DES-AB-STEROIDS BY A NEW METHOD OF CHOLESTEROL DEGRADATION†

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Abstract - A two-step procedure for Westphalen diol diacetate 1 fragmentation to keto-aldehyde 5 and (4S)-4-hydroxy-2-methylcyclohexanones (6a and 6b) has been developed. Ozonolysis of a double bond in 1 followed by retroaldolization afforded compound 5 in 42 % yield.

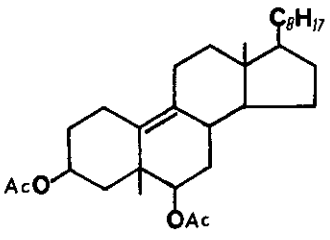
In our search[1,2] for an even better route to des-AB-steroids, and bearing in mind their potential application in the synthesis[3] of vitamin D derivatives, we turned our attention once again to Westphalen rearrangement[4] product 1. This compound seemed to be very convenient for the purpose of degradation since it contains a $C_{(9)}$-$C_{(10)}$ double bond and a functional group at C-6. Although the cleavage of the double bond does not present any problems (it can be achieved by ozonolysis in a high yield[5]) the further degradation of 2 by fission of either the $C_{(5)}$-$C_{(6)}$ or $C_{(6)}$-$C_{(7)}$ bond proved to be rather difficult.[6] The β-hydroxy-ketone system in 2 should, in principle, undergo retroaldolization[7] under basic conditions. However, the first attempt[5] undertaken many years ago was unsuccessful. The starting material for this reaction was, unfortunately, 6β-hydroxy-10-ketone 3 with a 9β-methoxyl group. The failure of the reaction was probably due to an intramolecular hydrogen bond between the 6β-hydroxyl group and an ether oxygen at C-9 rendering the hydroxyl proton less accessible.

In this communication, we report the results of our investigations of the compound 2a reaction with NaOH/MeOH/H_2O or NaOMe/MeOH. The first experiment carried out with a large excess of sodium hydroxide in aqueous methanol at reflux (1h) was not promising. A complex mixture of many products of either neutral or acidic character was obtained. For this reason in the next attemp only two equivalents of NaOH in MeOH/H_2O and much milder reaction conditions (room temperature, 0.5 h) were applied. The major product of the reaction (about 70 %) was 6-monoacetate 2b. The acetate group at C-6 is more resistant to hydrolysis than that at C-3 owing to the steric hindrance. However, by using more base (preferably MeOMe/MeOH) and a longer reaction

†Dedicated to Professor Sir Derek Barton on the occasion of his 70th birthday.

time, the 6-acetate group can be hydrolyzed. The structure of the product depends on the isolation method but it is never 2c. If the reaction mixture containing methanol was poured into water, acidified and extracted with chloroform the product was acetal 4a. When methanol was removed from an alkaline medium before extraction, the reaction product appeared to be a mixture of hemiacetals 4b and 4c. In a separate experiment the hemiacetal mixture in methanol solution was treated with a drop of concentrated hydrochloric acid to afford a single stereoisomer of methyl acetal 4a, presumably a more thermodynamically stable 9R-epimer. The mixture of 4b and 4c can never be obtained by hydrolysis of 2a or 2b in more than 35 % yield. This is due to its fragmentation proceeding under the reaction conditions and the side reaction accompanying the hydrolysis of 6-acetate, i.e. an intramolecular acetyl transfer (see below). The fragmentation of the hemiacetal mixture by a retroaldol mechanism shown in the Scheme (A) becomes significant on prolonging the reaction time. The products of fragmentation are: keto-aldehyde 5 (45%), (2R,4S)-4-hydroxy-2-methyl-cyclohexanone 6a (35%) and (2S,4S)-4-hydroxy-2-methylcyclohexanone 6b (31%) - the epimeric relationship between the two latter compounds was proved by their mutual equilibration under basic conditions (sodium methoxide in methanol at reflux). The total yield of the ring A fragments is higher than that of keto-aldehyde 5, which can be explained on taking into account the relative unstability of 5 in the reaction mixture (for this reason too high a concentration of the base and too long a reaction time should be avoided). The rate of retroaldolization considerably increases with the water content in the reaction mixture. However, the step determining the rate of the whole process (from 2a to the fragmentation products) is probably the slow hydrolysis of 6-acetate. In the latter reaction a stabilized carbanion at C-1 may compete successfully with a hydroxide (or methoxide) ion in a nucleophilic attack on an acetate carbonyl. This leads to an unusual reaction consisting in an intramolecular acetyl transfer from oxygen to carbon through a cyclic six-membered transition state (B in the Scheme). However, the β-diketone (C) obtained in such a way cannot be isolated from the reaction mixture since it immediately undergoes a nucleophilic attack on C-10 (probably in the intramolecular reaction with an alkoxyl ion derived from 3β-OH) with a cleavage of the $C_{(1)}$-$C_{(10)}$ bond. The mechanism suggested above explains the formation of a five-membered lacton 7 (as an epimeric mixture) or the corresponding hydroxy-carboxylate (in the case of an aqueous reaction medium) affording 7 on acidification. The yield of the by-product described usually does not exceed 10 % and it is easily removable from the reaction mixture by simple extraction.

