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REDUCTIONS OF 3,6-DIMETHOXYESTRAPENTAENE AND 3,6-DIMETHOXYESTRAHEXAENE CARBOXYLIC ACIDS

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Abstract—Palladium hydrogenation of the ester I gave an epimeric mixture II. The dicarboxylic acid diester III on hydrogenation with palladium in ethyl acetate furnished the esters V and VI which were isomerized to X and VII, respectively. The ester VIII, under similar hydrogenation conditions, gave the product IX, which was isomerized to VII. Hydrogenation of the esters V, VI and VII with palladium in acetic acid yielded the corresponding ring *A* tetrahydro compounds.

IN AN earlier paper[2] the preparation of several racemic ring D carboxylic acid derivatives of 3,6-dimethoxy-1,3,5(10),6,8-estrapentaene and 3,6-dimethoxy-1,3,5(10),6,8,14-estrahexaene was described. We now wish to report some reduction products thereof and discuss briefly their stereochemistry.

Hydrogenation of the ester I with palladium charcoal in acetic acid caused saturation of ring *A* with formation of a mixture of 3α and 3β epimers of methyl 3,6-dimethoxy-5(10),6,8-estratriene-17β-carboxylate II (Chart I). The alternative possibility of reduction having taken place in ring *B* and not *A* is not feasible since in naphthalenic steroids ring *A* is always more susceptible to reduction, except when specially prepared Raney nickel is used.[3]

When a solution of dimethyl 3,6-dimethoxy-1,3,5(10),6,8,14-estrahexaene-15,17α-dicarboxylate III[2] in ethyl acetate was hydrogenated in the presence of palladium, there was obtained a mixture of two dihydroesters to which the formulae V and VI are ascribed. These compounds, which were formed by addition of hydrogen from the β and the α side of the molecule, respectively, could be separated by fractional crystallization. A mixture of these two isomers was also obtained by palladium hydrogenation of the Δ^{11} derivative IV[2]. Each of the esters V and VI could be isomerized by treatment with boiling sodium methoxide solution in methanol: the first gave the 15β-isomer X; an isomerization of the 17α-carbomethoxy group is improbable due to the strong interaction of the angular methyl group and a 17β substituent, the two being eclipsed in C/D *cis* steroids.[4] Carbon 15 is the only site, then, where epimerization could have occurred. The second ester (VI) was isomerized at carbons 15 and 17 to afford the 15α,17β-isomer VII; for in C/D *trans* steroids a substituent at carbon 17 is more stable in the β-configuration and a β-substituent at position 15 would interfere with the angular methyl group.

The above considerations were based on the assumption that the isomers VI and

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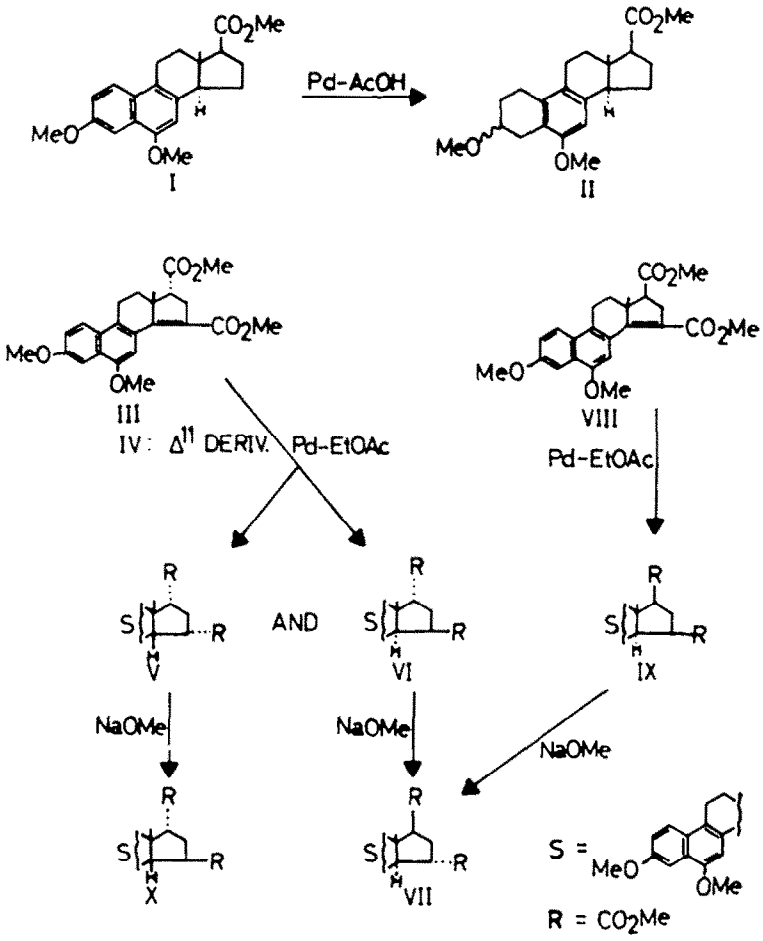
[2] M. Harnik and E. V. Jensen, *Israel J. Chem.* 3, 173 (1965).
[3] W. G. Dauben and L. Ahramjian, *J. Amer. Chem. Soc.* 78, 633 (1956).
[4] L. F. Fieser and M. Fieser, *Steroids* pp. 216–7. Reinhold, New York, N.Y. (1959).

