light, showed ultraviolet absorption for a dienone, λ_{max} 223 mμ, ε 4385 and 266 mμ, ε 600.

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Notes

4,5β-Epoxycholest-1-en-3-one

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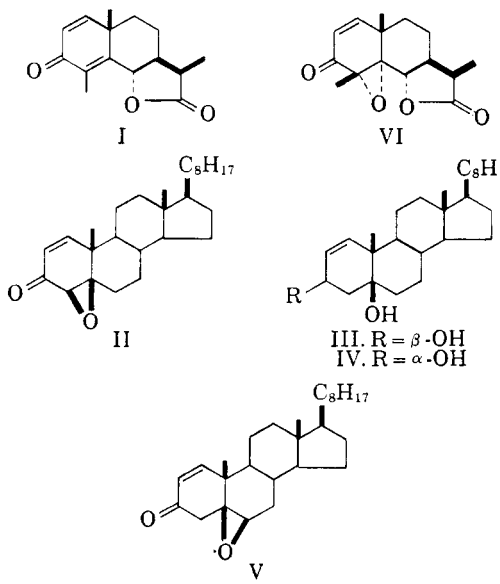
In connection with another problem it became desirable to synthesize a 1,2α-epoxide of a steroid 1,4-dien-3-one. It has been reported that the cross-conjugated dienone, santonin (I), yields a mixture of stereoisomeric 1,2-epoxides[2] upon treatment with perbenzoic acid or hydrogen peroxide in acetic acid.[3] Consequently we investigated the analogous epoxidation of the readily available cholest-1,4-dien-3-one and now wish to record our observations.

Prolonged treatment of cholest-1,4-dien-3-one with perbenzoic acid in refluxing benzene solution resulted in a low yield of a mono epoxide II, m.p. 123–124°, exhibiting infrared absorption at 1690 (—CO—) and 1610 (—C=C—) cm.$^{-1}$. Ultraviolet absorption occurred at 232 mμ, but no definitive structure assignment was possible based on these observations only. Lithium aluminum hydride reduction of this product proceeded smoothly and gave two unsaturated diols in a ratio of 1:4. The major diol III, m.p. 173.5–174.5°, possessed infrared absorption at 1650 (—C=C—) and 3550 (intermolecular hydrogen bonded —OH) cm.$^{-1}$ while the minor diol IV, m.p. 135–136°, exhibited an additional absorption at 3600 (nonbonded —OH) cm.$^{-1}$.



Hydrogenation of III yielded cholestan-5β-ol[4] (50%), m.p. 80°, and cholestan-3,5β-diol[5] (50%), m.p. 129–130/149°, while IV under the same conditions gave cholestan-5β-ol and cholestan-3α,5β-diol,[5] m.p. 188.5–189° in a ratio of 1:2. Further verification of the position of the 1,3-diol system was obtained by oxidation of cholestan-3,5β-diol to cholestan-3-one-5β-ol, m.p. 158–159°, and subsequent dehydration to cholest-4-en-3-one identified by mixed melting point determination with an authentic sample.

The preceeding evidence can be rationalized if it is assumed that the initial epoxide possesses the 4,5β- (II) or 5,6β- (V) configuration. *trans*-Diaxial oxirane ring opening and carbonyl reduction by hydride affords the pair of unsaturated diols epimeric at C-3 since on catalytic hydrogenation both give the same hydrogenolysis product.

A 60 mc./sec. NMR spectrum of the original epoxide in carbon tetrachloride solution showed two vinylic hydrogens at low field. Spin-spin coupling[6] (J = 10 c.p.s.) between these *cis* hydrogens is responsible for the β-hydrogen doublet centered at 3.61 τ while the α-hydrogen quartet at 4.31 τ indicated additional transannular cou-

(1) National Science Foundation predoctoral fellow, 1960–1961.

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pling with the α-oriented hydrogen at C-4 (J = 2 c.p.s.). A doublet centered at 7.00 τ is due to this C-4 oxirane ring hydrogen[7] and again reflects transannular coupling. Its chemical shift indicates deshielding by the adjacent carbonyl group which disagrees with structure V.

It therefore follows that the initial epoxide is correctly represented by II and its formation by attack of the oxidizing agent on the β-face of the relatively more electrophilic C-4:C-5 double bond indicates more steric shielding by the 6α- and 9α-hydrogens than by the angular methyl group.

Dr. Teruo Matsuura of these laboratories has prepared a sample of "santonin α-epoxide," m.p. 211–213° (lit.,[8] m.p. 214°), $\lambda_{max}^{C_2H_5OH}$ 222 mμ (ϵ 8740), by oxidation of santonin with perbenzoic acid in hot chloroform solution. A 60 mc./sec. NMR spectrum in deuterochloroform solution exhibited a doublet (1 H) at 3.71 τ (J = 10 c.p.s.) and a second doublet (1 H) at 4.13 τ (J = 10 c.p.s.). Consequently "santonic α-epoxide" also is a 4,5-epoxide and chemical transformations subsequently studied by Prof. J. B. Hendrickson and Mr. Terry L. Bogard at the University of California, Los Angeles, established the 4,5α-epoxy configuration VI (*J. Chem. Soc., in press*).

