4-Aza-4-benzyl-5-cholestane (VII). 4-Aza-4-benzyl-5-cholesten-3-one (III) (1.6 g.) was added to a solution of 1.3 g. of lithium hydride in anhydrous ether by means of a Soxhlet extractor. The mixture was refluxed for 4 hr. after the addition was completed. The excess hydride was destroyed with water, and the inorganic salts were filtered and washed with ether. The ether solutions were combined and dried over sodium sulfate. The residue, obtained by evaporating the solvent, was crystallized from ether-acetone to yield VII as colorless needles; 1.47 g. (95%); m.p. 90–94°. An analytical sample was prepared by two additional crystallizations from ether-acetone; m.p. 97–101°; $[\alpha]_D$ −170°; λ_{max} 6.08 and 6.67 μ (6.02 and 6.67 μ in the presence of a slight excess of sulfuric acid).

Anal. Calcd. for $C_{33}H_{51}N$: C, 85.84; H, 11.13; N, 3.03. Found: C, 86.17; H, 11.03; N, 2.98.

4-Aza-4-methyl-5-cholestene (VIII). 4-Aza-4-methyl-5-cholesten-3-one (IV) (4.2 g.) was added to a solution of 3.8 g. of lithium aluminum hydride in 300 ml. of anhydrous ether by means of a Soxhlet extractor. After the addition was completed, the mixture was refluxed for 7 hr. The excess hydride was destroyed with water and the inorganic salts were filtered and washed with ether. The ether solutions were combined and dried over sodium sulfate. The solvent was evaporated and the residue crystallized from ether-acetone to yield 3.86 g. (95%) of VIII as colorless needles; m.p. 96–99°; $[\alpha]_D$ −136.7°; λ_{max} 6.08 μ (6.02 μ in the presence of a slight excess of sulfuric acid); (reported: an oil; λ_{max} 6.12 μ; 6.05 μ as the perchlorate).[11]

Anal. Calcd. for $C_{27}H_{47}N$: C, 84.07; H, 12.30; N, 3.63. Found: C, 84.03; H, 12.15; N, 3.44.

4-Aza-4-(β-hydroxyethyl)-5-cholestene (IX). A solution of 448 mg. of 4-aza-4-(β-hydroxyethyl)-5-cholesten-3-one (V) in 200 ml. of tetrahydrofuran was added to a solution of 800 mg. of lithium aluminum hydride in 100 ml. of tetrahydrofuran. The mixture was refluxed for 8 hr. The excess hydride was destroyed with water and the inorganic salts were filtered and washed with ether. The tetrahydrofuran and ether solutions were combined and dried over sodium sulfate. The residue obtained by distilling the solvent was crystallized from ethanol to yield 360 mg. (90%) of the monohydrate of IX as colorless needles; m.p. 108–112°; λ_{max} 6.08 μ (6.02 μ in the presence of a slight excess of sulfuric acid). The anhydrous base was so hygroscopic that we were able to obtain a better analysis on the monohydrate.

Anal. Calcd. for $C_{28}H_{51}O_2N$: C, 77.54; H, 11.85; N, 3.23. Found: C, 77.77; H, 11.76; N, 3.34.

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[CONTRIBUTION FROM THE PHARMACEUTICAL CHEMISTRY DEPARTMENT, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

Steroids. V. The Chemistry of 4-Oxa-5α-cholestan-3-one[1-3]

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All attempts to prepare 4-aza steroids from 4-oxa-5α-cholestan-3-one (I) by reaction with ammonia, methylamine, hydrazine, β-hydroxyethylamine, and benzylamine yielded only 5β-hydroxy-3,5-seco-4-nor-3-cholestanamides. All attempts to cyclize the amides resulted in the formation of I. The lactone I and 5β-hydroxy-*N*-methyl-3,5-seco-4-nor-3-cholestanamide were reduced with lithium aluminum hydride to 3,5-seco-4-norcholestane-3,5β-diol (VIII) and 5β-hydroxy-3-methylamino-3,5-seco-4-norcholestane, respectively. The cyclization of VIII with phosphorus oxychloride or tosyl chloride and the lithium aluminum hydride reduction of the boron trifluoride complex of I yielded 4-oxa-5α-cholestane.

