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INTRAMOLECULAR CYCLIZATION OF STEROIDAL DIKETO-ALDEHYDES TO ACETALS

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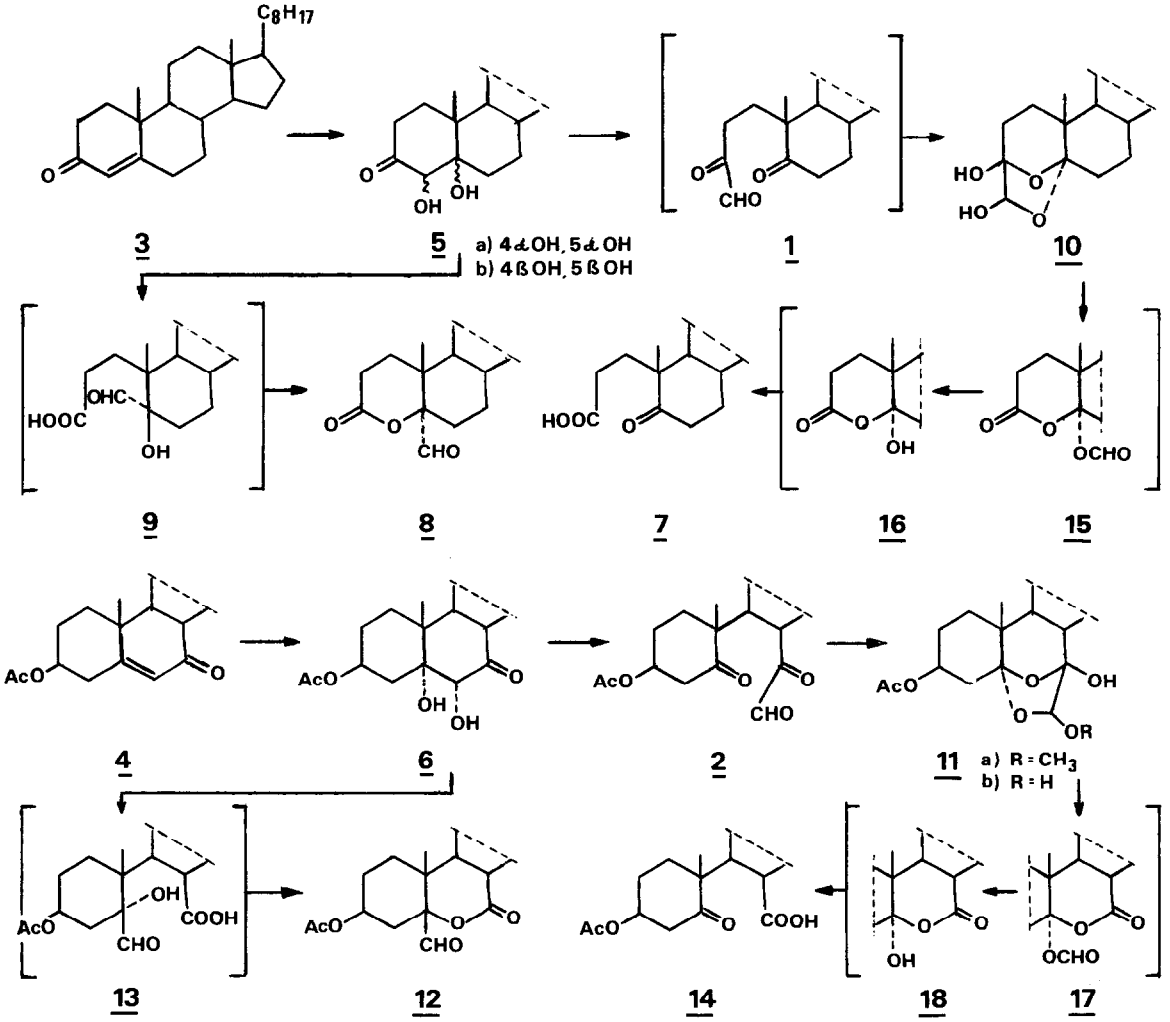
Abstract: The oxidative cleavage of rings A and B of steroidal keto-diols 5 and 6 led to the corresponding diketo-aldehydes 1 and 2. Compounds 1 and 2 spontaneously cyclized to acetals 10 or 11, respectively.

