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ELIMINATION OF 14ß-HYDROXY-12-MESYLOXY-5ß-STEROIDS

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Abstract: Elimination of a 12α-methanesulfoxy group in 3ß-acetoxy-14ß-hydroxy-12α-mesyloxy-5ß-androstane-17ß-carboxylic-acid-14ß-lactone under preventing Wagner-Meerwein rearrangements by steric fixation, is reported. Furthermore, the synthesis of this compound and the different elimination behaviors in the 12α- and the 12ß-isomers are described.

Elimination of 12-sulfoxy-groups in steroids for introduction of 11(12)-double-bonds is an important procedure in organic syntheses[1]. The major products, however, are Wagner-Meerwein rearranged products[2]. Reactions of 12ß-mesyloxy- or 12ß-tosyloxy steroids, especially in 5ß,14ß-hydroxy-cardenolides- and pregnanes gave high yields of rearranged products[3]. Instead of developing appropriate reagents and conditions for the introduction of the double-bond, we tried to modify the steroid in order to prevent undesired side reactions. We would now like to report that this rearrangement can be supressed, if the reaction is carried out with the 14ß,20-lactone, where the D-ring is fixed in a rigid conformation. The correspondent 12-mesyloxy,14ß,20-lactones were synthesized in the following way (scheme I):

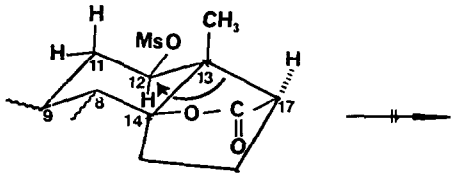
Oxidation of digoxin 1[4] using a modified procedure in DMF with CrO_3[5], resulted, after 30h, in a yield of 60% in 2, mp 270-272°C. By acetylation to 3 and degradation of the side-chain with $KMnO_4$[6], up to 52% of the 17ß-carboxylic-acid 4 was obtained, mp 235-238°C. After stirring 4 in THF with a slight excess of carbonyldiimidazol (CDI) for 1h, an excess of NaH was added and allowed to react for 1 more hour to yield 85% of the 14ß,20-lactone 5, mp 176-178°C.

This cyclization was carried out first with 11-oxo-14ß-hydroxy-20-carboxylic-acids using acetic anhydride/pyridine, by heating the reaction mixture under reflux[7]. Our conditions are smoother and can also be used for the lactonization of the 3ß,12ß,14ß-trihydroxy-5ß-androstane-17ß-carboxylic-acid

to the 3ß,12ß,14ß-trihydroxy-5ß-androstane-17ß-carboxylic-acid-14ß-lactone without acetylation of the alcohols.

Reduction with $NaBH_4$ led to a mixture of the 12α- and 12ß-alcohols 6, mp 154-156°C and 7, mp 202-203°C. The yields of the 12α-alcohol increased, depending upon the solvent, in the following sequence: butanol(27%), ethanol (33%), THF(70%). Sulfonation of the equatorial 12ß-alcohol 7 in pyridine with methane-sulfonyl-chloride is achieved quantitatively within 30 min. to 8, mp 199-201°C (scheme II). After heating 8 in collidine under reflux for 40h, only the unchanged starting material was recovered. Sulfonation of the axial 12α-alcohol 6 to 9 is achieved quantitatively with methane-sulfonyl-chloride/pyridine in 12h, mp 155-158°C. The increased reaction time is required, due to the steric hindrance of the axial hydroxy group. Elimination of 9 in collidine under reflux for 30h yielded 72% of the desired product 10, mp 180-181°C.

Obviously, it is possible to suppress the rearrangement[3] by steric fixation of the D-ring. Usually, the elimination of the sulfoxy-ester with following rearrangement is carried out with high yields within 1h. In the sterically fixed conformation of the 14ß,20-lactone, the C-17 carbon is not able to attack the C-12 position anymore:



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The prevented development of the 11(12)-double-bond in the 12ß-mesyloxy compound 8 is due to the low elimination tendency in the trans-diequatorial position of the ß-hydrogen and the sulfoxy-ester. In contrast to this observation, elimination of the 12α-mesyloxy-group 9 is possible, because of the trans-diaxial positions of the leaving groups.

All the substances described, were characterized via C,H analysis and their NMR spectra[8].

Further studies in using this valuable reaction for synthesis of 14ß-hydroxy-steroids, which are known to possess biological activity, are in progress.

