Hydrogenation of fluorenone XVIII. Fluorenone XVIII (1.0 g.) was dissolved in dioxane (40 ml.), copper-chromium oxide (0.5 g.) was added, and the reduction was carried out in a rocking bomb at an initial pressure of 1500 p.s.i. (at 25°). The hydrogenation was allowed to proceed for 8 hr. at 210–215°. The crude product, obtained after filtering the catalyst and concentrating the solution, was a viscous oil. This material was dissolved in benzene (5 ml.) and *t*-butyl alcohol (4 ml.) and oxidized with *t*-butyl chromate[21] solution (10 ml.). The mixture was stirred at 25–30° for 24 hr. and then with benzene and hydrochloric acid (75 ml., 6*N*) until all the solid material was in solution. The organic layer was separated and washed with dilute hydrochloric acid, water, and sodium carbonate solution. The solvent was evaporated and the residue chromatographed on alumina (30 g.) to yield 0.6 g. of a yellow oil. This oil had strong bands in the infrared spectrum at 5.82, 6.27, 6.35, and 6.88 μ indicating the presence of the desired ketone function and an unreduced aromatic ring. However, the derivatives prepared from the oil indicated that complete reduction and some hydrogenolysis[22] had occurred.

(21) H. H. Inhoffen, *Ber.*, 84, 90 (1951).

(22) A similar hydrogenolysis of a hydroxyl group has also been found to take place with a palladium catalyst at 175°; see R. A. Barnes and A. H. Sherman, *J. Am. Chem. Soc.*, 75, 3013 (1953).

Treatment of the crude ketonic material with semicarbazide acetate yielded a crystalline material which melted at 261–262°.

Anal. Calcd. for $C_{18}H_{27}ON_3$: C, 69.27; H, 9.81. Found: C, 69.59; H, 9.63.

The infrared spectrum was that expected for a semicarbazone; λ_{max}^{KBr} 2.91, 3.18, 5.92, 6.33, 6.90, and 7.30 μ, *etc.*

A second small crop of the semicarbazone melted at 189–194°; this substance may be largely the derivative of a stereoisomeric form of ketone XIX.

Anal. Calcd. for $C_{18}H_{27}ON_3$: C, 69.27; H, 9.81. Found: C, 68.75; H, 9.70.

The ketonic product obtained from another run of the hydrogenation under similar conditions was characterized as the 2,4-dinitrophenylhydrazone, m.p. 114–115°. The derivative in this experiment must have resulted from a ketone (XX) in which hydrogenation was complete and in which hydrogenolysis was not as extensive.

Anal. Calcd. for $C_{31}H_{38}O_8N_4$: C, 60.42; H, 6.76. Found: C, 60.26; H, 6.63.

The infrared spectrum for this derivative had bands in agreement with the structure suggested; λ_{max}^{KBr} 2.95, 3.04, 6.17, 6.28, 6.60, 6.66, 7.08 μ, *etc.*

NEW BRUNSWICK, N. J.

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

Steroids. IV. Synthesis of Some 4-Azacholestanes[1–4]

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Reaction of 5-oxo-3,5-seco-4-norcholestan-3-oic acid with ammonia, benzylamine, methylamine, and ethanolamine at elevated temperatures yielded the enamine lactams, 4-aza-5-cholesten-3-one, 4-aza-4-benzyl-5-cholesten-3-one, 4-aza-4-methyl-5-cholesten-3-one, and 4-aza-4-(β-hydroxyethyl)-5-cholesten-3-one. The reduction of these lactams with lithium aluminum hydride gave 4-aza-4-cholestene, 4-aza-4-benzyl-5-cholestene, 4-aza-4-methyl-5-cholestene, and 4-aza-4-(β-hydroxyethyl)-5-cholestene, respectively, as products.

In recent years considerable attention has been given to the synthesis of aza steroids.[1,6] The nitrogen in nearly all of the reported aza steroids is unsubstituted. In the hope of finding new types of structures with useful pharmacodynamic or cancer chemotherapeutic properties, a program directed to the synthesis of a series of 4-substituted aza steroids was initiated. This paper describes the synthesis of some derivatives of 4-azacholestane.

The first substituted 4-aza steroid to be described was 4-aza-4-benzyl-5-cholesten-3-one (III).[7] It was prepared by refluxing 5-oxo-3,5-seco-4-norcholestan-3-oic acid (I) in excess benzylamine, the reaction temperature being about 185°. The related unsubstituted lactam, 4-aza-5-cholesten-3-one (II), has been prepared by the reaction of ammonia with I at temperatures of 140–200°[2,8,9] or with 4-oxa-5-cholesten-3-one at room temperature.[10] In this investigation II was prepared from I and ammonia at 200° and III was prepared by Woodward's procedure.

