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REACTION OF PREGNENOLONE AND 3α,5-CYCLO-5α-PREGNAN-6β-OL-20-ONE WITH TRIFLUOROPERACETIC ACID

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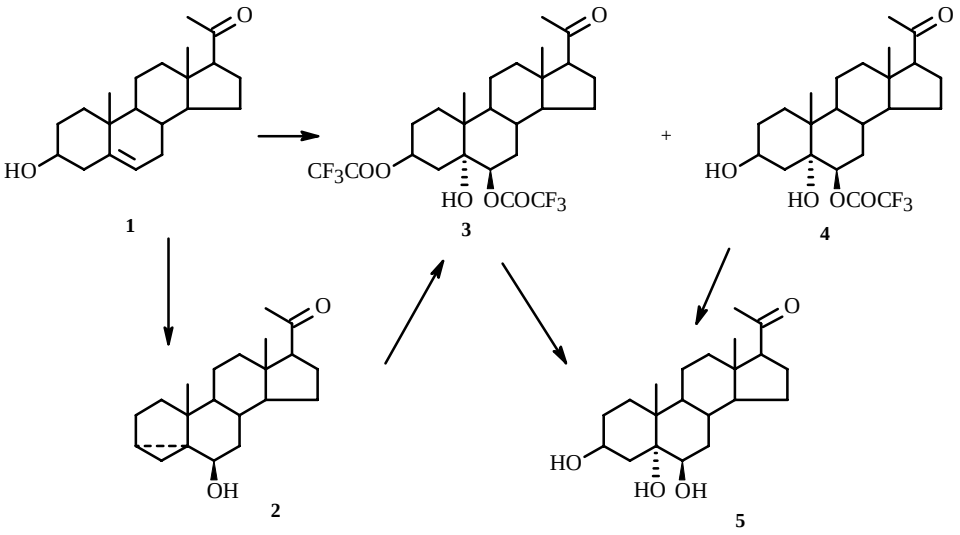
The reaction of pregnenolone and 3α,5-cyclo-5α-pregnan-6β-ol-20-one with trifluoroperacetic acid produces the trifluoroacetates, hydrolysis of which gives the 3β,5α,6β-triol.

Key words: pregnenolone, 3α,5-cyclo-5α-pregnan-6β-ol-20-one, trifluoroperacetic acid.

We have previously studied the reaction of 3β-chloro-Δ^5-steroids with trifluoroperacetic acid [1]. It was found that 5α-6β-diols and their 6-trifluoroacetates are obtained under these conditions together with the corresponding 5α,6α-epoxides. It was shown later that the acetates are formed via opening of the 5α,6α-epoxides by trifluoroacetic acid, which is always present in the reaction mixture [2]. In continuation of this work we studied the products from oxidation of pregnenolone (**1**) and 3α,5-cyclo-5α-pregnan-6β-ol-20-one (**2**), which are pregnane steroids, by trifluoroperacetic acid. Only a few reports on the oxidation of the 5(6)-double bond in pregnanes by peracids have appeared in the scientific literature [3-6]. It was shown that perbenzoic and monoperphthalic acids produce 5α,6α-epoxides whereas peracetic acid oxidized Δ^5-pregnanes to the corresponding 5α,6β-diols. Furthermore, application of trifluoroperacetic acid in this area has not previously been investigated.



