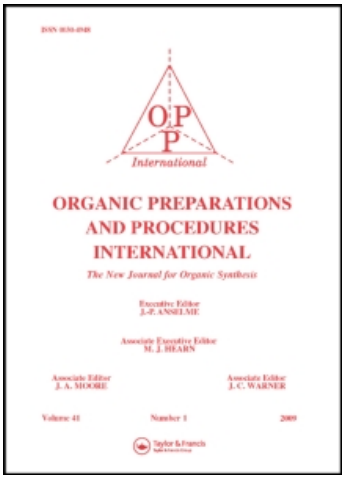

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5α-HYDROXY-3α-CHOLESTANECARBOXYLIC LACTONE

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5α-HYDROXY-3α-CHOLESTANECARBOXYLIC LACTONE

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(10/4/82)

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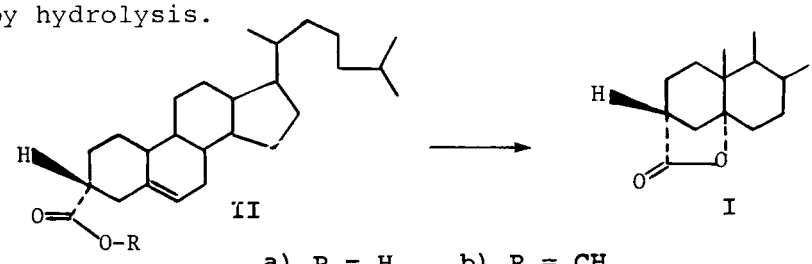
Given the large number of synthetic lactones as well as those isolated from natural sources in recent years, it is surprising that compound I has not been reported.[1] Several years ago[2] we noted a slow isomerization (IR) of the 3α-acid (IIa), presumably to I. We have now prepared this lactone (I). After the requisite 3α-acid (IIa) was obtained from the 3β-acid via a procedure essentially equivalent[2] to that used by Shoppee and Stephenson,[3] I was synthesized directly from IIa as well as from IIb by hydrolysis.



II I

a) R = H b) R = CH_3

EXPERIMENTAL[4]

Procedure A (from IIa).- The necessary 3α-acid was prepared according to a procedure used by Wintersdorf,[2] starting with cholesteryl chloride instead of cholesteryl bromide used earlier by Shoppee and Stephenson.[3] To a solution made up of 4.5 ml of dioxane, 0.44 ml of water and 0.56 ml of perchloric acid (90% aqueous dioxane, 0.2 N in perchloric acid) was added 100 mg of IIa. The mixture was placed in a long stem flask, which was filled with argon gas and placed in a Dry Ice-acetone bath

while the stem was drawn off and sealed. The flask was placed in an oil bath at 80° for ten days. At the end of this period the contents were poured into an evaporating vessel and the liquid removed under reduced pressure (25°). The residue was mixed with 25 ml of 2 N cold sodium hydroxide[5] and extracted three times with 50 ml portions of ether, separating any suspended material along with the aqueous phase. The ethereal extracts were combined and washed with cold 0.01 N aqueous hydrochloric acid and then water. The ethereal layer was then dried over magnesium sulfate and 3Å molecular sieves. Evaporation of the solvent yielded 30 mg (30%) of a colorless solid, mp. 164.5-165.2°. A 50:50 mixture (by weight) of the product with IIa. mp. 151.2-151.7°, resulted in a melting point depression, mp. 147.4-156.0°.

NMR ($CDCl_3$): δ 0.63 (C_{18}-CH_3), 0.88 (C_{19}-CH_3), 2.60 (C<u>H</u>-C=O), no -CO_2<u>H</u> (in IIa δ 11.4); no vinyl proton (in IIa δ 5.37); IR (KBr): 1765 cm^{-1} (lactone), no peak at 1700 cm^{-1} (C=O in IIa); MS (70 eV, 100°): m/e (relative intensity) 414 (M^+, 61.4); 386 ($(M-CO)^+$, 24.5); 370 ($(M-CO_2)^+$, 26.8); 329 (4.86); 301 ($(M-C_8H_{17})^+$, 29.1);[6] 288 (50.0); 274 (62.3); 260 ($(M-C_{11}H_{22})^+$, 79.1);[6] 259 ($(M-C_{11}H_{23})^+$, 100).[6]

<u>Anal</u>. Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18.
Found: C, 81.18; H. 11.38.

<u>Procedure B (from IIb)</u>.- Using diazomethane generated from EXR-101,[7] the 3α-acid (IIa) was converted to its methyl ester (IIb). NMR($CDCl_3$): δ 2.48 (C<u>H</u>-C=O), 3.65 (-CO_2CH_3), 5.36 (vinyl H); IR(KBr): 1728 cm^{-1}.

Methyl 3α-cholestene-Δ^5-carboxylate (IIb) (100 mg) when

subjected to the same conditions as those described in procedure A, yielded 25 mg (26%) of a colorless solid, mp. 164.2-165.3°, which when mixed with an equal weight of IIa, resulted in a melting point depression, mp. 147.0-157.8°. When the product was mixed with the product in A, there was no mp. depression, mp. 164.2-165.8°.

NMR ($CDCl_3$): no $-CO_2H$, no vinyl proton; IR(KBr) 1765 cm^{-1} (lactone), no peak at 1700 cm^{-1} ($-CO_2H$).

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