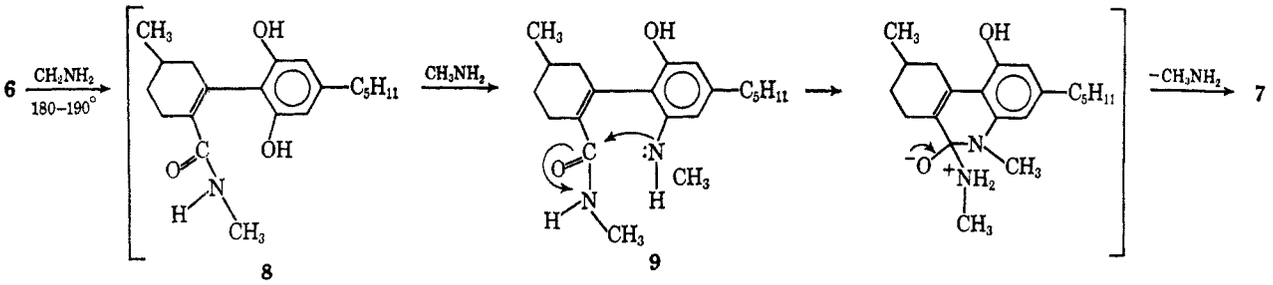
SCHEME I



Experimental Section

Melting points were determined on a Thomas–Hoover Unimelt and are uncorrected. Ultraviolet spectra were determined on a Beckman Model DK-2A ultraviolet spectrophotometer in methanol solution, unless otherwise stated. Ascending thin layer chromatography was performed on Eastman silica gel chromatogram sheets, K301R. Analyses were performed by Mr. Charles Pouchert of our analytical department.

7,8,9,10-Tetrahydro-1-hydroxy-5,9-dimethyl-3-*n*-pentylphenanthridin-6-one (7).—A mixture of 0.5 g (1.67 mmol) of 7,8,9,10-tetrahydro-1-hydroxy-3-*n*-pentyl-6-dibenzopyrone[3] (6) and 2.7 g (35 mmol) of 40% aqueous methylamine was heated in a Carius tube at 190 ± 5° for 42 hr. After cooling to room temperature, methylene chloride was added and the mixture was washed with 2 *N* hydrochloric acid. The organic layer was dried over magnesium sulfate and evaporated to dryness yielding 0.5 g (95.5% theory) of the product, mp 216–219°. Recrystallization from ethyl acetate yielded fine colorless needles, mp 219–220°.

Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.83; H, 8.45; N, 4.39.

7,8,9,10-Tetrahydro-1-hydroxy-5,6,6,9-tetramethyl-3-*n*-pentylphenanthridine Hydrochloride (5) and 7,8,9,10-Tetrahydro-1-hydroxy-5,6,9-trimethyl-3-*n*-pentylphenanthridinium Chloride (10).—To a refluxing solution of 1.8 g (5.74 mmol) of 7,8,9,10-tetrahydro-1-hydroxy-5,9-dimethyl-3-*n*-pentylphenanthridin-6-one (7) in 125 ml of dry benzene, 16.7 ml (50 mmol) of a 3 *N* solution of methylmagnesium bromide in ether was added over a 5-min period. After heating under reflux for 26 hr, addition of 50 ml of 2 *N* hydrochloric acid to the cooled (0°) reaction mixture resulted in the formation of a yellow-orange precipitate. The solid (shown by tlc with 1:1 methanol–ethyl acetate on silica to contain two components) was twice recrystallized from 5% aqueous methanol, yielding 0.72 g (34.6% theory) of **5** (the faster moving component on tlc) as colorless plates: mp 233–235° dec; $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 27,400), 293 (6000); $\lambda_{max}^{CH_3OH\text{-}HCl}$ 262 mμ (ε 12,100), 304 (8500); $\lambda_{max}^{CH_3OH/pH\ 11}$ 242.5 mμ (ε 25,600); ir absorption, 3.26 (OH), 4.01 (⁺NH), 6.11 (s, conjugated C=C), 6.35 μ (Ph).

Anal. Calcd for $C_{22}H_{34}ClNO$: C, 72.59; H, 9.42; Cl, 9.74; N, 3.85. Found: C, 72.61; H, 9.45; Cl, 9.79; N, 3.96.