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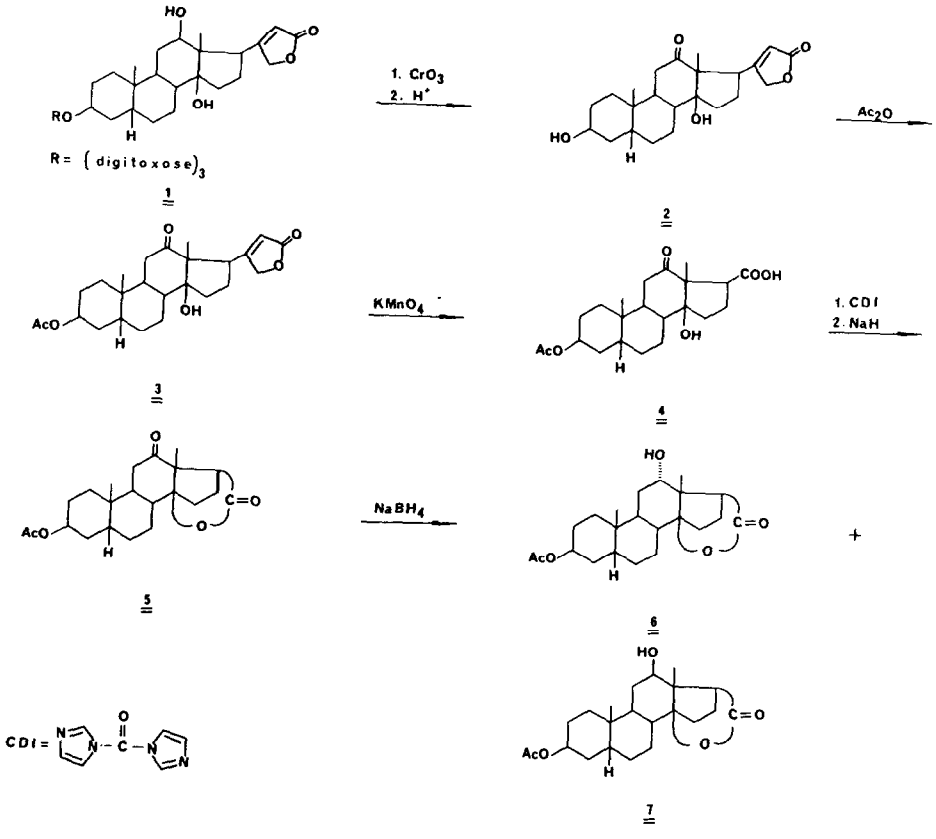
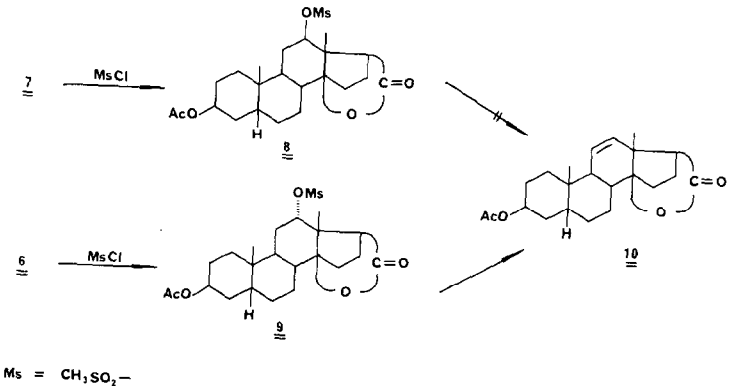
Scheme I



Scheme II



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8. ^{1}H-NMR data (300 MHz, $CDCl_3$): 4 δ=1.0(s,3H,H-19), 1.2(s,3H,H-18), 3.9 (d,d,1H,J=4.5Hz,J=9Hz,H-17), 5.1(pseudo s,1H,H-3); 5 δ=1.1(s,3H,H-19) 1.25(s,3H,H-18), 2.95(pseudo d,1H,H-17), 5.1(pseudo s,1H,H-3), 6 δ=1.0 (s,6H,H-18 and H-19), 2.05(s,3H,CH_3COO), 2.8(pseudo d,1H,H-17), 4.1 (pseudo s,1H,H-12), 5.1(pseudo s,1H,H-3); 7 δ=1.05(s,6H,H-18 and H-19), 2.05(s,3H,CH_3COO), 2.8(pseudo d,1H,H-17), 3.75(d,d,1H,J=5Hz,J=11Hz, H-12), 5.1(pseudo s,1H,H-3); 8 δ=1.1(s,3H,H-19), 1.15(s,3H,H-18), 2.05 (s,3H,CH_3COO), 2.9(pseudo d,1H,H-17), 3.1(s,3H,CH_3SO_2), 4.85(pseudo d, 1H,H-12), 5.1(pseudo s,1H,H-3); 9 δ=1.0(s,3H,H-19), 1.15(s,3H,H-18), 2.05(s,3H,CH_3COO), 2.88(pseudo d,1H,H-17), 3.05(s,3H,CH_3SO_2), 4.9 (pseudo s,1H,H-12), 5.1(pseudo s,1H,H-3); 10 δ=1.0(s,3H,H-19), 1.1(s, 3H,H-18), 2.05(s,3H,CH_3COO), 2.7(pseudo d,1H,H-17), 5.1(pseudo s,1H, H-3), 5.5(d,1H,J=4Hz,H-12), 5.75(d,d,1H,J=4Hz,J=9Hz,H-11).

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