CHART I



VII belong to the C/D *trans* series. This view became substantiated when the hexaene VIII[8] was hydrogenated in ethyl acetate solution in the presence of palladium to a broad-melting solid which must have contained the ester IX, produced by addition of hydrogen to the α side of the molecule. Isomerization of this solid with sodium methoxide gave a high yield of the previously isolated ester VII by inversion at C_{18}, for reasons brought forth at the end of the preceding paragraph.

Finally, several of the 15,17-dicarbomethoxy products obtained above were further reduced with palladium charcoal in acetic acid with saturation of ring *A*. Thus, in the 14-iso series the compound V (or its precursor IV) afforded the tetrahydro derivative XI. In the 14α-series, the esters VI and VII gave the tetrahydro compounds XII and XIII, respectively. It is to be expected that the configuration of the still unisomerized carbomethoxy groups in V and VI did not change as a result of the acetic acid–palladium treatment at room temperature. In these hydrogenations a mixture of the 3α and 3β isomers could be anticipated; however the compounds XI

and XII isolated appeared to be single isomers, and only the product XIII was a mixture of epimers.

EXPERIMENTAL

All hydrogenation experiments were carried out at room temp and atmospheric pressure using American Platinum Works 10% Pd–C catalyst. The catalyst was filtered off and the solvent distilled *in vacuo*.

Methyl 3ξ,6-*dimethoxy*-5(10),6,8-*estratriene*-17β-*carboxylate* (II). A solution of 4·7 g ester I[3] in 350 ml warm AcOH was hydrogenated for 48 hr in the presence of 2 g Pd–C. After the first 24 hr 2 g more of the Pd–C was added. The product was made to crystallize by digestion with hot MeOH to afford 3·4 g, m.p. 147–159°. A repeated digestion raised the m.p. to 151–156°. Recrystallization from ethyl acetate gave 2·46 g, m.p. 155–180°. (Found: C, 73·77; H, 8·50; $C_{22}H_{30}O_4$ requires: C, 73·71; H, 8·44%.)

Hydrogenation of dimethyl 3,6-*dimethoxy*-1,3,5(10),6,8,14-*estrahexaene*-15,17α-*dicarboxylate* (III) *in ethyl acetate*. A solution of 200 mg ester III[3] in 20 ml AcOEt was hydrogenated for 5 hr with 100 mg Pd–C. Crystallization from 30 ml heptane gave 105 mg *dimethyl* 3,6-*dimethoxy*-1,3,5(10),6,8-*estrapentaene*-14-*iso*-15α,17α-*dicarboxylate* (V) in the form of voluminous ball-like clusters of fine needles, m.p. 173·5–175°. Two additional recrystallizations gave the analytical sample, m.p. 176–177°. (Found: C, 69·89; H, 6·81; $C_{24}H_{32}O_6$ requires: C, 69·88; H, 6·84%.) The UV spectrum was like that of the ester I; λ_{max}^{KBr} 5·82 μ.

The original heptane filtrate was concentrated to 10 ml. After 30 min the heavy prisms of *dimethyl* 3,6-*dimethoxy*-1,3,5(10),6,8-*estrapentaene*-15β,17α-*dicarboxylate* (VI) were collected; 54 mg, m.p. 133–134°. The pure compd melted at 133·5–134·5° (heptane). (Found: C, 70·06; H, 6·86; $C_{24}H_{32}O_6$ requires: C, 69·88; H, 6·84%.) The UV spectrum was like that of the isomer VII; λ_{max}^{KBr} 5·79 and 5·83 μ.

Further concentration of the heptane filtrate afforded 18 mg of a product, m.p. 121–130°. Treatment of its filtrate with boiling MeONa solution afforded 8 mg of the ester VII, m.p. 203–204°, the rearrangement product of VI, identified by its IR spectrum.

Isomerization of V *to dimethyl* 3,6-*dimethoxy*-1,3,5(10),6,8-*estrapentaene*-14-*iso*-15β,17α-*dicarboxylate* (X). A solution of 150 mg isomer V in 15 ml 2·3% MeONa solution in MeOH was refluxed for 16 hr. The clear solution was cooled and the separated solid was washed with MeOH and then with water; 72 mg, m.p. 166–177°. Recrystallization from heptane afforded 40 mg prismatic needles, m.p. 171·5–172·5°. The analytical sample melted at 173–173·5°. (Found: C, 69·86; H, 6·89; $C_{24}H_{32}O_6$ requires: C, 69·88; H, 6·84%.) The mixed m.p. with the starting ester V was 160–168° and their IR spectra were different.