Evaporation of the mother liquor to dryness gave a solid which upon recrystallization from ethyl acetate gave 0.55 g (38.4% theory) of **10** as a yellow solid: mp 138–145° after charring at 125°; $\lambda_{max}^{CH_3OH}$ 267 mμ (ε 43,500), 289 (7500); $\lambda_{max}^{CH_3OH\text{-}HCl}$ 267 mμ (ε 54,100); $\lambda_{max}^{CH_3OH/pH\ 11}$ 284 mμ (ε 35,000), 340 (3500), 470 (4900); ir absorption, 2.97 (OH), 6.18 (C=C), 6.40 μ (Ph).

Anal. Calcd for $C_{21}H_{30}ClNO$: C, 72.49; H, 8.69; Cl, 10.19; N, 4.02. Found: C, 72.59; H, 8.68; Cl, 10.20; N, 4.09.

7,8,9,10-Tetrahydro-1-hydroxy-5,6,6,9-tetramethyl-3-*n*-pentylphenanthridine Hydrochloride (5) from 7,8,9,10-Tetrahydro-1-hydroxy-5,6,9-trimethyl-3-*n*-pentylphenanthridinium Chloride (10).—A solution of methylmagnesium bromide (16.7 ml, 3 *N*, 50 mmol) in ether was added to a refluxing solution of 1.7 g (4.9 mmol) of **10** in 125 ml of dry benzene over a 5-min period. After heating under reflux for 24 hr, the cooled (0°) reaction mixture was decomposed with 50 ml of 2 *N* hydrochloric acid; the yellow precipitate which separated was taken up in methylene chloride and washed with 2 *N* hydrochloric acid. A white solid, insoluble in either phase, was filtered, yielding 0.7 g (39.3% theory) of **5**. The methylene chloride solution was dried and the solvent evaporated, yielding 0.9 g of the starting material.

Registry No.—**5**, 16666-72-1; **7**, 16666-73-2; **10**, 16666-74-3.

A Novel Synthesis of 2,3-Seco-A-nor-5α-cholestane-2,3-diol[1a]

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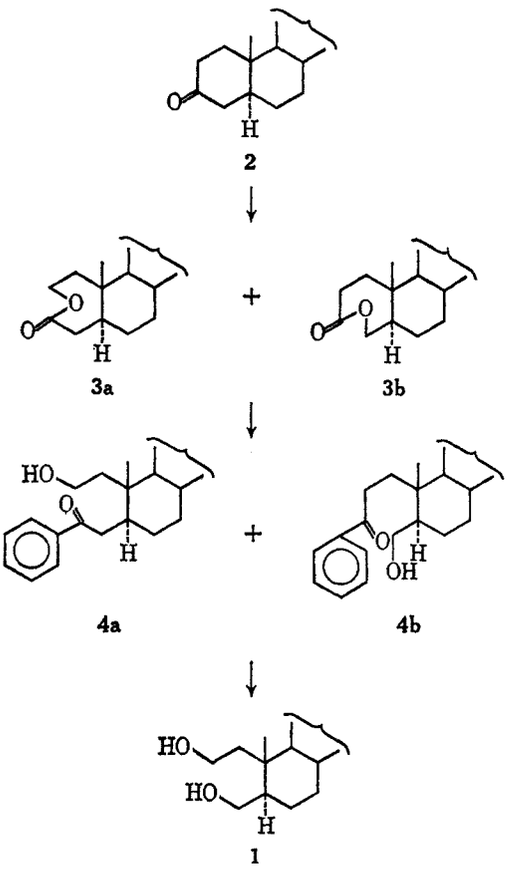
In connection with other work in these laboratories, it became necessary to prepare 2,3-seco-A-nor-5α-cholestane-2,3-diol [**1** (Scheme I)]. Seconordiols, useful intermediates in the synthesis of thia[2,3] and oxa[4]

SCHEME I



(1) (a) This work was supported by the Air Force Office of Scientific Research under Grant No. AF-AFOSR-1188-67. (b) National Defense Education Act Fellow, 1967–1968.

(2) R. Nagarajan, B. H. Chollar, and R. M. Dodson, *Chem. Commun.*, 550 (1967).

(3) P. B. Sollman, R. Nagarajan, and R. M. Dodson, *ibid.*, 552 (1967).

