

cooled mixture was added a solution of 0.65 ml. (5.9 mmoles) of titanium tetrachloride in 10 ml. of ethylene dichloride and the mixture heated under reflux for 22 hr. While still warm, 85 ml. of aqueous saturated sodium bicarbonate was added with vigorous stirring. After 2 hr., the mixture was filtered through Celite and, after washing the cake with chloroform (3 × 20 ml.), the organic phase was separated from the filtrate and evaporated to near dryness *in vacuo* at 40°. The residue was dissolved in 40 ml. of chloroform, washed with 40 ml. of 30% aqueous potassium iodide and water (40 ml.), dried over magnesium sulfate, filtered, and evaporated to dryness *in vacuo* at 60° to give the crude, blocked nucleoside (XVIII) as a yellow foam which hardened to a glass; yield, 1.71 Gm. (74.7%); $\nu_{\text{max}}^{\text{KBr}}$ (cm.⁻¹) 1750 (acetate C=O), 1720 (benzoate C=O), 1690 sh (amide C=O), 1605, 1580 (C=N and C=C), 1270 (benzoate C—O—C), 1220 sh (acetate C—O—C), 1085, 1070, 1020 (sugar C—O—C), 710 (monosubstituted phenyl).

A solution of 1.66 Gm. of the crude, blocked nucleoside (XVIII) in 35 ml. of 0.1 *N* methanolic sodium methoxide was heated under reflux for 2.5 hr. The cooled solution was neutralized with glacial acetic

acid, then set aside at 5° overnight, during which the crude product separated as a nearly white, crystalline solid. The crude nucleoside was collected on a filter, washed with 5 ml. of methanol, and dried; yield, 0.437 Gm. [39% from the diacetate (XVII)], m.p. 216–219°. For analysis, a sample was recrystallized from 90% aqueous ethanol with light charcoaling and again from water, and the white, crystalline solid was dried for several hours *in vacuo* at 100°, m.p. 221–222°; $\lambda_{\text{max}}^{\text{D}^{\text{H}}1}$ (m μ) 257 (ϵ 14,600); $\lambda_{\text{max}}^{\text{D}^{\text{H}}13}$ (m μ) 258 (ϵ 15,000), $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ (m μ) 259 (ϵ 14,900), ν_{max} (cm.⁻¹) 3300, 3150 (OH, NH), 1610, 1570 (C=C and C=N); $[\alpha]_{\text{D}}^{25}$ -38° (c 1.19, supersaturated in H₂O).

Anal.—Calcd. for C₁₀H₁₃N₅O₃: C, 47.80; H, 5.22; N, 27.88. Found C, 47.28; H, 5.17; N, 27.66.

Literature (7) m.p. 222–224°; $[\alpha]_{\text{D}}^{27}$ -42°.

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Steroids XXV

Synthesis of Some 4-Azapregnes

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The reaction of 3,5-seco-4-norpregnane-5,20-dion-3-oic acid (I) with methylamine yielded 4-methyl-4-aza-5-pregnene-3,20-dione (V) and 4-methyl-20-methylimino-4-aza-5-pregnen-3-one (VII). VII was hydrolyzed by hydrochloric acid to V. The reaction of I with ethanolamine gave 4-(β -hydroxyethyl)-4-aza-5-pregnene-3,20-dione. 5 ξ -Hydroxy-4-methyl-4-azapregnane-3,20-dione (VI) was formed by the reaction of 4-oxa-5-pregnene-3,20-dione and methylamine at room temperature. VI was dehydrated to V by heating above 100 or by the use of an acid catalyst. Reduction of 4-aza-5-pregnene-3,20-dione (II), V, and VII with lithium aluminum hydride yielded 4-aza-4-pregnen-20 β -ol, 4-methyl-4-aza-5-pregnen-20 β -ol, and 4-methyl-20 β -methylamino-4-aza-5-pregnene, respectively. By the following sequence of reactions, 4-methyl-4-aza-5-pregnen-20-one was prepared from V: ketal formation, lithium aluminum hydride reduction, and acid hydrolysis.

INTEREST in azasteroids has been increasing because of their potential value as pharmacodynamic and chemotherapeutic agents. 4-Aza-

steroids with antimicrobial (1–4), hypotensive (5), anti-inflammatory (5, 6), and hypocholesterolemic (5, 7) activities have been prepared in this laboratory. This paper describes the synthesis of some 4-azapregnes.