We have found that the principal products from the reaction of **1** with trifluoroperacetic acid, which is produced directly in the reaction mixture from trifluoroacetic anhydride and hydrogen peroxide, are the trifluoroacetates **3** and **4**, which are isolated in yields of 29 and 52%, respectively. Their structures were proved using spectral data. Thus, the IR spectra of both compounds contain bands at 3435-3450, 1790, and 1705 cm^{-1} that are characteristic of stretching vibrations of hydroxyls, trifluoroacetate, and 20-ketones, respectively. The ^1H NMR spectra of **3** and **4** lack signals of H-6 vinylic protons, which proves that the reaction occurs at the 5(6)-double bond of pregnenolone. The spectra of these compounds typically have a multiplet

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for the H-6α proton at δ 4.87-4.88 ppm. This is indicative of a 6β-trifluoroacetate in their structures [1, 2]. The signal for H-3α in the spectrum of **4** is markedly shifted downfield (δ 4.07 ppm) compared with its position in the spectrum of the starting pregnenolone (δ 3.54 ppm). This shift is undoubtedly caused by the hydroxyl in the 5α-position of **4**, which is oriented 1,3-diaxial relative to H-3. The conclusion that **3** contains both a 5α-hydroxyl and a 3-trifluoroacetate can be made based on the chemical shift of H-3α (δ 5.37 ppm).

Convincing evidence that **3** and **4** are trifluoroacetates comes from results of their base hydrolysis to the known 3β,5α,6β-triol **5** [3, 4]. The structure of **5** was proved using ^{1}H NMR spectra (see Experimental). We also found that **1** can be converted in high yield to **5** by oxidation with trifluoroperacetic acid and subsequent base hydrolysis of the resulting trifluoroacetates without separation or purification.

We also studied the effect of trifluoroperacetic acid on **2**, which was prepared as usual by rearrangement of pregnenolone mesylate. We supposed that selective Bayer—Villager oxidation of the 20-ketone in **2** by trifluoroperacetic acid could produce the corresponding androstane derivative. For example, such a conversion was described for the synthesis of rubrosterone from poststerone [7]. However, it turned out that the group in rings *A* and *B* are more reactive under these conditions. Thus, **3** and **4** are obtained from **2**. They are most probably formed via initial isomerization of **2** by trifluoroacetic acid into **1**, which then is oxidized by trifluoroperacetic acid.

Thus, our results indicate that oxidation of the 5(6)-double bond in steroids by trifluoroperacetic acid is highly selective, even in the presence of a 20-ketone. This reaction can be viewed as a synthetic method for introducing 5α,6β-diols into steroids. In this sense we note that 5α,6β-dihydroxysteroids have been isolated from various natural sources [8, 9]. They are interesting as intermediates in the synthesis of ecdysteroids [10]. We propose on this basis that oxidation of Δ^5-steroids by trifluoroperacetic acid, taking into account the mild reaction conditions and selectivity, is interesting for the preparation of these compounds.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were recorded on a UR-20 instrument in the range 700-3600 cm^{-1} as films. ^{1}H NMR spectra of solutions in $CDCl_3$ were obtained on a Bruker AC-200 NMR spectrometer at working frequency 200 MHz. Chemical shifts are given relative to TMS as an internal standard.

Reaction of 1 with Trifluoroperacetic Acid. A solution of trifluoroacetic anhydride (0.7 ml) in methylenechloride (10 ml) was slowly treated with stirring and cooling on an ice bath with hydrogen peroxide (0.5 ml, 30%). The resulting solution of triflurorperacetic acid was treated successively with a solution of **1** (0.20 g) in methylenechloride (10 ml) and $Na_2HPO_4 \cdot 12H_2O$ (0.60 g). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under vacuum. The solid was dissolved in a mixture of ethanol (10 ml) and THF (3 ml) and treated over 1 h with aqueous NaOH (5% aqueous, 2 ml). After neutralization with HCl (1:1), the mixture was diluted with water and extracted with ether. The ether extract was evaporated under vacuum. The solid was chromatographed on an aluminum-oxide column with elution by ether. Two fractions were obtained.

Fraction 1 contained amorphous 3β,6β-bis(trifluoroacetoxy)-5-hydroxy-5α-pregnan-20-one (**3**), 0.098 g (29%). IR spectrum (cm^{-1}): 3450 (OH), 1790 (CF_3CO), 1705 (C=O). ^{1}H NMR spectrum (δ, ppm): 0.64 (18-Me, s), 1.18 (19-Me, s), 2.13 (21-Me, s), 4.88 (H-6α, m, W/2 = 8 Hz), 5.37 (H-3α, m, W/2 = 24 Hz).