4-Oxa-5α-cholestan-3-one (I) is easily prepared by the persulfuric acid oxidation of 4-cholesten-3-one.[4] It seemed to us that a series of 4-aza steroids might be prepared by the reaction of I with amines. 4-Aza steroids have been prepared by the reaction of ammonia with 4-oxa-5-cholesten-3-one.[5,6] δ-Valerolactone has been treated with 2,3-dimethoxyphenylethylamine[7] and *o*-phenylenediamine[8] to yield 1-(3,4-dimethoxyphenolethyl)-2-piperidone (66%) and 1,2,3,4-tetrahydropyrido[*a*]-benzimidazole (15%) respectively. There are many reports of the synthesis of lactams from γ-lactones which are derived from primary, secondary, and tertiary alcohols as well as enols and phenols.[9–12] Temperature control was often important to assure the formation of the lactam instead of the γ-hydroxy amide.

All attempts to prepare 4-aza steroids by the reaction of the lactone (I) with amines resulted in the formation of δ-hydroxyamides. Methylamine reacted readily at room temperature, but ammonia, a less nucleophilic reagent, required elevated temperatures. The lactone was treated with each of these amines in a sealed tube at temperatures ranging from 140° to 280°. Only δ-hydroxy amides were obtained. Thus, the reaction of the lactone with ammonia,

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(3) Presented at the 1960 meeting of the American Association for the Advancement of Science in New York City, Dec. 29, 1960.

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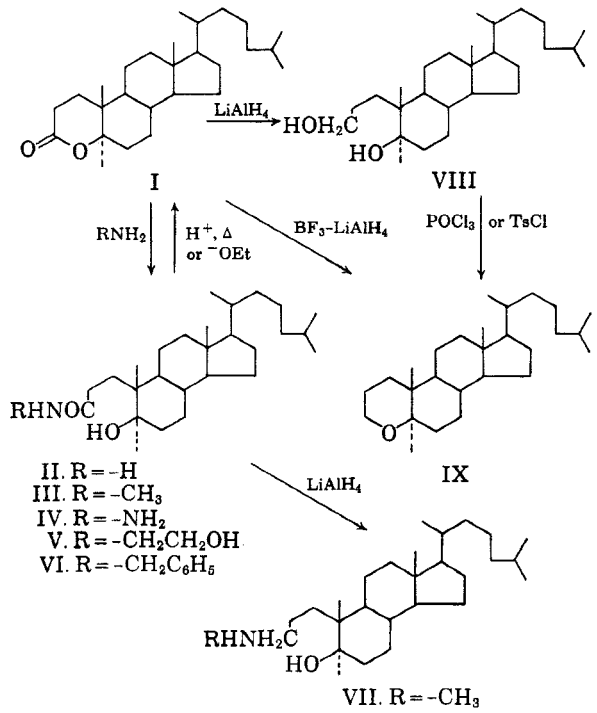
methylamine, hydrazine, β-hydroxyethylamine, and benzylamine yielded 5β-hydroxy-3,5-seco-4-nor-3-cholestanamide (II), 5β-hydroxy-*N*-methyl-3,5-seco-4-nor-3-cholestanamide (III), *N*-amino-5β-hydroxy-3,5-seco-4-nor-3-cholestanamide (IV), 5β-hydroxy - *N* - (β - hydroxyethyl) - 3,5 - seco - 4-nor-3-cholestanamide (V), and *N*-benzyl-5β-hydroxy-3,5-seco-4-nor-3-cholestanamide (VI), respectively. Other investigators have reported similar difficulty in preparing lactams directly from lactones.[9,11,13,14]

Reppe[11] succeeded in preparing pyrrolidone in 79% yield by heating γ-hydroxybutyramide in an autoclave at 250° for seven hours. In a similar manner a large series of *N*-substituted pyrrolidones was prepared. All attempts to prepare 4-aza steroids from the 5β-hydroxy-3,5-seco-4-nor-3-cholestanamides by pyrolysis or by the use of such catalysts as acetic acid, polyphosphoric acid, calcium oxide, and sodium ethoxide yielded I.



