Department of Pharmaceutical Chemistry, School of Pharmacy,
University of Maryland

Steroids. XXI. (1) Some N-Amino-4-azasteroids (2)

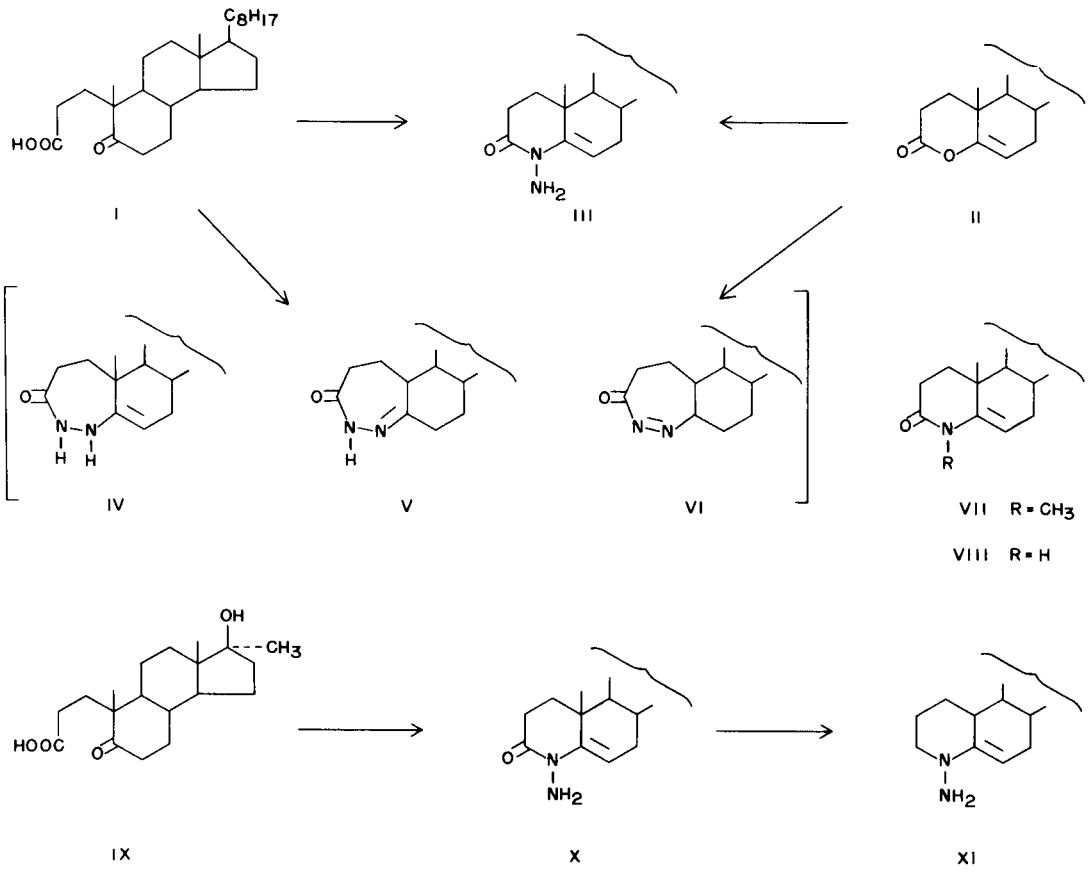
Norman J. Doorenbos (3) and Mu Tsu Wu

As part of a continuing study of 4-azasteroids, *e.g.*, 4-alkyl-4-azasteroids (4), 3,4-dialkyl-4-azasteroids (5), 4-hydroxy-4-azasteroids (6) and pyrimidino- and imidazolino-steroids (7), a convenient route to 4-amino-4-azasteroids was sought. The reaction of hydrazine with 3,5-seco-4-norcholestan-5-on-3-oic acid (I) or 4-oxa-5-cholesten-3-one (II) in glacial acetic acid at about 95° was found to give 4-amino-4-aza-5-cholesten-3-one (III) in 35-40% yield. Higher yields were obtained when the reaction was conducted in ethanol solution in a sealed tube at 150°.

The structure of III was established by analysis and spectra. The analysis was as expected. It was conceivable that the product of these reactions might possess a structure represented by IV, V or VI. These structures each have the same formula, $C_{26}H_{44}ON_2$. For this reason, it was necessary to eliminate these possibilities as well as confirm III by spectra.

The infrared spectra of these products contained peaks at 2.92 and 3.02 μ which is characteristic of primary amines (8) and lacked peaks which could be attributed to N-H stretching in a lactam (IV or V). The carbonyl stretching of III would be expected to be similar (9) to 4-methyl-4-aza-5-cholesten-3-one (VII) which is reported as 6.13 μ (4a). The carbonyl absorption of IV and V would be expected to be similar (9) to 4-aza-5-cholesten-3-one (VIII) which is reported as 6.04 μ (10). The carbonyl absorption of the products obtained by the reaction of I or II with hydrazine is 6.13 μ.

Ultraviolet spectra provided added evidence for assigning III as the structure of the products ob-



tained by the reaction of hydrazine with I or II. The amino substituent would be expected to cause a greater bathochromic shift than the methyl group (11). The absorption maximum of the unsubstituted lactam, VIII, is 233 mμ (log ε 4.13) (10), the N-methyl lactam, VII, is 234 mμ (log ε 4.13) (4a), and the N-amino lactam, III, is 244 mμ (log ε 4.12). The lack of absorption in the visible region eliminated the diazo derivative, VI.

