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ADDITION TO STEROID POLYENES IV[1]

Ring D-fission and ring C-aromatisation in 4,4-dimethyl-$\Delta^{5,7}$-steroidal systems

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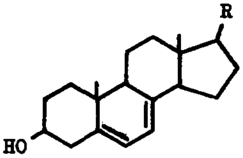
In the course of our investigations on addition of dimethyl-azodicarboxylate to steroidal polyenes[3] the latter reaction has been carried out with a number of 4,4-dimethyl-$\Delta^{5,7}$-dienes, the results of which will be published in the near future.

During these investigations a remarkably facile C_{13}-C_{17} bond fission has been observed, which in acidic medium occurs to 4,4-dimethyl-$\Delta^{5,7}$-progesterone in high yield, under relatively mild reaction circumstances. In this communication a description of this fission process, which is followed by ring C-aromatization, will be given.

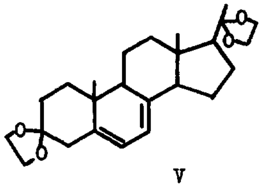
Oxidation of 7-dehydrocholesterol (Ia) with aluminium isopropoxide/cyclohexanone in toluene[4] gave a mixture of the dienones IIa [$\nu_{\max}^{KBr}$ 1660 cm^{-1} (carbonyl); $\delta_{CDCl_3}^{TMS}$ 0.59 singlet (C_{18}-CH_3), 1.15 singlet (C_{19}-CH_3)] and IIIa [$\nu_{\max}^{KBr}$ 1700 cm^{-1} (carbonyl); $\delta_{CDCl_3}^{TMS}$ 0.59 singlet (C_{18}-CH_3), 1.15 singlet (C_{19}-CH_3)], which upon methylation with methyliodide/potassium butoxide[5] afforded the 4,4-dimethyl-5,7-diene IVa[6] [m.p. 156-158°; $\nu_{\max}^{KBr}$ 1700 cm^{-1} (carbonyl); $\delta_{CDCl_3}^{TMS}$ 0.59 singlet (C_{18}-CH_3), 1.15 singlet (C_{19}-CH_3); $\lambda_{\max}^{EtOH}$ 273 (9.700), 282 (10.000), 294 (5.500) nm] in high yields.

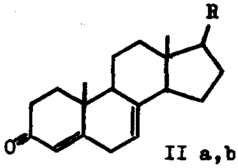
Oxidation of ergosterol (Ib) gave the dienone IIb[7] [m.p. 128-131°; ν^{KBr}_{max} 1660 cm^{-1} (carbonyl); $\delta^{TMS}_{CDCl_3}$ 0.61 singlet (C_{18}-CH_3), 1.16 singlet (C_{19}-CH_3); λ^{EtOH}_{max} 236 (18.400) nm] as a single product[8], which upon methylation afforded the 4,4-dimethyl-5,7-diene IVb*, m.p. 163-165°; the spectral data were identical with the corresponding ones of IVa.

Finally, the 4,4-dimethyl-$\Delta^{5,7}$-progesterone IVc [m.p. 193-195°; $\delta^{TMS}_{CDCl_3}$ 0.94 singlet (C_{19}-CH_3), 0.56 singlet (C_{18}-CH_3)] was obtained via careful acid hydrolysis of the ketal V[9], followed by methylation of the resulting 4,7-dienone IIc[4] [m.p. 118-120°; ν^{KBr}_{max} 1670 and 1700 cm^{-1} (carbonyls); $\delta^{TMS}_{CDCl_3}$ 0.58 singlet (C_{18}-CH_3), 1.18 singlet (C_{19}-CH_3)].

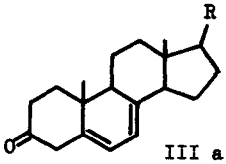


I a,b

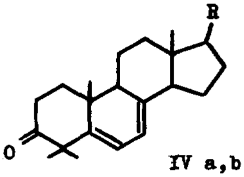

V



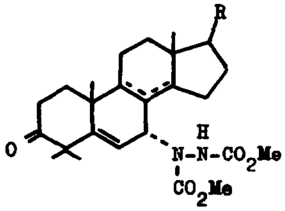
II a,b,c



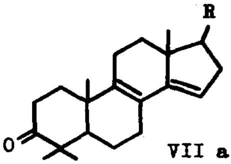
III a



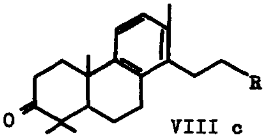
IV a,b,c



VI a,b,c



VII a,b,c



VIII c

a : R = C_8H_{17}

b : R = C_9H_{17}

c : R = $COCH_3$

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* All crystalline compounds gave satisfactory elementary analyses.

