Steroid B-Ring Lactones and Derivatives of 5,6-Seco Steroids

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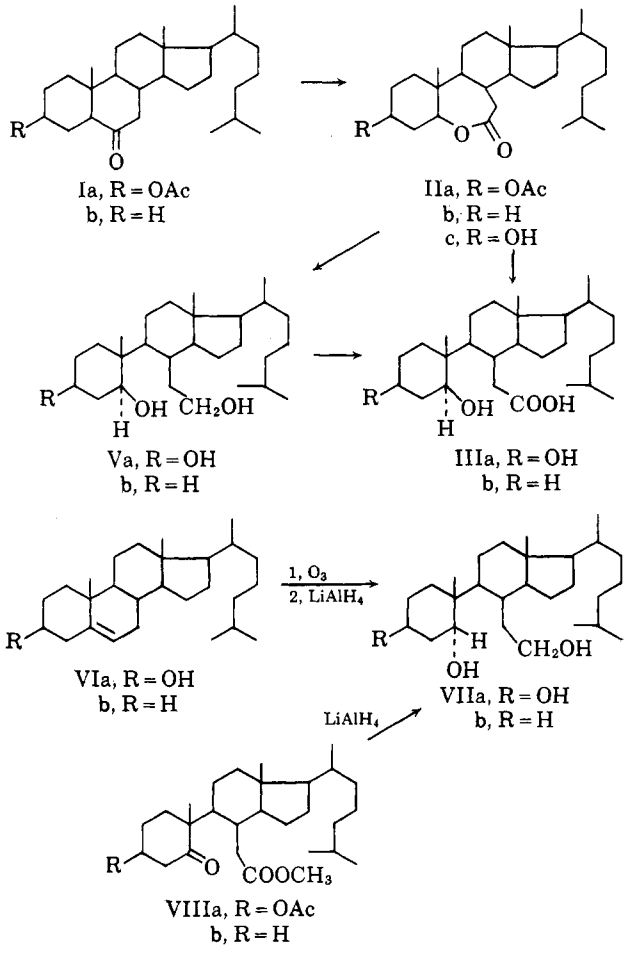
The preparation of lactones from cholestan-6-one and 3β-hydroxycholestan-6-one by the Baeyer–Villiger reaction is described. A number of 5,6-seco derivatives of the cholestane nucleus have been prepared, and structural and stereochemical assignments of these materials have been put forth.

The synthetic modification of steroids has been a major chemical endeavor in the past several decades. Among the numerous modes of modification one finds skeletal modifications involving the introduction of heteroatoms at various sites in the steroid nucleus.[1] The introduction of such atoms has been based largely on processes involving the preparation of suitable ring-opened intermediates and subsequent recyclization of a derivative containing a suitable heteroatom.[1-4] Among the various seco steroids which have been prepared for such purposes one finds the 5,6-seco derivatives which have been described by a number of investigators.[5-7a] Some of the derivatives of these 5,6-seco sterols have been shown to possess cytotoxic behavior[5] and are thus of possible interest as antitumor agents.

In the present investigation we have developed a new route to derivatives of 5,6-seco sterols based on the Baeyer–Villiger oxidation of 6-keto sterols to B-ring lactones. Further elaboration of these materials has led to a proof of stereochemistry of the cytotoxic substance described by Lettre and Hotz[5] and to the preparation of other substances of possible physiological interest.

The Baeyer–Villiger oxidation of steroid ketones and similar substances has been shown to be a stereospecific process[7b,8] leading to lactones in a number of cases.[9-11] By analogy one would anticipate the peracid reaction with a 6-keto sterol to yield a derivative of a 5,6-seco steroid 5,β-hydroxy-6-oic acid lactone. Accordingly, we have assigned structures IIa and IIb, respectively, to the lactones thus derived from 3β-acetoxycholestan-6-one (Ia) and cholestan-6-one (Ib). Support of these assignments of structure and stereochemistry is gained from the chemical conversions described.