The hydroxyamide (III) and the lactone (I) were reduced with lithium aluminum hydride to 5β - hydroxy - 3 - methylamino - 3,5 - seco - 4-norcholestane (VII) and 3,5-seco-4-norcholestane-3,5β-diol (VIII), respectively. The diol (VIII) was cyclized to 4-oxa-5α-cholestane (IX) by phosphorus oxychloride (85% yield) and tosyl chloride in pyridine (60% yield). 4-Oxa-5α-cholestane (IX) was also prepared by the lithium aluminum hydride reduction of its boron trifluoride complex utilizing the reaction recently reported by Pettit and Kasturi.[15] This confirmed the structure of IX[16] since the configuration at position 5 should be unaffected.

4-Oxa-5α-cholestane has been prepared recently from 4,5-seco-3-cholesten-5-one[16] by the following sequence of reactions: (a) ozonolysis, (b) lithium aluminum hydride reduction to diol which was not isolated in pure form, and (c) cyclization with benzenesulfonyl chloride. A product, with physical properties similar to IX, was isolated in 20% yield from the cyclization and assigned the structure of IX. Although we are in agreement with the structural assignment, we do not believe that lithium aluminum hydride reduction of the 5-keto group is sufficiently stereospecific to establish a 5α-configuration, when only a small portion is isolated. The steric course of the lithium aluminum hydride reduction of 3,5-seco-4-norcholestan-5-ones is now under investigation in this laboratory.

EXPERIMENTAL[17]

4-Oxa-5α-cholestan-3-one (I) was prepared from 4-cholesten-3-one by oxidation with persulfuric acid.[4,18]

5β-Hydroxy-3,5-seco-4-nor-3-cholestanamide (II). 4-Oxa-5α-cholestan-3-one (2.50 g.) was dissolved in 200 ml. of absolute ethanol which had previously been saturated with ammonia. The solution was heated in a sealed tube at 150° for 8 hr. The solvent was removed, and the residue crystallized from methanol yielding 1.82 g. (70%) of 5β-hydroxy-3,5-seco-4-nor-3-cholestanamide, m.p. 168.2–170.2°; $[\alpha]_D^{25}$ +40.0° (*c* 0.5, chloroform); $\lambda_{max}^{CHCl_3}$ 2.72, 2.90, 2.98, and 6.00 μ.

Anal. Calcd. for $C_{26}H_{47}O_2N$: C, 76.98; H, 11.68; N, 3.45. Found: C, 76.73; H, 11.44; N, 3.36.

5β-Hydroxy-N-methyl-3,5-seco-4-nor-3-cholestanamide (III). 4-Oxa-5α-cholestan-3-one (2.0 g.) was dissolved in 100 ml. of absolute ethanol which had previously been saturated with methylamine. After 30 min., the solvent was removed, and the solid residue was crystallized from methanol to give 1.55 g. (72%) of 5β-hydroxy-*N*-methyl-3,5-seco-4-nor-3-cholestanamide; m.p. 151–152.6°; $[\alpha]_D^{25}$ +38.7° (*c* 2.0, chloroform); $\lambda_{max}^{CHCl_3}$ 2.72, 2.90, 2.98, 6.02, 6.53 μ.

Anal. Calcd. for $C_{27}H_{49}O_2N$: C, 77.27; H, 11.78; N, 3.34. Found: C, 77.09; H, 11.50; N, 3.41.

N-Amino-5β-hydroxy-3,5-seco-4-nor-3-cholestanamide (IV). 4-Oxa-5α-cholestan-3-one (1.0 g.) and 0.5 ml. of hydrazine hydrate (85%) were dissolved in 10 ml. of ethanol and refluxed for 4 hr. After concentration to approximately 3.0 ml., 0.93 g. (86%) of *N*-amino-5β-hydroxy-3,5-seco-4-nor-3-cholestanamide was obtained as large colorless platelets; m.p. 178–181°. An analytical sample was obtained by recrystallization from methanol; m.p. 178.6–181.8°; $[\alpha]_D^{25}$ +38.8° (*c* 2.0, chloroform); λ_{max}^{KBr} 2.94, 3.02, 6.05, and 6.50 μ.

Anal. Calcd. for $C_{26}H_{48}O_2N_2$: C, 74.23; H, 11.50; N, 6.66. Found: C, 74.49; H, 11.16; N, 6.55.