4-Aza-4-methyl-5-cholesten-3-one (IV) was synthesized (a) by heating the methylamine salt of I at 180° and (b) by heating a solution of I in ethanol, which had been previously saturated with methylamine, in a pressure vessel at 180°. The first of these methods gave poorer yields as the result of the

(1) For paper III see N. J. Doorenbos and M. T. Wu, *J. Org. Chem.*, 26, 2548 (1961).

(2) Presented, in part, at the 136th meeting of the American Chemical Society in Atlantic City, Fall, 1959.

(3) Abstracted from a thesis submitted by Chien Li Huang to the graduate faculty of the University of Maryland in partial fulfillment of the requirements for the Ph.D. in Pharmaceutical Chemistry, June 1960.

(4) This paper was awarded second prize for the Southern District in the 1960 Lunsford-Richardson Awards sponsored by Vick Chemical Co.

(5) Sterling-Winthrop Research Fellow 1958–1959.

(6) T. L. Jacobs and R. B. Brownfield, *J. Am. Chem. Soc.*, 82, 4033 (1960).

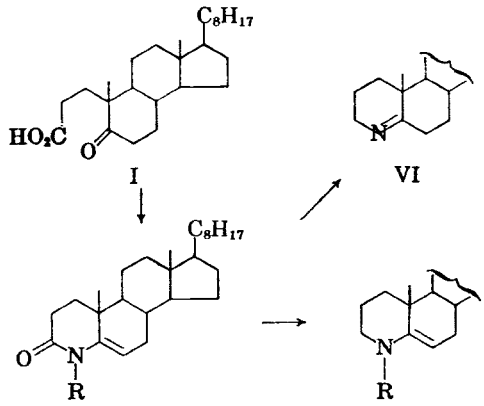
(7) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, 74, 4223 (1952).

(8) N. J. Doorenbos, C. L. Huang, C. R. Tamorria, and M. T. Wu, *J. Org. Chem.*, 26, 2546 (1961).

(9) R. S. Wildi, U. S. Patent 2,897,202 (July 28, 1959).

(10) M. Uskoković and M. Gut, *Helv. Chim. Acta*, 42, 2258 (1959).

decomposition of a portion of the salt to I and methylamine. 4-Aza-4-(β-hydroxyethyl)-5-cholesten-3-one (V) was prepared by refluxing I in a slight excess of ethanolamine or by refluxing I and ethanolamine in benzene. The latter procedure gave the higher yield.



II. R = H—
III. R = $C_6H_5CH_2$—
IV. R = CH_3—
V. R = $HOCH_2CH_2$—

VII. R = $C_6H_5CH_2$—
VIII. R = CH_3—
IX. R = $HOCH_2CH_2$—

The lithium aluminum hydride reduction of II, III, IV, and V yielded 4-aza-4-cholestene (VI), 4-aza-4-benzyl-5-cholestene (VII), 4-aza-4-methyl-5-cholestene (VIII), and 4-aza-4-(β-hydroxyethyl)-5-cholestene (IX), respectively. Diethyl ether was used as the solvent for 4-aza-4-benzyl-5-cholesten-3-one and 4-aza-4-methyl-5-cholesten-3-one. Tetrahydrofuran was used as the solvent for the other lactams, 4-aza-5-cholesten-3-one and 4-aza-4-(β-hydroxyethyl)-5-cholesten-3-one, because of their insolubility in diethyl ether. Each of these amines was obtained as a low melting, white, crystalline solid. Compound VIII was obtained previously as an oil by the mercuric acetate oxidation of 4-aza-4-methyl-5α-cholestane.[11]

The weak absorption of VII, VIII, and IX at 6.08 μ has been assigned to C=C stretching of the 5,6-double bond. Each of these enamines was shown to be an α,β-unsaturated amine by a comparison of the infrared spectra of the bases and their hydrogen sulfate salts. The absorption of the double bond of the salts had shifted from 6.08 to 6.02 μ and increased in intensity.[12] The 6.03 μ band of VI did not shift or change in intensity when the salt was made. It is interesting that although these three enamines absorb above 220 mμ, the peak appears to be below 220 mμ. This indicates that there is poor conjugation between nitrogen and the double bond since most α,β-unsaturated amines absorb at longer wave lengths.[6]