The synthesis of 4-aza-5-pregnene-3,20-dione (8) by two methods has been described (9): (a) the reaction of ammonia with 3,5-seco-4-norpregnane-5,20-dion-3-oic acid (I) at 150° and (b) the reaction of ammonia with 4-oxa-5-pregnene-3,20-dione (III) to yield 5 ξ -hydroxy-4-aza-pregnan-3-one (IV) which was then dehydrated by an acid catalyst or by heating above -100°. In this investigation, 4-methyl-4-aza-5-

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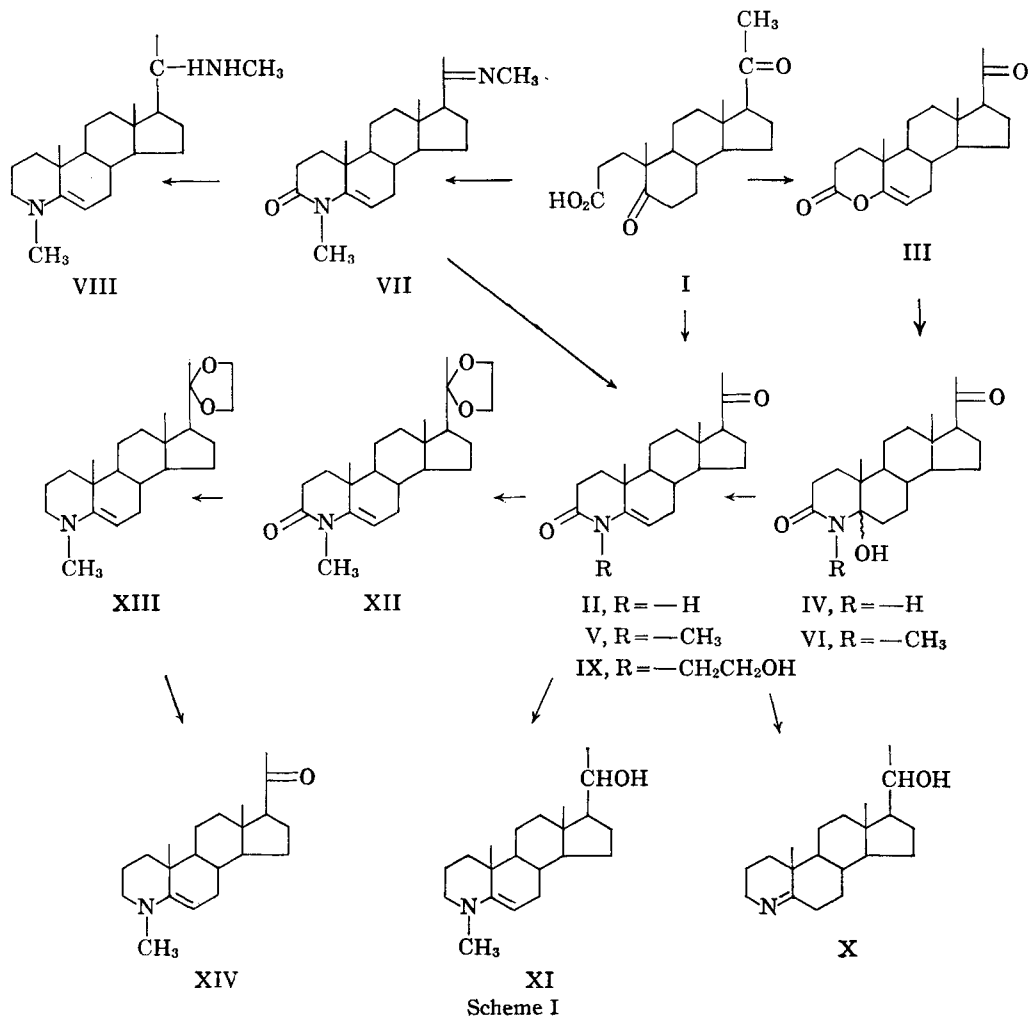
pregnene-3,20-dione (V) was prepared by a similar sequence of reactions. The reaction of I with methylamine in refluxing amyl alcohol (140°) yielded V. The reaction of III with methylamine at room temperature yielded 4-methyl-5 ξ -hydroxy-4-azapregnone-3,20-dione (VI). VI was dehydrated to V by heating above 100°. The reaction is over in a few seconds above the melting point. VI was also dehydrated rapidly by treatment with acid catalysts at room temperature.