When Ia was allowed to react with perbenzoic acid the lactone IIa was obtained in good yield. Hydrolysis of IIa gave the dihydroxy acid IIIa, or the hydroxy lactone IIc, depending on the care with which the hydrolysis reaction mixture was worked up. The dihydroxy acid IIIa readily lactonizes to IIc and acetylation of IIc leads again to IIa. Reduction of either IIa, IIc or IIIa afforded a triol to which we have assigned the structure 5,6-secocholestane-3β,5β,6-triol (Va). A similar triol, VIIb, has been prepared by the reduction of the ozonide of cholesterol[6] and of 3β-acetoxy-5-oxo-5,6-secocholestane-6-carboxylic acid methyl ester (VIIIa)[12] and has been assigned the 5α-hydroxy configuration.[6]



Support of our assignment of the 5β-hydroxy configuration to Va rests on the already mentioned stereospecificity of the Baeyer–Villiger oxidation and the fact that the reduction of the lactone with lithium aluminum hydride should not affect the configuration of the carbon–oxygen bond at C-5.[13] Additional support of our assignment is gained from the study of a similar lactone derived from cholestan-6-one Ib.

The reaction of cholestan-6-one Ib with perbenzoic acid afforded as the only isolable substance, and in good yield, the lactone IIb. Reduction of IIb with lithium aluminum hydride gave the diol Vb which is isomeric with the diol VIIb obtained by Lettre[5] by lithium alu-

(1) A brief review of such modifications is contained in an article by T. L. Jacobs and R. B. Brownfield, *J. Am. Chem. Soc.*, **82**, 4033 (1960).
(2) N. J. Doorenbos and M. T. Wu, *J. Org. Chem.*, **26**, 4550 (1961).
(3) G. R. Pettit and T. R. Kasturi, *ibid.*, **26**, 4557 (1961).
(4) H. Lettre and L. Knof, *Chem. Ber.*, **93**, 2860 (1960).
(5) H. Lettre and D. Hotz, *Ann.*, **620**, 63 (1959).
(6) H. Lettre and A. Jahn, *ibid.*, **608**, 43 (1957).
(7a) L. Knof, *ibid.*, **647**, 53 (1961); (b) T. F. Gallagher and T. H. Kritchevsky, *J. Am. Chem. Soc.*, **72**, 882 (1950).
(8) R. B. Turner, *ibid.*, **72**, 878 (1950).
(9) N. L. Wendler, D. Taub, and H. L. Slates, *ibid.*, **77**, 4559 (1955).
(10) M. F. Murray, B. A. Johnson, R. L. Pederson, and A. C. Ott, *ibid.*, **78**, 981 (1956).
(11) H. Heusser, A. Segre, and P. A. Plattner, *Helv. Chim. Acta*, **31**, 1183 (1948).
(12) H. Lettre, D. Hotz, and C. Scholtissek, *Ann.*, **621**, 79 (1959).
(13) D. S. Noyce and D. B. Denny, *J. Am. Chem. Soc.*, **74**, 5912 (1952).

minum hydride reduction of the ozonide of Δ^5-cholestene VIb or the keto acid methyl ester VIIb.[14]

A structural and stereochemical correlation of Vb and VIIb was effected in the following fashion. Oxidation of Vb with chromic anhydride in acetic acid followed by methylation of the crude acid with diazomethane gave VIIIb in good yield. Similar oxidation of VIIb also gave VIIIb. Thus they are isomeric 5,6-secocholestane-5,6-diols. The stereospecificity of the Baeyer–Villiger oxidation and the lithium aluminum hydride reduction led us to formulate Vb as the 5β-hydroxyl isomer thus supporting the 5α-hydroxyl configurational assignment of VIIb made by Lettre.[5] One final piece of experimental data further bears out these assignments. The 5α-hydroxy isomer VIIb must have its hydroxyl axial and one should therefore be able to equilibrate it to the equatorial 5β-hydroxy isomer Vb. In accord with prediction it was found that when VIIb was allowed to reflux in a solution of isopropyl alcohol containing aluminum isopropoxide and a small amount of acetone one obtained Vb. These data fully support our stereochemical assignments to Vb, VIIb, and, by implication, the previously mentioned stereochemistry of Va and VIIa.