Fraction 2 contained amorphous 6β-(trifluoroacetoxy)-3β,5-dihydroxy-5α-pregnan-20-one (**4**), 0.147 g (52%). IR spectrum (cm^{-1}): 3435 (OH), 1790 (CF_3CO), 1705 (C=O). ^{1}H NMR spectrum (δ, ppm): 0.64 (18-Me, s), 1.12 (19-Me, s), 2.14 (21-Me, s), 4.07 (H-3α, m, W/2 = 24 Hz), 4.87 (H-6α, m, W/2 = 7 Hz).

Hydrolysis of 3. A solution of **3** (0.202 g) in ethanol (5 ml) was treated with aqueous NaOH (2 ml, 5%). The mixture was boiled for 1 h 20 min, cooled to room temperature, neutralized with HCl (1:1), and diluted with water. The reaction product was extracted with ether. The ether extract was evaporated under vacuum. Yield 0.058 g (44%) of amorphous 3β,5,6β-trihydroxy-5α-pregnan-20-one **5**. ^{1}H NMR spectrum (δ, ppm): 0.64 (18-Me, s), 1.18 (19-Me, s), 2.16 (21-Me, s), 3.60 (H-6α, m, W/2 = 6 Hz), 4.20 (H-3α, m, W/2 = 24 Hz).

Hydrolysis of 4. A solution of **4** (0.265 g) in ethanol (8 ml) was treated with aqueous NaOH (3 ml, 5%). The reaction mixture was boiled for 1 h, cooled to room temperature, neutralized with HCl (1:1), and diluted with water. The mixture was extracted with ether. The ether extract was evaporated under vacuum. Yield 0.074 g (36%) of triol **5**.

(3*α*,5)-Cyclo-5α-pregnan-6β-ol-20-one (2). A solution of pregnenolone (1.0 g) in pyridine (15 ml) was treated with

methanesulfonylchloride (1 ml). The reaction mixture was held at room temperature for 23 h and diluted with water (90 ml). The precipitate of pregnenolone mesylate that formed was filtered off, thoroughly washed on the filter with water, and dissolved in acetone (150 ml). The resulting solution was treated with sodium acetate trihydrate (1.0 g) in water (25 ml). The reaction mixture was refluxed for 16 h. The solvent was removed under vacuum. The solid was washed with water and dried. Yield 0.936 g (94%) of **5**, mp 150-166°C (acetone). IR spectrum (cm^{-1}): 3520 (OH), 1705 (C=O). ^1H NMR spectrum (δ, ppm): 0.54 (H-3β, t, J = 4 Hz), 0.68 (18-Me, s), 1.07 (19-Me, s), 2.12 (21-Me, s), 3.28 (H-6α, m, W/2 = 7 Hz).

Reaction of 3α,5-Cyclo-5α-pregnan-6β-ol-20-one (2) with Trifluoroperacetic Acid. Trifluoroacetic anhydride (1.34 ml) was dissolved in methylenechloride (10 ml) and treated slowly with stirring and cooling on an ice bath with hydrogen peroxide (0.74 ml, 30%). The resulting solution of trifluoroperacetic acid was treated first with **2** (0.4 g) in methylenechloride (10 ml) and then with $Na_2HPO_4 \cdot 12H_2O$ (1.0 g). The reaction mixture was stirred at room temperature for 21 h and filtered through a layer of aluminum oxide. The filtrate was evaporated under vacuum. The solid was chromatographed on a silica-gel column with elution by hexane: ether (3:1 and then 1:1) and finally pure ether. Two fractions were obtained: fraction 1, 0.050 g (7%) of **3**; fraction 2, 0.189 g (34%) of **4**.

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