Two moles of amine reacted with I when I was heated at 140° in a sealed tube with an excess of methylamine. The product formed was 4-methyl-20-methylimino-4-aza-5-pregnen-3-one (VII). This structure was assigned on the basis of its ultraviolet spectrum. The other possible structure would be an enamine with a double bond between carbons 17 and 20. The intense C=O absorption in the infrared at 6.13 μ obscures any possible absorption by C=C or C=N. The intensity of the absorption at 234

μ ($\log \epsilon$ 4.13) is in agreement with that observed for 4-methyl-4-aza-5-cholesten-3-one (234 μ , $\log \epsilon$ 4.13) (10). Enamines are known to absorb in this same region, while imines absorb at much lower wavelengths. The agreement in the ultraviolet spectra of these two compounds rules out the presence of an enamine structure. VII was hydrolyzed in good yield by warming with hydrochloric acid. VII is soluble in hydrochloric acid, and V crystallizes as it is formed by hydrolysis.

4-(β -Hydroxyethyl)-4-aza-5-pregnone-3,20-dione (IX) was prepared in 30% yield by the reaction of I with ethanolamine at 140°.

II, V, and VII were reduced by lithium aluminum hydride to 4-aza-4-pregnen-20 β -ol (X), 4-methyl-4-aza-5-pregnen-20 β -ol (XI), and 4-methyl-20 β -methylamino-4-aza-5-pregnone (VIII), respectively. The double bond in X has been assigned to position 4 because of the absorption at 6.03 μ . Earlier studies demonstrated that 4-aza-5-cholesten-3-one and 17 α -methyl-4-aza-



5-androsten-17 β -ol-3-one are reduced by lithium aluminum hydride to 4-aza-4-cholestene (10) and 17 α -methyl-4-aza-4-androsten-17 β -ol (8), respectively. Their structures were established by a comparison of molecular rotation values. The absorption at 6.03 μ was shown to be due to C=N. The configuration of the hydroxyl groups in X and XI was recently established in another project.¹ The stereochemistry of the hydride reduction of the imine group in VII should be the same as for the reduction of the carbonyl group in II and V. For this reason, the methylamino group has been assigned tentatively to the β -configuration.

In order to prepare 4-methyl-4-aza-5-pregnen-20-one (XIV) from V, the ketone carbonyl group was protected by reaction with ethylene glycol to form a ketal, 20-ethylenedioxy-4-methyl-4-aza-5-pregnen-3-one (XII). XII was reduced with lithium aluminum hydride to 20-ethylenedioxy-4-methyl-4-aza-5-pregnene (XIII) and then hydrolyzed to XIV. (Scheme I.)

Samples of most of these new steroids were submitted to the Cancer Chemotherapy National Service Center and the Sterling-Winthrop Research Institute for biological screening. III and V have mild antiandrogenic activity. They showed no other endocrine activity.

EXPERIMENTAL²

4 - Methyl - 4 - aza - 5 - pregnene - 3,20 - dione (V).—3,5-Seco-4-norpregnane-5,20-dion-3-oic acid (I) (11) (10.00 Gm.) was dissolved in 100 ml. of *n*-amyl alcohol with the aid of a few milliliters of ethanol. Excess methylamine was added, and the solution was refluxed 11 hr. The residue, obtained by distillation of the solvent, was dissolved in ether, washed with 1.5 *N* hydrochloric acid, then with 1% sodium carbonate solution, and finally with water. Removal of the solvent and crystallization from dilute ethanol gave 4.16 Gm. (43%) of V as white crystals, m.p. 256–259°; $[\alpha]_D -76.0^\circ$; λ_{max} . 234 m μ (log ϵ 4.12), 5.87 and 6.13 μ with a slight inflection at 5.99 μ (this inflection is due to C=C stretching) (8, 10).

Anal.—Calcd. for C₂₁H₃₁NO₂: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.84; H, 9.42; N, 4.16.

5 ξ - Hydroxy - 4 - methyl - 4 - azapregnane-3,20-dione (VI).—Dry methylamine gas was bubbled for 2 hr. through a solution of 600 mg. of 4-oxa-5-

pregnene-3,20-dione (III) (12) in 150 ml. of anhydrous benzene (9.14). After 2 days, the solvent was evaporated, and the white crystalline residue was washed with ether and filtered. Crystallization from benzene-ether yielded 122 mg. (22%) of VI, m.p. 160.5–162°; $[\alpha]_D +152^\circ$; λ_{max} . 2.78, 2.94, 5.87, and 6.12 μ .

Anal.—Calcd. for C₂₁H₃₃ON₃: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.26; H, 9.49; N, 4.00.