EXPERIMENTAL[9]

4,5β-Epoxycholest-1-en-3-one (II). Cholest-1,4-dien-3-one (90.0 g., 0.241 mole) was refluxed in 400 ml. of a freshly prepared 0.5 *M* solution of perbenzoic acid in benzene. At 6-hr. intervals two additional 400-ml. portions of the perbenzoic acid solution were added and reflux continued for a total of 16 hr. The resulting solution was washed with 10% aqueous sodium carbonate (3 × 750 ml.) followed by water (5 × 100 ml.). The benzene layer was dried over sodium sulfate and evaporated *in vacuo*, and the oily residue (88 g.) was chromatographed over activity I alumina (2.5 kg.). Elution with 3:1 pentane–benzene mixtures afforded 12.38 g. of 4,5β-epoxycholest-1-en-3-one which deposited as fine needles after two crystallizations from ethanol, it had m.p. 123–124°, [α]D +214° (*c* 1.186), $\lambda_{max}^{C_2H_5OH}$ 232 mμ (ϵ 9300), $\nu_{max}^{CCl_4}$: 1690, 1610, 875, and 840 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}O_2$: C, 81.61; H, 10.33. Found: C, 81.19; H, 10.08.

Cholest-1-en-3,5β-diol (III) *and cholest-1-en-3α,5β-diol* (IV). 4,5β-Epoxycholest-1-en-3-one (6.2 g., 0.0155 mole) in dry redistilled tetrahydrofuran (50 ml.) was added dropwise during a period of 30 min. to a stirred solution of lithium aluminum hydride (0.45 g.) in tetrahydrofuran (250 ml.) at 30°. After refluxing for 2 hr. ethyl acetate (30 ml.) was added followed by water (10 ml.) and sodium sulfate (20 g.). This mixture was stirred for 10 min., filtered, and evaporated to dryness *in vacuo*. The crystalline residue was chromatographed over activity III alumina (300 g.). An increasing chloroform in benzene linear gradient eluted first 4.2 g. of cholest-1-en-3,5β-diol which deposited as large leaflets upon one crystallization from methanol, m.p. 173.5–174.5°, [α]D +108° (*c* 0.6160), $\lambda_{max}^{C_2H_5OH}$ 210 mμ (ϵ 530), $\nu_{max}^{CHCl_3}$ 3550, 1650, 1090, 1050, and 830 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.39; H, 11.40. Found: C, 80.26; H, 11.56.

Further elution afforded 1.0 g. of cholest-1-en-3α,5β-diol which separated in small needles after two crystallizations from methanol, m.p. 135–136°, [α]D +46.1° (*c* 1.3720), $\lambda_{max}^{C_2H_5OH}$ 210 mμ (ϵ 630), $\nu_{max}^{CHCl_3}$ 3700, 3500, 1640, 1050, 1030, 1010, and 840 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.39; H, 11.40. Found: C, 80.53; H, 11.59.

Cholest-3,5β-diol and cholestan-5β-ol. Cholest-1-en-3,5β-diol (2.0 g., 4.95 mmoles) was hydrogenated in an ether–ethanol mixture (1:3, 200 ml.) over platinum oxide catalyst (200 mg.) at 27°. After 35 min. 1.6 equivalents of hydrogen has been consumed and the mixture was filtered, the filtrate concentrated *in vacuo* and benzene (50 ml.) was added. Solvent was removed by distillation and the residue chromatographed over activity II alumina (60 g.). An increasing chloroform in benzene linear gradient eluted first 1.05 g. of cholestan-5β-ol which deposited as leaflets of the solvate upon three crystallizations from methanol and after drying had m.p. 80°, [α]D +31.2° (*c* 2.420), Lit.,[4] m.p. 81–82°, [α]D +37°. Further elution afforded 0.9 g. of cholestan-3β,5β-diol which yielded fine prisms after three crystallizations from methanol, m.p. 129–130°, resolidfying (needles) and then having m.p. 149°, [α]D +35.2° (*c* 2.182). Lit.,[5] m.p. 148–149°, [α]D +52.8° (*c* 1.232).

Cholestan-3α,5β-diol. Cholest-1-en-3α,5β-diol (200 mg., 0.494 mmole) was hydrogenated as described previously and afforded after chromatography 57 mg. of cholestan-5β-ol, m.p. 80°, both pure and admixed with the previously obtained product. Further elution afforded 133 mg. of cholestan-3α,5β-diol which crystallized in slender needles on crystallization from methanol, m.p. 188.5–189°, [α]D +37.4° (*c* 0.7580). Lit.,[5] m.p. 192–193°, [α]D +47.1° (*c* 1.047).

Cholestan-3-one-5β-ol. Cholestan-3β,5β-diol (105 mg., 0.259 mmole) in acetone (18 ml.) was stirred under nitrogen at 0–5° with a standard solution[10] of chromium trioxide in sulfuric acid (0.2 ml.) for 5 min. The solution was diluted with water (20 ml.), concentrated *in vacuo* at 5°, extracted with ether (2 × 50 ml.), and the ether layer washed with water (4 × 50 ml.). After drying over sodium sulfate and removal of the solvent *in vacuo*, the residue (99 mg.) after one crystallization from hexane yielded felted needles of cholestan-3-one-5β-ol, m.p. 158–159°. Lit.,[5] m.p. 151–152°.

Cholest-4-en-3-one. Cholestan-3-one-5β-ol (72 mg., 0.178 mmole) in ethanol (5 ml.) containing concd. hydrochloric acid (0.1 ml.) was refluxed for 1 hr., concentrated to one-fourth volume *in vacuo*, and evaporated to dryness after adding benzene (50 ml.). The residue (69 mg.) was crystallized five times from ethanol to afford large needles of cholest-4-en-3-one, m.p. 79–80°, both pure and admixed with an authentic sample.

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