The double bond of VI was assigned to the 4,5-position for several reasons: (1) VI does not exhibit N—H stretching in the infrared. (2) VI has a moderately strong sharp peak at 6.03 μ which is not reduced in intensity by further treatment with lithium aluminum hydride. A similar peak was reported by Jacobs[6] for 6-aza-5-cholestene. (3) The M_D value changed +555° upon reduction while the M_D values of the other lactams became more negative. The shift of a double bond from the 5,6-position to a 4,5-position in natural steroids results in a change in M_D of about +500°.[13] Jacobs shifted the double bond in the other direction when he reduced 6-aza-4-cholesten-7-one to 6-aza-5-cholestene with lithium aluminum hydride. He reported a change in M_D of −606°.[6]

EXPERIMENTAL[14]

4-Aza-4-benzyl-5-cholesten-3-one (III). Following Woodward's procedure,[7] 5-oxo-3,5-seco-4-norcholestan-3-oic acid (I)[15] was refluxed in excess benzylamine to yield III; m.p. 124–127°; $[\alpha]_D$ −93.1°; λ_{max} 235 mμ, log ε 4.05; λ_{max} 6.13 μ with an inflection at 6.00 μ.

Anal. Calcd. for $C_{33}H_{49}ON$: C, 83.32; H, 10.38; N, 2.94. Found: C, 83.52; H, 10.55; N, 2.80.

4-Aza-4-methyl-5-cholesten-3-one (IV). A 40.4 g. sample of the keto acid (I)[15] was dissolved in 250 ml. of ethanol which had been previously saturated with methylamine. The solution was heated in a sealed tube for 8 hr. at 140°. The solvent was removed and the residue crystallized from petroleum ether (b.p. 30–60°) to yield 32.0 g. (80%) of IV, m.p. 102–104°. An analytical sample was prepared by an additional crystallization; m.p. 103–105°; $[\alpha]_D$ −122°; λ_{max} 234 mμ, log ε 4.13; λ_{max} 6.13 μ with an inflection at 6.00 μ.

Anal. Calcd. for $C_{27}H_{45}NO$: C, 81.12; H, 11.35; N, 3.50. Found: C, 81.30; H, 11.48; N, 3.47.

4-Aza-4-(β-hydroxyethyl)5-cholesten-3-one (V). Ethanolamine (10 ml.) and 15.0 g. of the keto acid (I)[15] were dissolved in 100 ml. of benzene and refluxed for 8 hr. The cooled mixture was washed with water and dried over sodium sulfate. The residue obtained by removing the solvent was crystallized from acetone to yield 4.8 g. (30%) of V as colorless needles; m.p. 165–166°; $[\alpha]_D$ −80°; λ_{max} 234 mμ, log ε 4.08; λ_{max} 6.13 μ with an inflection at 6.00 μ.

Anal. Calcd. for $C_{29}H_{47}O_2N$: C, 78.25; H, 11.03; N, 3.26. Found: C, 78.27; H, 10.74; N, 3.14.

4-Aza-4-cholestane (VI). 4-Aza-5-cholesten-3-one (II)[8] (0.485 g.) was added to a solution of 1.0 g. of lithium aluminum hydride in 300 ml. of tetrahydrofuran by means of a Soxhlet extractor. The solution was refluxed for 8 hr. following the addition. The excess hydride was destroyed with water. The inorganic salts were filtered and washed with ether. The ether solutions were combined and dried over sodium sulfate. The solvent was distilled and the residue crystallized from ether to yield 0.460 g. (99%) of VI as colorless needles; m.p. 92–96°; $[\alpha]_D$ +64.3°; λ_{max} 6.03 μ.

Anal. Calcd. for $C_{26}H_{45}N$: C, 84.05; H, 12.12; N, 3.77. Found: C, 83.97; H, 12.13; N, 4.06.

(11) J. McKenna and A. Tulley, *J. Chem. Soc.*, 945 (1960).

(12) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(13) L. F. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Corp., New York, 1959, p. 178.

(14) Melting points were taken on a Fisher-Johns block and are uncorrected. Specific rotations were taken on 1.00% solutions in chloroform at 25°. Ultraviolet spectra were obtained on ethanol solutions with a Beckman DU. Infrared spectra were obtained on chloroform solutions with a Perkin-Elmer Infracord. Analyses were obtained from Sterling-Winthrop Research Institute.

(15) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 579 (1950).

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,

(1) For paper IV in this series see N. J. Doorenbos and C. L. Huang, *J. Org. Chem.*, **26**, 4548 (1961).

(2) This work was supported by Research Grant CY-4132 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. Steroid intermediates were furnished by the Cancer Chemotherapy National Service Center, National Institutes of Health.

(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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(9) H. Meyer, *Monatsh. Chem.*, **20**, 717 (1899).

(10) E. Späth and J. Lintner, *Ber.*, **69**, 2727 (1936).

(11) W. Reppe and co-workers, *Ann.*, **596**, 158 (1955).

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