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5,10-SECO-STEROIDS, A NEW TYPE OF STEROID DERIVATIVES CONTAINING A TEN-MEMBERED RING[a]

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We wish to report the preparation of a new type of polycyclic compounds derived from steroids, i.e. the 5,10-seco-steroids, containing a medium-sized ten-membered ring instead of the two fused cyclohexane rings A and B. These compounds were obtained by applying the lead tetraacetate reaction to 5-hydroxy-steroids, fragmentation occurring, as expected from our previous studies(1), between the carbinol carbon atom in position 5 and the adjacent quaternary carbon atom in position 10.

Thus, by treating 3β-acetoxycholestan-5α-ol (I) with one molar equivalent of lead tetraacetate in boiling benzene in

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[a]Paper II of the series Reactions with Lead Tetraacetate. For paper I see V. M. Mićović, R. I. Mamuzić, D. Jeremić and M. Lj. Mihailović, Tetrahedron Letters No. 29, 2091 (1963).

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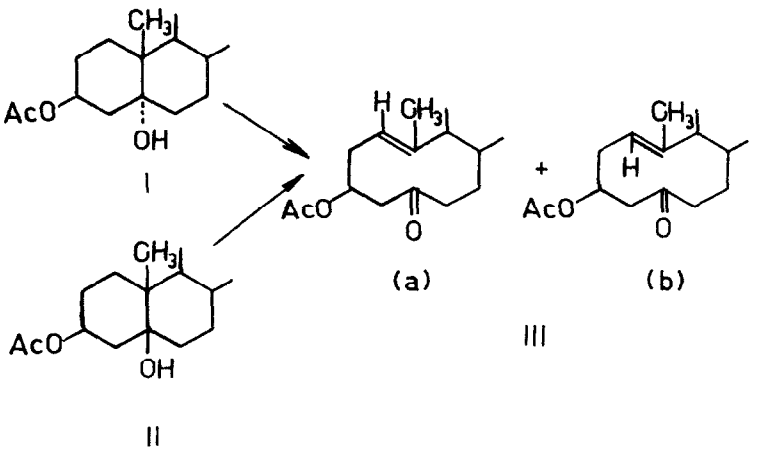
the presence of anhydrous calcium carbonate, and after chromatography of the crude reaction mixture, beside small amounts of cholestan-3β-yl acetate and cholesteryl acetate (total yield 6%), two major products were isolated in a total yield of 49%, which according to analytical data[d] and physical evidence (IR and NMR spectra) are the geometrical isomers of 3β--acetoxy-5,10-seco-$\Delta^{1(10)}$-cholesten-5-one (IIIa and IIIb).[e] In addition, about 30% of unreacted alcohol (I) was recovered from the reaction mixture. 3β-Acetoxycholestan-5β-ol (II) reacted with lead tetraacetate in the same way as its epimer (I) and afforded the 5,10-seco compounds (IIIa and IIIb) in comparable yields.



[d]Satisfactory analytical data were obtained for all new compounds.

[e]These stereoisomers are designated in the text as B and M compounds, since the configuration on the $\Delta^{1(10)}$-double bond was not definitely established.

The unsaturated 5,10-seco-acetoxy-ketone B (III; a or b) was obtained in 17% yield from alcohol (I); m.p. 138°; $[\alpha]_D$ +31° (c = 1.61, chloroform; IR (KBr) 1739, 1709 and 1250 cm^{-1}. Oxime, m.p. 158-159°; IR (KBr) 3390, 1745 and 1238 cm^{-1} (no ketone band). Upon mild hydrolysis, compound B was converted to the corresponding unsaturated 5,10-seco-hydroxy-ketone, m.p. 116-118°; IR (KBr) 3279 and 1695 cm^{-1} (no acetate bands).

The stereoisomeric unsaturated 5,10-seco-acetoxy-ketone M (III; a or b) was obtained in 32% yield from alcohol (I); m.p. 136°; $[\alpha]_D$ +3° (c = 3.03, chloroform); IR (KBr) 1733, 1709 and 1238 cm^{-1}. Oxime, m.p. 141-142°; IR (KBr) 3448, 3247, 1739 and 1248 cm^{-1} (no ketone band). When hydrolized under mild conditions, acetoxy-ketone M gave the corresponding 5,10-seco-$\Delta^{1(10)}$--cholesten-3β-ol-5-one, m.p. 158°; IR (KBr) 3448 and 1698 cm^{-1} (no acetate bands).

Confirmation of the 5,10-seco-$\Delta^{1(10)}$-structure (III) for the acetoxy-ketones B and M follows from measurements of NMR spectra, using double irradiation. Spectra of both B and M compounds show the presence of a vinyl proton (quartet at δ = 5.25 for isomer B and at δ = 4.81 for isomer M), thus eliminating the possibility that one of the seco products might be the stereoisomeric $\Delta^{9(10)}$-compound. The 100 m.c. spectra with double resonance indicate that the 19-methyl group at δ = 1.72 (for compound M) and δ = 1.73 (for compound B) is coupled with the vinyl proton, the order of allylic coupling being 0.5 to 1.5 c.p.s; decoupling by irradiation at the frequency of the 19--methyl group results in the sharpening of the vinyl proton quartet in both spectra. Therefore the grouping  must be present in compounds B and M.

Although further evidence is necessary in order to ascertain the stereochemistry of the $\Delta^{1(10)}$-double bond in compounds B and M (III), it should be noted that a difference of 0.4

p.p.m. was observed for the two vinyl protons, the proton of product B being in the "normal" position and the corresponding proton of product M having moved upfield. According to Dreiding models, in the stable conformation of the cis isomer (IIIa) the vinyl proton should be oriented outside of the ten-membered ring and therefore in a "normal" position in the NMR spectrum, while in the trans isomer (IIIb) the vinyl proton is expected to lie just above the carbonyl double bond of the keto group, i.e. in the region of positive shielding, suggesting that the 1,10-seco-acetoxy-ketone B might be the cis isomer (IIIa) and the acetoxy-ketone M the trans isomer (IIIb)

With a view to investigate the chemistry and biological properties of stereoid derivatives containing medium-sized rings, we intend to continue our studies on 5,10-seco-steroids and to apply the lead tetraacetate reaction to the synthesis of 13,14-seco-steroids.[f]

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[f] A previous attempt to convert 3,5-cyclo-6β-methoxy-17β-tosyloxyandrostan-14α-ol, by reaction with base, to the corresponding 13,14-seco-derivative failed, 3,5-cyclo-6β-methoxy-Δ^{14}-androsten-17β-ol being obtained instead.[2]

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