Dehydration of 5 ξ -Hydroxy-4-methyl-4-azapregnane-3,20-dione (VI).—A solution of 30 mg. of VI in 5 ml. of acetic acid was treated with 2 drops of freshly distilled boron trifluoride-etherate. After 2 hr., 50 ml. of ether was added, and the solution was washed with water, dilute sodium bicarbonate solution, and again with water. The ether was evaporated, after drying over sodium sulfate, to obtain 24 mg. of V as a white crystalline solid, m.p. 256–259°. The identity of this product was confirmed by a mixed melting point and comparison of infrared spectra.

VI was dehydrated with other acid catalysts and by heating above 100°. The dehydration was complete in a few seconds above the melting point of VI.

4 - Methyl - 20 - methylimino - 4 - aza - 5 - pregnen - 3 - one (VII).—3,5 - Seco - 4 - norpregnane-5,20-dion-3-oic acid (I) (8) (15.0 Gm.) was dissolved in 275 ml. of absolute ethanol which had been saturated previously with methylamine. The solution was heated in a sealed reaction vessel at 140° for 9 hr. The reaction mixture was cooled and filtered to obtain 9.6 Gm. (63%) of VII as white crystals, m.p. 238–239° dec.; $[\alpha]_D -116^\circ$; λ_{max} . 234 m μ (log ϵ 4.13), 6.13 μ with a slight inflection at 5.99 μ . There was no ketone C=O stretching absorption.

Anal.—Calcd. for C₂₂H₃₄N₂O: C, 77.14; H, 10.01; N, 8.18. Found: C, 76.91; H, 9.83; N, 8.25.

Hydrolysis of 4-Methyl-20-methylimino-4-aza-5-pregnen-3-one (VII).—VII (5.5 Gm.) was dissolved in 300 ml. of 3% hydrochloric acid and refluxed 15 min. The white crystalline precipitate, which separated as the solution refluxed, was filtered and recrystallized from chloroform-ethanol to obtain 4.4 Gm. (88%) of V, m.p. 256–259°. The identity of this product was confirmed by a mixed melting point and comparison of infrared spectra.

4 - Methyl - 20 β - methylamino - 4 - aza - 5 - pregnene (VIII).—4-Methyl-20-methylimino-4-aza-5-pregnen-3-one (VII) (4.0 Gm.) was added, by means of a Soxhlet extractor, to a slurry of 6.5 Gm. of LiAlH₄ in a mixture of 300 ml. of benzene and 500 ml. of anhydrous ether. The mixture was refluxed 100 hr. The excess hydride was decomposed by adding ether, saturated with water, and then water. The inorganic salts were filtered and washed with ether. The residue obtained by distilling the ether, after drying over sodium sulfate, was crystallized twice from ether to yield 0.70 Gm. (18%) of VIII, m.p. 123–125°; $[\alpha]_D -218^\circ$; λ_{max} . 3.00 and 6.08 μ .

Anal.—Calcd. for C₂₂H₃₆N₂: C, 79.94; H, 11.59; N, 8.48. Found: C, 79.98; H, 11.58; N, 8.04.

4 - (β - Hydroxyethyl) - 4 - aza - 5 - pregnene-3,20-dione (IX).—3,5-Seco-4-norpregnane-5,20-dion-3-oic acid (I) (11) (4.0 Gm.) and 1.8 ml. of ethanolamine were dissolved in 200 ml. of absolute ethanol and heated 8 hr. in a sealed reaction vessel at 145°.

¹ Doorenbos and Patel have established the configuration of the hydroxyl group in a study carried out since this project was completed. The details will be included in a future paper. The configuration was established by a comparison of the molecular rotation values of the alcohol and its acetate ester. The molecular rotation values of the acetates were about 60° more positive than the alcohol, establishing a β -configuration. (Fieser, L. F., and Fieser, M., "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 614.)

² Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Specific rotations were determined at 25° on 1% solutions in chloroform. Ultraviolet spectra were obtained with a Perkin-Elmer spectracord on solutions in 95% ethanol. Infrared spectra were obtained with a Perkin-Elmer Infracord using chloroform solutions. Analyses were obtained from Drs. Weiler and Strauss, Oxford, England.

The residue obtained after removing the solvent was a yellow oil. The oil resisted all direct attempts at crystallization. The oil was then dissolved in ether, washed with water, sodium carbonate solution, and again with water. The solvent was evaporated, after drying over sodium sulfate, to obtain a crystalline residue. One crystallization from ethanol-ether gave 1.3 Gm. (30%) of IX, m.p. 187-189°; $[\alpha]_D -65^\circ$; λ_{\max} . 235 $m\mu$ ($\log \epsilon$ 4.09), 2.92, 5.87, and 6.13 μ with a slight inflection at 5.99 μ .

Anal.—Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.32; H, 9.19; N, 4.04.