SCHEME:



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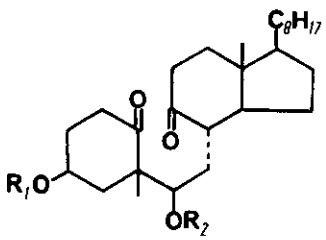
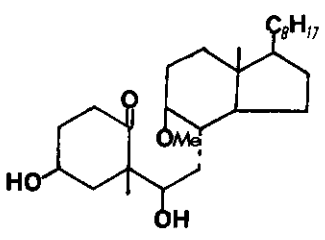


2a: $R_1=R_2$=Ac
b: R_1=H; R_2=Ac
c: $R_1=R_2$=H



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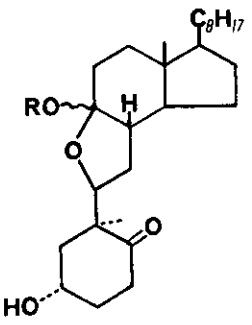
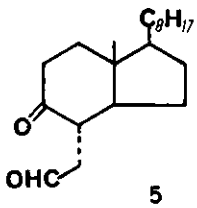


4a: R=Me (9R)
b: R=H (9R)
c: R=H (9S)



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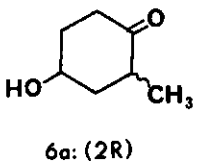
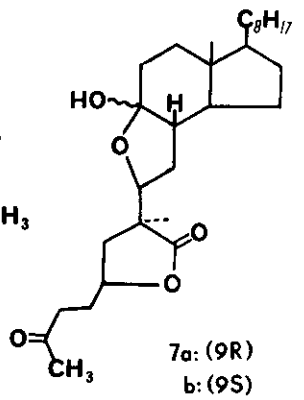
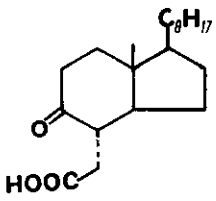


6a: (2R)
b: (2S)



7a: (9R)
b: (9S)



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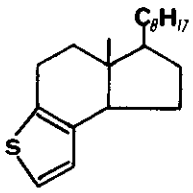

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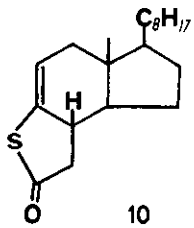

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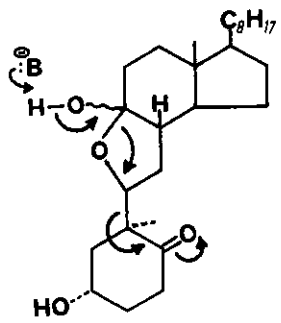
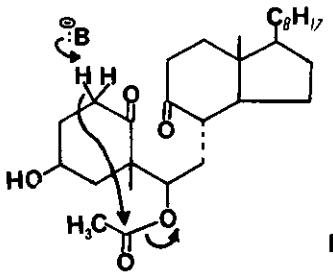
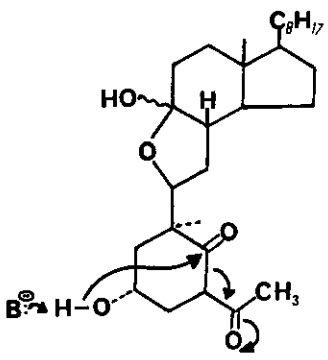


A



B



C

The most important product of retroaldolization, keto-aldehyde 5, appeared to be air sensitive. When allowed to stand in benzene solution in an open flask, it underwent entirely autoxidation to keto-acid 8 within one week. The presence of a 1,4-dicarbonyl system in the keto-aldehyde 5 was confirmed by its reaction with phosphorus pentasulphide.[8] The reaction afforded a thiophene derivative 9 in an almost quantitative yield. Keto-acid 8 with the same reagent gave unsaturated thiolactone 10.

Further investigations on the possible application of the above compounds in the synthesis of vitamin D_3 relatives are being carried out.

The Spectroscopic Data of the Potential CD Fragments for the Synthesis of Vitamin D_3 Relatives

Compound No.	Ir ($\nu_{max}^{CCl_4}$; cm^{-1})	^{1}H-Nmr (δ, $CDCl_3$)	Ms (70 eV; m/z)	Uv (λ_{max}^{EtOH})
5	1706, 1717 (ketone and aldehyde C=O), 2713 (aldehyde C-H)	9.77 (m, w/2 = 3.5 Hz, -CHO), 1.02 (s, 18-H)	306 (M^+, 9%), 278 (M^+-CO, 100%), 264 (M^+-CH_2=C=O, 29%), 193 (M^+-C_8H_{17}, 29%)	-
8	1707 (ketone and acid C=O), 2500-3300 (COOH)	8.43 (broad band, -COOH), 1.01 (s, 18-H)	322 (M^+, 72%), 304 (M^+-H_2O, 44%), 263 (M^+-CH_2COOH, 100%)	-
9	853, 2925 (C-H)	7.05 (d, J = 5 Hz, 6-H), 6.73 (d, J = 5 Hz, 7-H), 0.62 (s, 18-H)	304 (M^+, 20%), 191 (M^+-C_8H_{17}, 10%), 94 ($C_7H_{10}^+$, 100%)	238 nm (ε=4900)
10	1640 (C=C), 1724 (C=O)	5.67 (m, w/2 = 9 Hz 11-H), 0.76 (s, 18-H)	320 (M^+, 100%) 207 (M^+-C_8H_{17}, 17%)	219 nm (ε=2900) 255 nm (ε=1500)

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