Isomerization of VI *to dimethyl* 3,6-*dimethoxy*-1,3,5(10),6,8-*estrapentaene*-15α,17β-*dicarboxylate* (VII). A solution of 104 mg isomer VI in 7 ml of 2·3% methanolic MeONa was refluxed for 18 hr, during which a crystalline solid separated. After refrigeration the mixture was filtered and the solid washed with MeOH and water; 102 mg, m.p. 202–203·5°. Recrystallization from AcOEt raised the m.p. of VII to 203–204°. (Found: C, 70·03; H, 6·89; $C_{24}H_{32}O_6$ requires: C, 69·88; H, 6·84%.)

Hydrogenation of dimethyl 3,6-*dimethoxy*-1,3,5(10),6,8,11,14-*estraheptaene*-15,17α-*dicarboxylate* (IV) *in ethyl acetate*. A solution of 135 mg heptaene IV[3] in 10 ml AcOEt was hydrogenated for 2·5 hr in the presence of 200 mg Pd–C. The product was crystallized from MeOH to afford 76 mg, m.p. 120–170°. Recrystallization from heptane gave 30 mg, m.p. 174–175°, identical with the *ester* V.

Evaporation of the methanolic filtrate and refluxing the residue with 3 ml of 2·3% methanolic MeONa for 7 hr furnished 35 mg isomerized *ester* VII, m.p. 201–203°.

Hydrogenation of dimethyl 3,6-*dimethoxy*-1,3,5(10),6,8,14-*estrahexaene*-15,17β-*dicarboxylate* (VIII). A solution of 200 mg VIII[3] in 40 ml AcOEt was hydrogenated for 6 hr in the presence of 200 mg Pd–C. The product melted at 136–146°. Recrystallization from heptane or EtOH yielded samples of *dimethyl* 3,6-*dimethoxy*-1,3,5(10),6,8-*estrapentaene*-15β,17β-*dicarboxylate* (IX), m.p. 152–158° range. Chromatography over alumina was not helpful; the product was recrystallized from MeOH, m.p. 153·5–158°. (Found: C, 70·03; H, 6·89; $C_{24}H_{32}O_6$ requires: 69·88; H, 6·84%.) The UV spectrum was identical with that of the ester I; λ_{max}^{KBr} 5·79 μ.

Isomerization of IX *to* VII. A solution of 30 mg IX, m.p. 153·5–158·5°, in 8 ml 2·3% methanolic MeONa was refluxed for 6 hr. The crystalline solid was washed with MeOH and water, yield 25 mg, m.p. 203·5–204·5°, identical with a sample of VII obtained above.

Dimethyl 3ξ,6-*dimethoxy*-5(10),6,8-*estratriene*-14-*iso*-15α,17α-*dicarboxylate* (XI). (a) A solution of 31 mg ester V in 10 ml AcOH was hydrogenated for 19 hr with 50 mg Pd–C. The product was recrystallized from MeOH and then from heptane, yield 12 mg, m.p. 181–181·5°. (Found: C, 69·32; H, 7·47; $C_{24}H_{32}O_6$ requires: C, 69·21; H, 7·74%.) (b) A solution of 71 mg ester IV in 15 ml AcOH was hydrogenated with 200 mg Pd–C for 20 hr. The product was crystallized from MeOH, yield 22 mg, m.p. 176–177·5°. A further recrystallization raised the m.p. to 180–181°; the compound was identical with XI obtained above.

Dimethyl 3ξ,6-*dimethoxy*-5(10),6,8-*estratriene*-15β,17α-*dicarboxylate* (XII). A solution of 25 mg ester VI in 10 ml AcOH was hydrogenated for 20 hr in the presence of 70 mg Pd–C. The product was recrystallized from MeOH, yield 20 mg, m.p. 135–136°. A further recrystallization from heptane raised the m.p. to 137–138°. (Found: C, 69·41; H, 7·88: $C_{24}H_{32}O_6$ requires: C, 69·21; H, 7·74%.)

Dimethyl 3ξ,6-*dimethoxy*-5(10),6,8-*estratriene*-15α,17β-*dicarboxylate* (XIII). A solution of 51 mg isomer VII in 10 ml AcOH was hydrogenated for 19 hr with 150 mg Pd–C. The product, after 3 recrystallizations from MeOH, melted at 149–160°. (Found: C, 69·33; H, 7·64; $C_{24}H_{32}O_6$ requires: C, 69·21; H, 7·74%.)