(13) E. L. Neugebauer, *Ann.*, **227**, 97 (1885).
(14) R. Fittig, *Ann.*, **256**, 147 (1889).
(15) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **25**, 875 (1960).
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(17) The melting points are corrected unless stated otherwise. Most of the analyses, corrected melting points, and rotation data were furnished through the courtesy of the Sterling-Winthrop Research Institute. Other analyses were obtained from Schwarzkopf microanalytical laboratory. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer.
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5β-Hydroxy-N-(β-hydroxyethyl)-3,5-seco-4-nor-3-cholestanamide (V). 4-Oxa-5α-cholestan-3-one (1.0 g.) and 6.0 ml. of freshly distilled ethanolamine were heated at 170° in a nitrogen atmosphere for 5 hr. The excess ethanolamine was removed, and the residue crystallized from methanol to yield 0.88 g. (75%) of 5β-hydroxy-*N*-(β-hydroxyethyl)-3,5-seco-4-nor-3-cholestanamide; m.p. 185.4–186.0°; $[\alpha]_D^{25}$ +32.2° (*c* 0.5, chloroform); λ_{max}^{KBr} 3.00, 6.14, and 6.50 μ.

Anal. Calcd. for $C_{29}H_{51}NO_3$: C, 74.78; H, 11.43; N, 3.11. Found: C, 75.01; H, 11.29; N, 3.28.

N-Benzyl-5β-hydroxy-3,5-seco-4-nor-3-cholestanamide (VI). 4-Oxa-5α-cholestan-3-one (1 g.) and 6.0 ml. of freshly distilled benzylamine were heated in a nitrogen atmosphere at 180° for 1 hr. The cooled solution was diluted with 100 ml. of ether and washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and water. The solvent was removed after drying over sodium sulfate. The residue, after crystallization from petroleum ether (b.p. 30–60°), yielded 1.21 g. (99%) of *N*-benzyl-5β-hydroxy-3,5-seco-4-nor-3-cholestanamide; m.p. 145.2–147.2°, $[\alpha]_D^{25}$ +34.3° (*c* 1.0, chloroform); λ_{max}^{KBr} 3.00, 6.07, and 6.58 μ.

Anal. Calcd. for $C_{33}H_{53}O_2N$: C, 79.94; H, 10.77; N, 2.83. Found: C, 80.19; H, 10.70; N, 2.68.

5β-Hydroxy-3-methylamino-3,5-seco-4-norcholestane (VII). 5β-Hydroxy-*N*-methyl-3,5-seco-4-nor-3-cholestanamide (1.0 g.) was added to a refluxing slurry of 3 g. of lithium aluminum hydride in 250 ml. of anhydrous ether by means of a Soxhlet extractor. The addition was complete in 2 hr. The mixture was refluxed for 48 hr. and then the excess hydride was destroyed with water. The precipitate was filtered and washed with ether (4 × 150 ml.). The ether was evaporated after drying the solution with sodium sulfate. The residue, after crystallization from acetone, yielded 0.71 g. (74%) of 5β-hydroxy-3-methylamino-3,5-seco-4-norcholestane, m.p. 98–100°. Two recrystallizations from acetone yielded an analytical sample; m.p. 102.6–105.6°; $[\alpha]_D^{25}$ +23.8° (*c* 1.0, chloroform); λ_{max}^{KBr} 2.88, 3.01, and 3.12 μ.

Anal. Calcd. for $C_{27}H_{51}ON$: C, 79.92; H, 12.67; N, 3.45. Found: C, 80.11; H, 12.63; N, 3.24.

3,5-Seco-4-norcholestan-3,5β-diol (VIII). 4-Oxa-5α-cholestan-3-one (0.5 g.) was added to a refluxing solution of 0.5 g. of lithium aluminum hydride in 100 ml. of anhydrous ether by means of a Soxhlet extractor. The addition was complete in 0.5 hr. The mixture was refluxed for 6 hr. The excess hydride was destroyed with water-saturated ether. The precipitate was filtered and washed with ether (4 × 100 ml.). The ether was evaporated after the solution had been dried over sodium sulfate. The residue was crystallized from 80% methanol to yield 0.47 g. (95%) of 3,5-seco-4-norcholestan-3,5β-diol, m.p. 129.4–131.8°; $[\alpha]_D^{25}$ +23.9° (*c* 0.5, chloroform); $\lambda_{max}^{CHCl_3}$ 2.75 and 2.92 μ. There was no carbonyl absorption.