We have been interested in the synthesis of diketo-aldehydes 1 and 2 as intermediates required for the synthesis of heterocyclic steroids. As an attempt to prepare these intermediates conjugated ketones 3 and 4 were converted to the respective keto-diols 5 and 6 [1,2] which were treated with periodic acid and independently with lead tetraacetate. However, instead of the desired diketo-aldehydes 1 and 2, unexpected and interesting cyclized products were obtained.

Treatment of the mixture of isomeric keto-diols 5 with periodic acid in methanol gave two known compounds: keto-acid 7 [3] (85 %) and lactone-aldehyde 8 [4] (10 %). Compound 8 apparently derived by the cyclization of the intermediate hydroxy-aldehyde-acid 9 which was formed by cleavage of $C_{(4)}-C_{(5)}$ bond in one of the isomeric keto-diols 5. Trans fusion of the six-membered lactone and B ring showed that lactone-aldehyde 8 could be formed from keto-diol 5b with 4β and 5β hydroxyl groups.

When keto-diols 5 were treated with lead tetraacetate in benzene in the presence of glacial acetic acid keto-acid 7 (10%) and acetal 10 (70%) were formed. The structure of product 10 was established by its elemental analysis and ir, ^{1}Hnmr and ^{13}Cnmr spectra.[5] The configuration at C-3 and C-4 atoms was established by a novel method consisting in Cotton's effects studies of transition metal complex with diols.[6] A fusion of the acetal and B ring was confirmed by nOe's effect between 4-H and 2α-H. The elucidation of the structure of acetal 10 will be a subject of a separate paper.[7]

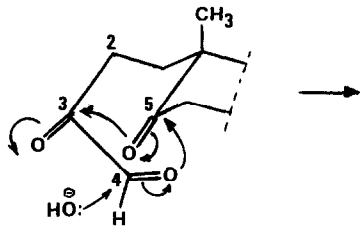
The keto-diol 6 treated with periodic acid in methanol afforded methoxy--acetal 11a (10%) and 3β-acetoxy-lactone-aldehyde 12 [8] (80%). Structures of compounds 11a and 12 followed from their analytical and spectral data. [5] Treatment of keto-diol 6 with lead tetraacetate in benzene and methanol (10:1) gave a mixture of methoxy-acetal 11a (70%), acetal 11b (15%) and known keto-acid 14 [9] (6%), whereas a similar reaction without methanol afforded acetal 11b (78%) and keto-acid 14 (15%). Analytical and spectral data of 11b indicated the presence of hydroxyl groups and acetal rings. [5] The configurations at C-5 and C-6 atoms were assigned by CD method as in analogical acetal 10. [7] Application of nOe's effect between 6-H and 9α-H protons to determine the fusion of acetal and B rings shown that the molecular conformation of compound 11b to be as pictured below. It should be noted that the structure of acetal 11b is similar to that for acetal 10.



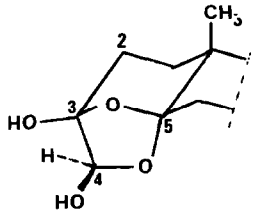
In order to gain more information about the cyclization reaction further oxidations of acetals 10 and 11b with lead tetraacetate were carried out. In both cases the oxidation reaction led to known keto-acids 7 and 14, respectively. It suggested that the formation of these compounds, during the reaction of keto-diols 5 and 6 with lead tetraacetate must arise not directly, but via intermediates 15 and 16 or 17 and 18, respectively.

In order to obtain evidence for the formation of acetals 10 and 11b various modifications were tried. When keto-diols 5 were treated with lead tetraacetate in benzene without glacial acetic acid the same product 10 as in the previous experiment was obtained. Inspection of the course of the reaction by tlc analysis showed the presence of a non-polar product in the reaction mixture. However, attempts of isolation of this compounds failed and only acetal 10 was isolated. When keto-diol 6 was treated in similar manner diketo-aldehyde 2 was formed in 81% yield. ^{1}Hnmr spectrum showed that compound 2 is a mixture of two conformers as it is pictured below. The diketo-aldehyde 2 appeared sensitive to chromotography being readily cyclized to acetal 11b.

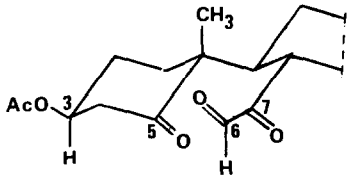
In view of the above findings it is evident that acetals 10 and 11b are formed by cyclization of diketo-aldehydes 1 and 2, respectively, as it is presented below.