(4) *Cf.* C. Djerassi, Ed., "Steroid Reactions, an Outline for Organic Chemists," Holden-Day, Inc., San Francisco, Calif., 1963, Chapter 12.

steroids, and possible precursors to aza and phospha steroids, are obtainable at present only through lengthy reaction sequences, *e.g.*, by an eleven-step synthesis[2] from 5α-cholestan-3-one (**2**). The present paper describes a simple synthesis of seconordiol **1** by a four-step synthesis from **2**.

Baeyer–Villiger oxidation of **2**[5,6] with *m*-chloroperbenzoic acid afforded a mixture of A-homo-3-oxacholestan-4-one (**3a**) and A-homo-4-oxacholestan-3-one (**3b**). Reaction of the crude lactone mixture with phenylmagnesium bromide gave a mixture of the phenyl hydroxy ketones **4a** and **b**.[7] Oxidation with *m*-chloroperbenzoic acid,[8] followed by saponification, gave **1** in 16% yield based on **2**. No systematic attempts were made to maximize the yield.

Identification of **1** was based on its conversion to 3α- and 3β-thiacholestane oxides (**5a** and **5b**) by reaction of the dimesylate of **1** with sodium sulfide, followed by oxidation and separation of the diastereomeric sulfoxides.[2] The physical properties of **5a** and **5b** prepared from **1** are in accord with those previously described.[2]

We believe that this abbreviated synthesis, in essence amounting to the extrusion of a carbonyl group, may prove generally applicable to the synthesis of precursors to hetero steroids.

Experimental Section[9]

Oxidation of 5α-Cholestan-3-one.—A solution of 18.7 g (48.5 mmol) of 5α-cholestan-3-one and 15 g of 85% *m*-chloroperbenzoic acid in 150 ml of chloroform was stirred for 42 hr at room temperature and then heated for 2 hr at reflux. During this period the reaction mixture was protected from light. Approximately 75 ml of water and 25 ml of ether were poured into the reaction mixture and the organic layer was washed with dilute (*ca.* 5%) sulfuric acid, dilute (*ca.* 5%) aqueous sodium carbonate, and water until neutral. The organic layer was dried over anhydrous magnesium sulfate and filtered; the solvent was removed under reduced pressure. The resulting solid was recrystallized from benzene–pentane mixtures to give 15.4 g (79%) of material (mixture of lactones **3a** and **3b**) of mp 176–185° (lit.[5] mp 180–183°).

2,3-Seco-A-nor-5α-cholestane-2,3-diol.—The mixture of lactones from the oxidation of **2** (9.82 g, 24.4 mmol) was dissolved in 90 ml of anhydrous ether and 80 ml of anhydrous benzene. The solution was kept under a nitrogen atmosphere and cooled to −25° as freshly prepared phenylmagnesium bromide (approximately 24 mmol) in ether was added over a period of 2.5 hr. After stirring for 0.5 hr more, the reaction mixture was hydrolyzed with saturated aqueous ammonium chloride and warmed to room temperature, and the organic layer was separated. The ether–benzene extract was washed with dilute hydrochloric-acid and water until neutral and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to yield 11.35 g of a mixture of the ketones **4a** and **4b**. The infrared spectrum of this mixture showed strong absorption at 3400 cm^{-1} (OH stretch) and at 1685 and *ca.* 1600 cm^{-1} (aryl carbonyl and aryl stretch).

The mixture of ketones (11.35 g) was dissolved in 75 ml of chloroform, and 7.5 g of 85% *m*-chloroperbenzoic acid was added. The reaction mixture was protected from light and stirred at room temperature for 46 hr. Sufficient ether and water was added to the reaction mixture to afford a clean separation. The organic layer was washed with dilute sulfuric acid (*ca.* 5%), aqueous sodium carbonate (*ca.* 5%), and water until neutral, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under reduced pressure. The glassy residue (9.31 g) was dissolved in a solution of alcoholic potassium hydroxide (2.0 g in 100 ml) and heated at reflux for 5 hr. The solvent was removed by distillation and the residue diluted with ether and water. The ether layer was washed with water until neutral, dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent under reduced pressure and recrystallization of the residue from pentane afforded 2,3-seco-A-nor-5α-cholestane-2,3-diol: mp 136.5–137.5°; $[\alpha]_D$ 17.1° (*c* 2.52, chloroform). The yield of diol based on cholestan-3-one was 16%. The nmr spectrum of **1** showed chemical shifts at 39.3 (18-Me) and 46.9 Hz (19-Me).