Reaction with diazo-ester led in all cases to good yields of the corresponding 7α-adducts (VI a,b,c), which upon acid hydrolysis, however, were not converted into products to be expected in the anthra-steroid rearrangement[3,10].

In connection herewith an eventual acid catalyzed reaction of the starting system IV was further investigated.

In the ergosterol and cholesterol series, a normal rearrangement[11] of the 5,7-double bond system leading to the 8,14-diene systems VIIb [$\delta^{TMS}_{CDCl_3}$ 0.85 singlet (C_{18}-CH_3), 0.85 singlet (C_{19}-CH_3), 5.40 multiplet (vinylic proton)] and VIIa [$\delta^{TMS}_{CDCl_3}$ 0.90 singlet (C_{18}-CH_3), 0.90 singlet (C_{19}-CH_3), 5.40 multiplet (vinylic proton)], was observed in agreement with recent reports on similar bond migrations in 3-desoxy-4,4-dimethyl steroids[12].

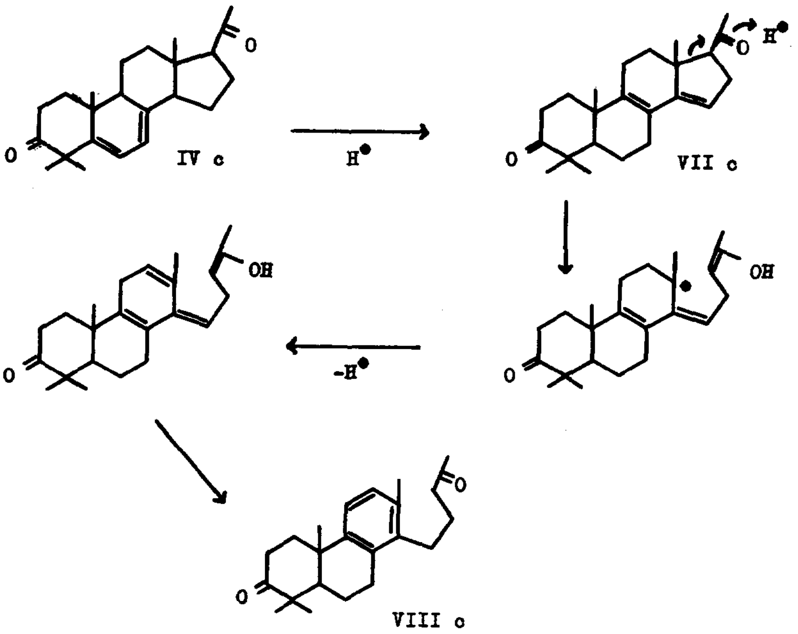
Upon refluxing (10 hrs) the progesterone derivative IVc with hydrochloric acid in methanol a mixture of two compounds A and B was obtained from which A was separated by trituration with n-hexane. Structure VIIc for A, m.p. 138-139°, was supported by the following spectral data : ν^{KBr}_{max} 1705 cm^{-1} (carbonyl); $\delta^{TMS}_{CDCl_3}$ 0.80 singlet (C_{18}-CH_3), 1.11 singlet (C_{19}-CH_3), 5.41 multiplet (vinylic proton); λ^{EtOH}_{max} 248 (15.000)nm.

Prolonged refluxing of IVc under the same reaction circumstances gave an oil, mainly consisting of compound B; in the oil no trace of A could be detected.

Upon heating (30 hrs) of A in methanol/HCl compound B was formed exclusively [m.p. 71-73°; ν^{KBr}_{max} 1696 and 1710 cm^{-1} (carbonyls); $\delta^{TMS}_{CDCl_3}$ 1.27 singlet (C_{19}-CH_3), 2.26 (C_{18}-CH_3), 7.[illegible]0 singlet (with an integrated intensity of two protons); λ^{EtOH}_{max} 267.5 (410)nm]. These data support structure VIIIc for compound B.

Additional evidence for the structure proof was also found in the mass spectrum of B, which possesses a molecular ion peak at m/e 340.

A possible mechanistic description of the conversion of IVc into VIIIc is given in Scheme I, which is based on a β-bond cleavage in acidic medium, originating via protonation of the carbonyl group at C_{20} and formation of the stabilized tertiary C_{13}-carbonium ion. Support for this mechanism is found in the isomerization of the 5,7- to the 8,14-diene system prior to the rearrangement and in the virtual absence of any rearrangement product upon prolonged treatment with methanol/HCl of the dienes VIIa and VIIb. This novel C/D-ring fission in steroidal systems has not



Scheme I

been described in literature thus far, although a similar type of cleavage was recently reported by Cross[13] and Boots[14], while UV-irradiation of C_{20}- and C_{17}-keto steroids is also known to result in C/D-ring fission[15].

Further studies of this type of rearrangement are currently under way in our laboratory.

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