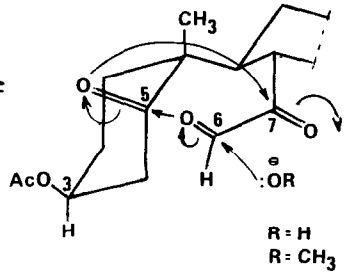


1



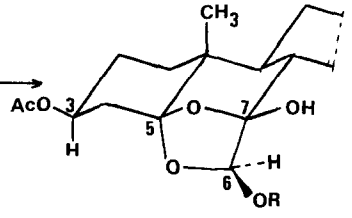
10





R = H
R = CH_3

2



11 a) R = H
b) R = CH_3

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References and Notes

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3. J.T. Edward, D. Holder, W.H. Lunn and I. Puskas, Can.J.Chem., 39, 599(1961).

4. J.T. Pinhey and K. Schaffner, Tetrahedron Lett., 10, 601(1965).

5. Physical properties and spectral data of new compounds, 10: mp. 165-167 C, $[\alpha]_D^{24}$ +5.1 , IR ν_{max} (KBr): 3390, 1140 cm^{-1}; ^{1}Hnmr $CDCl_3$, δ (100 MHz): 0.65 (s,3H,18-H), 1.04 (s,3H,19-H), 4.25 (m,1H, disappears on the addition of D_2O, OH), 4.96 (s,1H,4-H); ^{13}Cnmr $CDCl_3$, δ (22.63 MHz): 111.20 C-5, 102.62 C-3, 92.6 C-4. 11a: mp. 168-169 C, $[\alpha]_D^{24}$ + 3.9 , IR ν_{max} (KBr: 3400, 1735, 1010 cm^{-1}; ^{1}Hnmr $CDCl_3$, δ (100 MHz): 0.71 (s,3H,18-H), 1.00 (s,3H,19-H), 2.07 (s,3H,3β -CH_3COO), 2.45 (m,1H,w/2 = 15 Hz, disappears on the addition of D_2O,OH), 4.91 (m,1H,w/2 = 22.5 Hz, 3α-H), 5.01 (s,1H,6-H); ^{13}Cnmr $CDCl_3$, δ (22.63 MHz): 170.67 carbonyl of 3β -acetate, 109.50 C-5, 106.16 C-7 90.37 C-6, 70.98 C-3; 11b: foam, $[\alpha]_D^{23}$ +5,0 , IR ν_{max} (KBr): 3420, 1735, 1010 cm^{-1}; ^{1}Hnmr $CDCl_3$, δ (100 MHz): 0.71 (s,3H,18-H), 1.00 (s,3H,19-H), 2.04 (s,3H,3β -CH_3COO), 3.48 (s,3H,6-CH_3O), 3.90 (s.1H, disappears on the addition of D_2O, OH), 4.60 (s,1H,6-H), 4.94 (m,1H,w/2 = 22.5 Hz, 3α-H); ^{13}Cnmr $CDCl_3$, δ (22.63 MHz): 170.07 carbonyl of 3β-acetate, 109.66 C-5, 104.89 C-7, 96.16 C-6, 70.65 C-3, 54.78 7-CH_3O. 12: mp. 158-160 C, $[\alpha]_D^{25}$ +2.7 , IR ν_{max}(KBr): 1720, 1735, 1740, cm^{-1}: ^{1}Hnmr $CDCl_3$ δ (100 MHz): 0.69 (s,3H,18-H), 1.22 (s,3H,19-H), 2.02 (s,3H,3β -CH_3COO), 5.15 (m,1H,w/2= = 12Hz, 3α-H), 9.65 (s,1H,CHO).

6. J. Frelek and G. Snatzke, Fresenius Z. Anal. Chem., 316, 261(1983).

7. G. Snatzke, H. Duddeck, J. Frelek and Zb. Bończa-Tomaszewski, will be published.

8. Apparently 3β-acetoxy-aldehyde-lactone 12 must arise in the analogical way as 8 by cyclization of intermediate 13 which was formed by the cleavage of $C_{(6)}$ -$C_{(7)}$ bond in keto-diol 6.

9. B.S. Wildi, U.S. Patent 2, 897, 202(1959); C.A. 54, 646(1960).

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