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AN UNUSUAL CLEAVAGE OF RING D IN Δ^{14}-17-KETO STEROID AFTER A REACTION WITH ALKALINE HYDROGEN PEROXIDE

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Summary: Three new products of ring D cleavage of 3β-acetoxy-5α-androst-14-en-17-one with alkaline H_2O_2 were isolated and chemically identified.

Ring D in 17-keto steroids is susceptible to cleavage by reaction with hydrogen peroxide, peracids or similar reagents. Reaction of 3β-acetoxy-5α-androstan-17-one with O-nitrobenzylaldehyde and alkaline H_2O_2 caused cleavage of ring D and formation of the steroidal dicarboxylic acid, 3β-acetoxy-15, 17-seco-D-nor-5α-androstane-15, 17-dioic acid[1,2]. Baeyer-Villiger reaction also caused cleavage of ring D[3-7]. This reaction has two steps. In the first step, the 17-keto steroid is reacted with peracetic acid (CH_3COOOH) to form a six-membered lactone ring from ring D. In the second step, this lactone is opened after alkaline hydrolysis to give the hydroxyl and carboxylic acid functions. In such a cleavage of ring D, the hydroxyl group is located at position 13 and the carboxylic acid at position 16[3-7]. Reaction between 3β-acetoxy-5α-androst-14-en-17-one (1) and ozone gave the ozonide. Hydrogenolysis of the ozonide with H_2/Pd yielded cleavage of ring D at this bond[8].

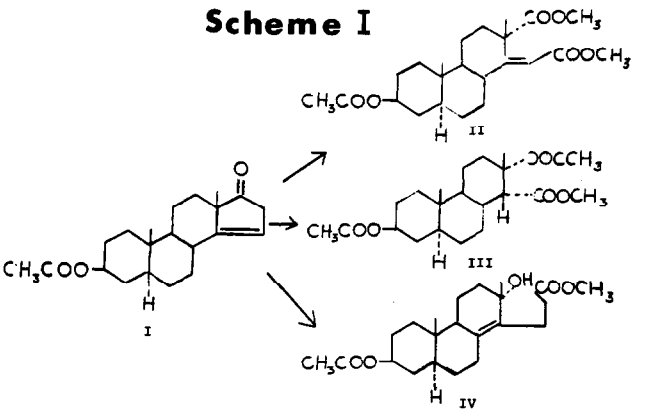
Reaction of (1) and H_2O_2 in the presence of an excess of a 4N NaOH solution caused formation of two new fractions[9]: neutral (15%) and acidic (85%). The same two fractions were obtained in a similar yield by a reaction between compound (I) and H_2O_2 in the presence of a methanolic solution of KOH[10].

The acidic fraction was esterified with CH_2N_2 and acetylated with Ac_2O and pyridine. This fraction was chromatographed and three products were isolated, purified and their chemical structures established. Evaluation of the spectrophysical data of these three products led to the assignment of the chemical structures of compounds (II), (III), and (IV), (Scheme I).

Compound (II) had a UV spectra with λmax-225 nm (ε 6,700) typical of α,β unsaturated methyl esters. Its IR indicated the presence of methyl esters, an acetate function and a double bond. The NMR indicated the presence of a single vinyl hydrogen (δ = 5.62), one acetate (δ = 1.96) and two methyl ester groups (δ = 3.60, 3.62). These spectrophysical data established the double bond between C-14 and C-15.

The highest fragment in the mass spectrum of compound III (M-HOAc-334) showed a loss of two carbons. Compound III was formed via a surmised intermediate in which isomerization of the double bond from positions 14,15to 15,16 tooks place analagous to the isomerization of Δ^{14}-17-ketosteroids to 14β-Δ^{15}-17-ketosteroids[11-14]. Oxidative cleavage of the proposed intermediate led to the formation of compound III without changing the 14β configuration (Scheme II). The NMR of compound III indicated the presence of two acetate groups (δ=2.02)

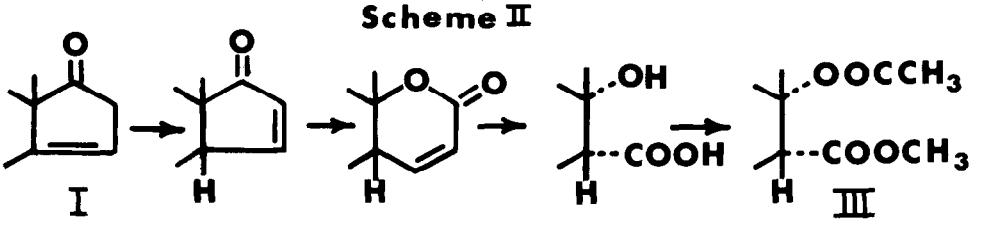
Scheme I



and a methyl ester (δ=3.44). The proton at C-14 appeared at 2.02 ppm. The proton at 14α in 17 mono alcohol analog was reported to be at 2.2 ppm[2].

The NMR of compound IV showed the presence of a methyl ester (δ=3.71) and an acetate group (δ=1.96). No vinyl protons were seen in the NMR, indicating a migration of the double bond to positions 8, 14 during the reaction. The IR indicated the presence of a free hydroxyl moiety, a double bond, methyl ester and acetate groups. Mass spectrum (M=358) confirmed the assignment of structure (IV). Compound (IV) was found by TLC to be the most polar of the three products. It was concluded that compound (IV) has a free hydroxyl group at position 13 which was not acetylated due to steric hindrance. The isolation and identification of compounds II, III, and IV indicate that the reaction between androst-14-en-17-one and alkaline H_2O_2 cause isomerization or epoxidation followed by oxidative cleavage.

Scheme II



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