Anal. Calcd. for $C_{26}H_{48}O_2$: C, 79.53; H, 12.32; O, 8.15. Found: C, 79.79; H, 12.13; O, 8.05.

4-Oxa-5α-cholestane (IX). *Method A.* A solution of 4-oxa-5α-cholestan-3-one (500 mg.) and 10 ml. of freshly distilled boron trifluoride etherate in 10 ml. of dry ether was added to an ice-cooled mixture of 0.5 g. of lithium aluminum hydride in 100 ml. of dry ether. The mixture was kept at 0–5° for 45 min., refluxed for 2 hr., and then treated with water-saturated ether followed by dilute sulfuric acid. The ether layer was separated, washed with water, and dried over sodium sulfate. The solvent was removed, and the resulting colorless oil was crystallized from methanol to yield 310 mg. (63%) of 3-oxa-5α-cholestane, as colorless needles, m.p. 88–90°. An analytical sample was obtained upon recrystallization from methanol, m.p. 91–92°; $[\alpha]_D^{25}$ +48.0° (*c* 1.0, chloroform); $\lambda_{max}^{CS_2}$ 9.02, 9.15 μ. There was no hydroxyl or carbonyl absorption.

Anal. Calcd. for $C_{26}H_{46}O$: C, 83.35; H, 12.38. Found: C, 83.44; H, 12.25.

Method B. 3,5-Seco-4-norcholestan-3,5β-diol (500 mg.) was treated with 10 ml. of phosphorus oxychloride at 80° for 0.5 hr. The excess phosphorus oxychloride was removed by distillation. The residue was poured onto ice, neutralized with sodium hydroxide, and extracted with ether. The ether was removed, after drying over sodium sulfate, and the resulting solid residue was crystallized from methanol to yield 400 mg. (85%) of 4-oxa-5α-cholestane, m.p. 91–92°. Infrared spectra and mixed melting points showed this sample to be identical with the sample prepared by method A.

Method C. A solution of 200 mg. of 3,5-seco-4-norcholestan-3,5β-diol and 200 mg. of tosyl chloride in 4 ml. of dry pyridine was kept at room temperature for 90 min. The solution was poured into water and extracted with ether. The ether extracts were washed with dilute hydrochloric acid, sodium bicarbonate solution, and water. The solvent was removed, after drying over sodium sulfate, and the solid residue was crystallized from acetone to yield 110 mg. (60%) of 4-oxa-5α-cholestane, m.p. 91–92°. Infrared spectra and mixed melting points showed this sample to be identical with the sample prepared by method A.

Attempted cyclization of various 5β-hydroxy-3,5-seco-4-nor-3-cholestanamides. (i) *By thermal dehydration.* 5β-Hydroxy-*N*-methyl-3,5-seco-4-nor-3-cholestanamide was heated in a nitrogen atmosphere at 240° for 15 min. The lactone (I) was obtained in over 80% yield and the infrared spectrum of the remaining 20% gave no indication of lactam. The expected lactam, 4-aza-4-methyl-5α-cholestan-3-one, absorbs at 6.13 μ.[19] Treatment of each of the 5β-hydroxy-3-cholestanamides at temperatures ranging from 140–280° gave similar results.

(ii) *By calcium oxide dehydration.* Fusion of the 5β-hydroxy-3-cholestanamides with calcium oxide at 240° for 15 min. gave the same result as described above.

(iii) *By acetic acid.* Amides II and III were refluxed for 2 hr. in glacial acetic acid. Lactone I, with some unchanged amide, was obtained.

(iv) *By hydrogen bromide.* A solution of amide III in glacial acetic acid was treated with dry hydrogen bromide for 0.5 hr. at 25°. An 85% yield of lactone I was obtained with no evidence of lactam.

(v) *By tosyl chloride.* A solution of amide III in dioxane was treated with an equal weight of *p*-toluenesulfonyl chloride at 40° for 15 min. Unchanged amide was recovered in 80% yield.

(vi) *By polyphosphoric acid.* Treatment of amide III with polyphosphoric acid for 1 hr. at 120° yielded a yellow oil which resisted crystallization. The infrared spectrum gave no indication of lactam.

(vii) *By basic catalyst.* The lactone I was obtained in 95% yield by refluxing amide III in an ethanolic solution of sodium ethoxide for 30 min.

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(19) N. J. Doorenbos and K. A. Kerridge, unpublished data.