One final item of interest is the apparently great stereospecificity of the hydride reduction of the C-5 carbonyl group in 5,6-seco sterols. Attempts to isolate both the 5α-hydroxy and 5β-hydroxy isomers Vb and VIIb from the crude reduction product of VIIIb were unsuccessful in that only the 5α-hydroxy isomer could be obtained. Yields of the latter were consistently in the neighborhood of 90%. Such specificity suggests that the approach of the hydride reducing agent must occur largely from the beta face of the molecule.

Experimental

Peracid Oxidation of 3β-Acetoxycholestan-6-one[15] (Ia).—A solution of 372 mg. (0.84 mmole) of 6-ketocholesteryl acetate in 10 ml. of chloroform was added to 10 ml. of a solution of perbenzoic acid in chloroform. The peracid solution contained 51 mg. of perbenzoic acid per milliliter. The mixture was allowed to stand at 20° for 3 days whereupon it was diluted with 50 ml. of ether, extracted with a 10% sodium carbonate solution, washed with water, and dried over anhydrous sodium sulfate. The dried solution was evaporated at reduced pressure leaving a residue which crystallized readily from methanol; yield, 302 mg. (78%) of the lactone IIa; m.p. 162–163°; $[\alpha]^{20}D$ +28° (chloroform).

Anal. Calcd. for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.83; H, 10.68.

5,6-Secocholestane-3β,5β-diol-6-carboxylic Acid (IIIa).—A solution of 100 mg. (0.21 mmole) of the acetate lactone IIa in 20 ml. of 5% sodium hydroxide in methanol was heated under reflux for 2 hr. The solution was diluted with water, carefully acidified with dilute acetic acid, and extracted with ether. The ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated at reduced pressure. The residue consisted of a colorless solid which was crystallized from methanol to give 70 mg. (75%) of the dihydroxy acid IIIa, m.p. 167–171°; $[\alpha]^{20}D$ −36° (chloroform).

Anal. Calcd. for $C_{27}H_{48}O_4$: C, 74.39; H, 11.08. Found: C, 74.53; H, 11.22.

5,6-Secocholestane-3β,5β-diol-6-carboxylic Acid Lactone (IIc).—A solution of 2.0 g. (4.3 mmoles) of IIa was dissolved in 50 ml. of a 5% solution of sodium hydroxide in methanol and refluxed for 2 hr. The solution was diluted with water, acidified to pH 1 with hydrochloric acid, and extracted with ether. The ether extracts were evaporated at reduced pressure leaving a crystalline residue which was recrystallized from methanol; yield, 1.2 g. (71%); m.p. 139–141°; $[\alpha]^{20}D$ +32° (chloroform).

Anal. Calcd. for $(C_{27}H_{46}O_3)$: C, 75.53; H, 10.98. Found: C, 75.70; H, 11.02.

5,6-Secocholestane-3β,5β,6-triol (Va).—A solution of 1.0 g. (0.225 mmole) of the lactone acetate IIa in 50 ml. of anhydrous ether was added dropwise to a stirred slurry of 1.0 g. of lithium aluminum hydride in 50 ml. of anhydrous ether. The mixture was allowed to stir at room temperature for 12 hr. whereupon the excess hydride was decomposed by cautious addition of 10 ml. of water. The ether phase was separated, washed with water, and dried over anhydrous sodium sulfate. Evaporation of the ether at reduced pressure left a crystalline residue which was recrystallized from methanol yielding 0.85 g. (94%) of product, m.p. 215–217°. Two further recrystallizations raised the melting point to 216–218°; $[\alpha]^{20}D$ −5° (chloroform).