Anal. Calcd for $C_{26}H_{48}O_2$: C, 79.53; H, 12.32. Found: C, 79.27; H, 12.65.

3-Thia-5α-cholestane (**6**).—A solution of diol **1** (1.25 g, 3.18 mmol) in 10 ml of dry pyridine was cooled to −20° as methanesulfonyl chloride (1 ml) was added. The solution was allowed to stand at −20° for 4.5 hr and at 5° for 18 hr. The brown solution containing crystals of pyridine hydrochloride was poured over ice and extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude dimesylate was dissolved in 75 ml of refluxing ethanol and 7.7 g of sodium sulfide nonahydrate dissolved in a minimal volume of water was added. The mixture was refluxed for 24 hr, after which time thin layer chromatography (silica gel plates, pentane developer, iodine stain) indicated that the reaction was complete. The ethanol was distilled and the residue was taken up in ether and water. The ether layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure to afford 3-thia-5α-cholestane (1.13 g, 91%). The product was recrystallized from methanol–ether mixtures to yield material of mp 98.5–99.5°. The nmr spectrum showed chemical shifts at 39.5 (18-Me) and 49.7 Hz (19-Me).

Anal. Calcd for $C_{26}H_{46}S$: C, 79.93; H, 11.87; S, 8.21. Found: C, 79.80; H, 12.00; S, 8.50.

3-Thia-5α-cholestane 3-Oxides.—The sulfide **6** (0.508 g, 1.30 mmol) was dissolved in 10 ml of methylene chloride and the resulting solution was held at 5° as a solution of 0.265 g of *m*-chloroperbenzoic acid in 5 ml of methylene chloride was added dropwise. The reaction mixture was stirred for 17 hr at 5° and for 3 hr at room temperature, poured into saturated aqueous sodium bicarbonate solution, and extracted two times more with sodium bicarbonate and once with water. The organic layer was separated, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under reduced pressure to yield a mixture of 3-thia-5α-cholestane 3-oxides. As determined from the relative intensities of the 18-Me group the mixture consisted of approximately 40% 3α epimer and 60% 3β epimer. The crude product weighed 0.51 g (97%).

The oxides were separated by column chromatography over 65 g of alumina. The column was developed with benzene and elution was achieved with 30% ethyl acetate in benzene. A compound identical with that reported[2] as 3-thia-5α-cholestane 3α-oxide (**5a**) was eluted first: mp 229–233°; nmr (benzene) 29.0 (18-Me), and 38.2 (Hz (19-Me); infrared (Nujol) absorption at 1020, 1030, and 1037 cm^{-1} [lit.[2] mp 227–229°; nmr 28.5 (18-Me) and 38 Hz (19-Me); infrared absorption at 1022, 1030, and 1038 cm^{-1}].

The second product eluted was identified as 3-thia-5α-cholestane 3β-oxide (**5b**): mp 230–233°; nmr (benzene) 33.5 (18-Me) and 35.3 Hz (19-Me); infrared (Nujol) absorption at 1060 cm^{-1} [lit.[2] mp 229–232°, nmr 32 (18-Me) and 35.5 Hz (19-Me); infrared absorption at 1060 cm^{-1}].

Registry No.—**1**, 16666-71-0; **4a**, 16666-68-5; **4b**, 16666-69-6; **6**, 16666-70-9.

(5) V. Burckhardt and T. Reichstein, *Helv. Chim. Acta*, **25**, 1434 (1942).

(6) S. Hara, N. Matsumoto, and T. Takeuchi, *Chem. Ind.* (London), 2086 (1962).

(7) The reaction of Grignard reagents with lactones to yield hydroxy ketones has been reviewed; see, for example, E. Müller, Ed., in Houben–Weyl's "Methoden der organischen Chemie," Vol. VI, Part 2, 4th ed, G. Thiem Verlag, Stuttgart, 1963, pp 799–802.

(8) In general, Baeyer–Villiger oxidation of primary alkyl aryl ketones yields mainly the product of aryl migration. However, examples of alkyl migration are known; *e.g.*, Baeyer–Villiger oxidation of *t*-butyl phenyl ketone and of 1-apocamphyl phenyl ketone yield the product of alkyl migration [M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Amer. Chem. Soc.*, **80**, 6393 (1958)].

(9) Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Nmr spectra were measured on a Varian A-60A spectrometer in *ca.* 10% solutions. Chemical shifts are reported in hertz downfield from internal TMS.