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REACTIONS OF Δ^7-STEROIDS. I. FORMYLATION OF Δ^7-CHOLESTEN-3-ONE

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In the last few years a number of naturally occurring C-4 monomethyl sterols (1) and triterpenes (2) have been isolated from plants and the former have also been extracted (3) from mammalian tissue. The ideas regarding the biogenetic implications of these compounds have been summarized by Richards and Hendrickson (4).

Pudles and Bloch (5) have reported the conversion of 4-hydroxymethylene-Δ^7-cholesten-3-one to CO_2 and cholesterol under aerobic conditions supporting the view that the C-4 methyl group is oxidized prior to elimination. On reinvestigating the structure of this precursor we obtained evidence which indicated the presence of a C-2 substituted compound.

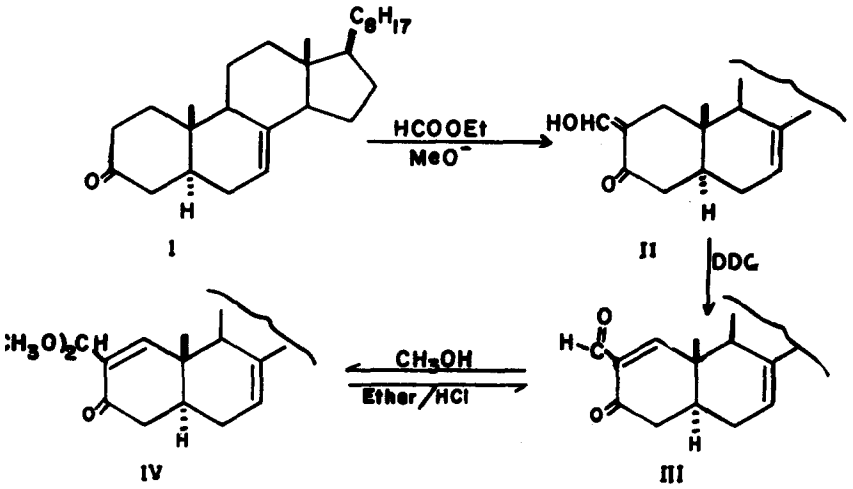
Formylation of Δ^7-cholesten-3-one (I) under the same conditions described by Pudles and Bloch (5) gave the hydroxymethylene compound with the same physical constants reported by these authors. Dehydrogenation of this substance with 1.2 moles of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane at room temperature (6) for 3 minutes gave a 65% yield of a light yellow solid purified by crystallization from aqueous t-butanol (m.p. 137-139°C ; $[\alpha]_D^{CHCl_3}$ + 3°; $\nu_{max}^{CHCl_3}$ 1710, 1678, 1600 cm^{-1}; λ_{max}^{EtOH} 239 mμ, log ε 3.91; in the presence of alkali λ_{max}^{EtOH} 306 mμ, log 4.23; n.m.r. in

$CDCl_3$ 5.25 (singlet 1 H), 7.80 (singlet 1 H) and 10.1 (singlet 1 H) p.p.m. The singlet at 5.25 p.p.m. was assigned to the C-7 proton (cf. 5.19 p.p.m. for I) while the singlet at 7.80 p.p.m. (in good agreement with the value of 7.93 p.p.m. reported by Edwards et al. (7) for 2-formyl-Δ^1-androstene-17β-ol-3-one*) indicates that the α-formyl-α,β-unsaturated ketone obtained must have structure III. The fact that the latter was the only major product of the reaction is strong evidence in favour of structure II for the hydroxymethylene compound.

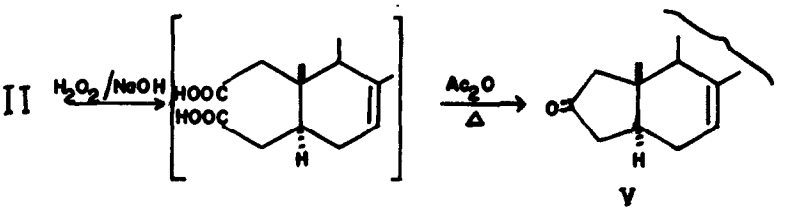
When III was crystallized from methanol, a dimethyl ketal (IV) could be isolated which analysed correctly for $C_{30}H_{48}O_3$ (m.p. 116-117°C; $[\alpha]_D^{CHCl_3}$ + 2°; $\nu_{max}^{CHCl_3}$ 1685, 1120, 1060 cm^{-1}; n.m.r. in $CDCl_3$ 3.36 (singlet 6 H), 5.22 (singlet 2 H), 7.16 (singlet 1 H) p.p.m.). The signal at 5.22 p.p.m. was assigned to fortuitous superposition of the singlets for the proton on the carbon attached to C-2 ($H\text{-}\overset{|}{C}(OR)_2$) and the proton on C-7. By using acetone as solvent, the former was observed at 5.15 and the latter at 5.28 p.p.m. respectively. The free aldehyde III could be regenerated by treating IV with ether saturated with HCl gas.

The crude dicarboxylic acid obtained by treatment of II with alkaline hydrogen peroxide was refluxed with acetic anhydride for 1.5 hours. Subsequent distillation at 280-310°C/.1 mm. yielded an oily liquid which showed one major spot by thin layer chromatography. This substance was unchanged on heating with alcoholic KOH solution. Chromatography over alumina gave an A-nor ketone (correct analysis for $C_{26}H_{42}O$; m.p. 106-107°C;

* We are grateful to Dr. J.A. Edwards (Syntex Research Laboratories, Palo Alto, California) for a sample of this compound for comparison purposes ($\nu_{max}^{CHCl_3}$ 1701, 1681, 1605 cm^{-1}; λ_{max}^{EtOH} 241 mμ, log ε 3.90; in the presence of alkali λ_{max}^{EtOH} 305 mμ, log 4.22).



$[\alpha]_D^{MeOH}$ + 92.5°; $\nu_{max}^{CHCl_3}$ 1725 cm^{-1}) in about 15% overall yield from II. Rotatory dispersion measurement* of this ketone gave a positive Cotton effect curve (c, 0.11 in methanol; $[\Phi]_{700}$ + 70°; $[\Phi]_{589}$ + 342°; $[\Phi]_{307}$ + 11,250°; $[\Phi]_{255}$ - 16,500°; $[\Phi]_{230}$ - 29,200°) in agreement (8) with structure V which could only be obtained from a C-2 substituted precursor.



* Professor W. Ayer (University of Alberta) kindly supplied this measurement.

Formylation of I under the conditions reported (5) is a reversible process (9) and on the basis of the observations published by Barton and his collaborators (10) it is not surprising that substitution occurs at C-2. No analogy can be drawn with the irreversible alkylation reaction (11), in which case convincing conformational arguments have been invoked (10, 12) to explain substitution at C-4.

The fact that cholesterol was obtained from II indicates that either the enzymes are non specific for the C-2 and C-4 positions or else that deformylation occurred without the influence of the enzymes themselves. Experiments are presently underway to clear up this point.

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