Anal. Calcd. for $(C_{27}H_{50}O_3)$: C, 76.72; H, 11.92. Found: C, 76.68; H, 12.08.

Peracid Oxidation of Cholestan-6-one[16] (Ib).—A solution of 2.0 g. of cholestan-6-one in 100 ml. of chloroform solution of perbenzoic acid containing 48 mg. per milliliter was allowed to stand at 20° for 36 hr. The solution was diluted with 200 ml. of ether, extracted twice with 200 ml. of 10% aqueous sodium carbonate solution, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent at reduced pressure left an oil which crystallized from methanol to yield 1.9 g. (94%) of lactone IIb, m.p. 140–142°. Several further recrystallizations gave material with m.p. 143–144°; $[\alpha]^{20}D$ +28° (chloroform).

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.53; H, 11.51. Found: C, 80.39; H, 11.69.

5,6-Secocholestan-5β,6-diol (Vb).—A 1.4-g. (0.35 mmole) portion of the lactone IIb was added to a slurry of 1.5 g. of lithium aluminum hydride in 60 ml. of absolute ether. The mixture was allowed to stir at room temperature for a period of 12 hr. and worked up in the manner described in the preparation of V. Evaporation of the solvent at reduced pressure left an oil which crystallized upon trituration with petroleum ether containing a few drops of ethyl acetate and there was obtained 1.1 g. (86%) of product m.p. 135–137°. Further recrystallization raised the melting point to 139–140°; $[\alpha]^{20}D$ + 20° (chloroform).

Anal. Calcd. for $C_{27}H_{50}O_2$: C, 79.74; H, 12.39. Found: C, 79.92; H, 12.43.

Oxidation of 5,6-Secocholestane-5β,6-diol. (Vb).—A 1.0-g. (0.25 mmole) portion of the diol Vb was added to a solution of 1.0 g. of chromic oxide in 50 ml. of 90% acetic acid. The mixture was allowed to stir at room temperature for 30 min., diluted with 300 ml. of water, and extracted with ether. The ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated leaving a colorless noncrystalline residue. The residue was taken up in 50 ml. of ether and allowed to react with an excess of an ether solution of diazomethane. When nitrogen evolution had ceased the solution was evaporated and the residue crystallized from methanol. The keto acid methyl ester VIIIb was isolated in a yield of 0.4 g. (39%), m.p. 102–103° (reported[14] m.p. 102–103°). The infrared spectrum was identical with that of an authentic sample prepared by the oxidation of cholestene.[14]

5,6-Secocholestane-5α,6-diol (VIIb).—A 3.0-g. (7.1 mmoles) sample of the keto ester VIIIb was reduced with lithium aluminum hydride as described by Lettre and Hotz[5]; yield, 2.7 g. (93%); m.p. 167–169° (reported[5] m.p. 166–167°); $[\alpha]^{25}D$ +14° (chloroform).

Equilibration of the 5α,6-Diol VIIb to the 5β,6-Diol Vb.—A solution of 2.0 g. (4.9 mmoles) of VIIb in 50 ml. of isopropyl alcohol containing 3 g. of aluminum isopropoxide and 1 ml. of acetone was allowed to reflux for 72 hr. The mixture was diluted with water, acidified with hydrochloric acid, and extracted with ether. Evaporation of the ether extracts left a noncrystalline residue which was triturated with petroleum ether and slowly crystallized. Repeated crystallization afforded 1.2 g. of Vb, m.p. 137–141°.

(14) H. Lettre, *Z. Physiol. Chem.*, **218**, 67 (1933).

(15) This material was prepared by the method of A. Windaus, *Ber.*, **36**, 3752 (1903); m.p. 128–129°; $[\alpha]^{20}D$ −16° (chloroform) (reported m.p. 128°).

(16) This material was prepared by the method of A. Windaus, *ibid.*, **53**, 488 (1920); m.p. 97–98° (reported m.p. 98–99°).