4-Amino-17α-methyl-4-aza-5-androsten-17β-ol-3-one (X) was prepared in 74% yield by the reaction of 17α-methyl-3,5-seco-4-norandrostan-17β-ol-5-on-3-oic acid (IX) with hydrazine in ethanol solution at 160° in a pressure vessel. The structure of X was established by analysis and spectra. Treatment of X with lithium aluminum hydride yielded 4-amino-17α-methyl-4-azaandrost-5-en-17β-ol (XI).

Biological Data (12).

III was administered subcutaneously at 20 mg./Kg./day to castrate male rats, in groups of seven for seven days in an endocrine screen. The granuloma dry weight was lowered 20% indicating mild anti-inflammatory activity. Sodium elimination was decreased to 1/4 of the controls.

In a similar assay, X increased seminal vesicle and ventral prostrate weights by 30% and 65% respectively and decreased thymus and adrenal weights by 25% each.

X was screened for hypotensive activity in rats and found to be inactive.

III and X were found to be inactive in an antibacterial and antifungal screen.

EXPERIMENTAL (13)

4-Amino-4-aza-5-cholesten-3-one (III).

Method A.

A mixture of 280 mg. (0.0007 mole) of 3,5-seco-4-norcholestan-5-on-3-oic acid (I) (10,14), 2.0 g. (0.05 mole) of 85% hydrazine hydrate, and 8 ml. of glacial acetic acid was heated 0.5 hours on a steam bath. The solvent was distilled. Water was added to the residue and the mixture extracted with ether, washed with dilute sodium carbonate solution and water. The ether was evaporated, after drying over sodium sulfate, and the residue was crystallized from acetone to yield 110 mg. (40%) of III, m.p. 155-158°. Further recrystallization from methanol gave an analytical sample, m.p. 158-159°; $[\alpha]_D^{25}$ -57.4° (c, 0.5, chloroform); λ max (EtOH) 244 mμ (log ε 4.12); λ max ($CHCl_3$) 2.92, 3.02 and 6.13 μ with an inflection at 6.00 μ.

Anal. Calcd. for $C_{26}H_{44}ON_2$: C, 77.94; H, 11.06; N, 7.00. Found: C, 77.83; H, 10.92; N, 7.13.

Method B.

A mixture of 300 mg. (0.0008 mole) of 4-oxa-5-cholesten-3-one (II) (14), 2.0 g. (0.05 mole) of 85% hydrazine hydrate, and 8 ml. of glacial acetic acid was heated on a steam bath for 0.5 hours. The solvent was distilled and water added. The mixture was extracted with ether and the extracts washed with dilute sodium carbonate solution and water. After drying over sodium sulfate, the solvent was evaporated. The solid residue was crystallized from methanol to obtain 110 mg. (35%) of III, m.p. 158-160°. Infrared spectra and a mixed melting point showed this sample to be identical with the sample prepared by method A.

Method C.

3,5-Seco-4-norcholestan-5-on-3-oic acid (I) (10,14) (5.0 g.) was dissolved in 100 ml. of ethanol. Two ml. of 85% hydrazine hydrate was added, and the solution was heated in a pressure vessel at 150° for 5 hours. The solvent was distilled and the residue crystallized from methanol to obtain 3.40 g. (68%) of III, m.p. 158-159°. A mixed melting point and a comparison of infrared spectra showed this sample to be identical to the sample prepared by method A.

4-Amino-17α-methyl-4-azaandrost-5-en-17β-ol-3-one (X).

A mixture of 10 g. (0.0310 mole) of 17α-methyl-3,5-seco-4-norandrostan-17β-ol-5-on-3-oic acid (IX) (4b) in 200 ml. of ethanol was treated with 5.5 ml. of 85% hydrazine hydrate. The mixture was placed in a pressure vessel at 160° for 4 hours. The solvent was evaporated and the residue crystallized from ether-methanol to give 6.15 g. of 4-amino-17α-methyl-4-azaandrost-5-en-17β-ol-3-one, m.p. 196-200°. By gradual concentration of the mother-liquors, a further quantity of the product (1.20 g.) was obtained. The total weight represents a 74% yield. An analytical sample was obtained by two recrystallizations from methanol, m.p. 204-205°; $[\alpha]_D^{25}$ -142.8° (c 1.0, chloroform); λ max (EtOH) 244 mμ (log ε 4.12); λ max ($CHCl_3$) 2.80, 2.92, 3.02 and 6.13 μ with an inflection at 6.00 μ.

Anal. Calcd. for $C_{19}H_{30}O_2N_2$: C, 71.66; H, 9.50; N, 8.80. Found: C, 71.44; H, 9.68; N, 9.02.

4-Amino-17α-methyl-4-azaandrost-5-en-17β-ol (XI).

4-Amino-17α-methyl-4-azaandrost-5-en-17β-ol-3-one (X, 1.0 g., 0.0031 mole) was added to a refluxing slurry of 4 g. of lithium aluminum hydride in 200 ml. of anhydrous ether by means of a Soxhlet extractor. The addition was complete in 2 hours. The mixture was refluxed 48 hours. The excess hydride was destroyed with water-saturated ether. The precipitate was filtered and washed with ether. The ether was evaporated after drying the solution with sodium sulfate. The residue, after crystallization from ether-hexane, yielded 0.48 g. (51%) of 4-amino-17α-methyl-4-azaandrost-5-en-17β-ol, m.p. 207-209°; $[\alpha]_D^{25}$ -41.04° (c, 1.0 chloroform); λ max ($CHCl_3$) 2.80, 2.92, 3.02 and 6.20 μ (weak).

Anal. Calcd. for $C_{19}H_{32}ON_2$: C, 74.95; H, 10.59; N, 9.20. Found: C, 74.87; H, 11.09; N, 8.98.

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