3α, m, W/2=24 Hz), 4.82 (H-6α, m, W/2=6 Hz).

**(24R)-3β-Chloro-5α-stigmast-22-ene-5,6β-diol 6-Trifluoroacetate (2c).** A solution of 0.201 g of (24R)-3β-chloro-5,6α-epoxy-5α-stigmast-22-ene (obtained from stigmasterol as in [2]) in 5 ml of chloroform was treated with 0.1 ml of trifluoroacetic acid. The reaction mixture was kept at room temperature for 19 h and was then treated with 10 ml of saturated aqueous sodium bicarbonate solution. The organic layer was separated from the aqueous layer and was washed with water, and the solvent was driven off in vacuum. The residue was chromatographed on a column of silica gel with elution first by hexane—benzene (5:1) and then by benzene. This gave 0.158 g of the amorphous trifluoroacetate (**2c**). Yield 63%.

IR spectrum (ν, $cm^{-1}$) 3570 (OH), 1795 ($CF_3CO$). $^1H$ NMR spectrum (δ, ppm): 0.68(18-Me, s), 1.01 (21-Me, d, J=7.0 Hz), 1.16 (19-Me, s), 4.30 (H-3α, m, W/2=24 Hz), 4.82 (H-6α, m, W/2=6 Hz), 5.06 (H-22, dd, $J_1$=14.0 Hz, $J_2$=6.0 Hz), 5.18 (H-23, dd, $J_1$=14.0 Hz, $J_2$=6.0 Hz).

**3β-Chloro-5α-cholestane-5,6β-diol (3a).** With continuous stirring on a magnetic stirrer, 2 ml of 5% aqueous caustic soda was added to a solution of 0.302 g of the trifluoroacetate (**2a**) in 10 ml of ethanol and 3 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 1 h and was then neutralized with a solution of hydrochloric acid (1:1). It was extracted with dichloroethane, and the extract was washed with water and evaporated in vacuum. This gave 0.256 g of

the diol (**3a**), mp 106—112°C (hexane), lit. [1]: mp 107—116°C. A sample had IR and $^1$H NMR spectra identical with those of the diol (**3a**) obtained previously [1].

**(24R)-3β-Chloro-5α-stigmastane-5,6β-diol (3b).** With stirring on a magnetic stirrer, 0.637 g of the trifluoroacetate (**2b**) was dissolved in 10 ml of ethanol and 5 ml of tetrahydrofuran. Then 2 ml of a 5% aqueous solution of caustic soda was added and the mixture was stirred at room temperature for 1 h. After this, it was neutralized with an aqueous solution (1:1) of hydrochloric acid and was diluted with water. The reaction product was extracted with dichloroethane, and the extract was washed with water and evaporated in vacuum. This gave 0.54 g of the diol (**3b**). Yield quantitative. mp 136—139°C (hexane), lit. [1]: mp 128—135°C. A sample had IR and $^1$H NMR spectra identical with those of the diol (**3b**) obtained previously [1].

**(24S)-3β-Chloro-5α-stigmast-22-ene-5,6β-diol (3c).** With stirring on a magnetic stirrer, 1 ml of a 5% aqueous solution of caustic soda was added to a solution of 0.135 g of the trifluoroacetate (**2c**) in 5 ml of ethanol and 2 ml of tetrahydrofuran. Stirring was continued at room temperature for 1 h, and the mixture was neutralized with hydrochloric acid (1:1) and diluted with water. It was then extracted with dichloroethane, and the extract was washed with water and evaporated in vacuum. This gave 0.106 g of the diol (**3c**). Yield 95%. mp 136—140°C (hexane).

IR spectrum (ν, cm$^{-1}$): 3450 (OH). $^1$H NMR spectrum (δ, ppm): 0.70(18-Me, s), 1.02 (21-Me, d, J=6.0 Hz), 1.22 (19-Me, s), 3.54 (H-6α, m, W/2=6 Hz), 4.36 (H-3α, m, W/2=24 Hz), 5.00-5.20 (H-22, and H-23, m).

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