4-Aza-4-pregnen-20 β -ol (X).—A solution of 300 mg. of 4-aza-5-pregnene-3,20-dione (II) in 250 ml. of anhydrous ether was added to a slurry of 1.0 Gm. of $LiAlH_4$ in 50 ml. of anhydrous ether. The mixture was refluxed 78 hr. Excess hydride was destroyed by ether saturated with water, and then water. The inorganic salts were filtered and washed with ether. The ether solutions were combined and dried over sodium sulfate. The solvent was evaporated to obtain an oil which resisted all attempts at crystallization. This oil had the following infrared spectrum: λ_{\max} . 2.74, 2.95, and 6.03 μ . (There was no ketone or lactam C=O absorption.)

Ten milligrams of this oil was dissolved in ethanol and treated with picric acid. Crystals which separated were washed with ether to obtain 5 mg. of 4-aza-4-pregnen-20 β -ol picrate, m.p. 220-223°.

Anal.—Calcd. for $C_{26}H_{36}N_4O_8$: N, 10.52. Found: N, 10.94.

4-Methyl-4-aza-5-pregnen-20 β -ol (XI).—A solution of 500 mg. of 4-methyl-4-aza-5-pregnene-3,20-dione (V) in 50 ml. of purified dioxane was added slowly to a refluxing slurry of 2.5 Gm. of $LiAlH_4$ in 200 ml. of dioxane. The mixture was refluxed 75 hr. The excess hydride was destroyed by the addition of ether, saturated with water, and then water. The inorganic salts were filtered and washed with ether. The filtrate and washings were combined and dried over sodium sulfate. The solvent was removed under vacuum to obtain a light yellow oil which resisted all attempts at crystallization. The oil had the following spectrum: 2.74, 2.94, and 6.08 μ . (There was no ketone or lactam C=O absorption.)

A picrate salt was prepared in ethanol and recrystallized from ethanol to yield a yellow crystalline solid, m.p. 240-242° dec.

Anal.—Calcd. for $C_{27}H_{38}N_4O_8$: C, 59.32; H, 7.01; N, 10.25. Found: C, 58.95; H, 7.46; N, 9.96.

20-Ethylenedioxy-4-methyl-4-aza-5-pregnen-3-one (XII).—A mixture of 1.00 Gm. of 4-methyl-4-aza-5-pregnene-3,20-dione (V), 20 ml. of ethylene glycol, 10 mg. of *p*-toluenesulfonic acid, and 600 ml. of anhydrous benzene was refluxed 9

hr. The water formed was removed with a Dean-Stark distilling receiver. The mixture was cooled, washed with 5% sodium bicarbonate solution and water, and dried over sodium sulfate. The residue obtained by distilling the solvent was crystallized from methanol to obtain 431 mg. (27%) of XII as white crystals, m.p. 165-167°; $[\alpha]_D -119^\circ$; λ_{\max} . 234 $m\mu$ ($\log \epsilon$ 4.12) and 6.13 μ with a slight inflection at 5.99 μ . (There was no ketone C=O absorption.)

Anal.—Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.44; N, 3.75. Found: C, 73.89; H, 9.23; N, 3.89.

20-Ethylenedioxy-4-methyl-4-aza-5-pregne-3-one (XIII).—A solution of 400 mg. of 20-ethylenedioxy-4-methyl-4-aza-5-pregne-3-one (XII) in 50 ml. of tetrahydrofuran was added slowly to a slurry of 2.0 Gm. $LiAlH_4$ in 125 ml. of tetrahydrofuran. The mixture was refluxed 25 hr. Excess hydride was decomposed with ether, previously saturated with water, and then water. The inorganic salts were filtered and washed with ether. The filtrate and washings were combined and dried over sodium sulfate. Evaporation of the solvent under vacuum yielded white crystals which were crystallized from acetone-ether to obtain 270 mg. (70%) of XIII, m.p. 137-139°; λ_{\max} . 6.09 μ (C=C). (There was no ketone or lactam C=O absorption.)

Anal.—Calcd. for $C_{23}H_{37}ON_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.88; H, 10.05; N, 4.08.

4-Methyl-4-aza-5-pregnen-20-one (XIV).—20-Ethylenedioxy-4-methyl-4-aza-5-pregnene (25 mg.) was dissolved in 25 ml. of 2% hydrochloric acid. The solution was warmed 30 min. and neutralized with sodium hydroxide. A white precipitate formed. The precipitate was extracted with chloroform and dried over sodium sulfate. Evaporation of the chloroform yielded 22 mg. of XIV, m.p. 182-185°; λ_{\max} . 5.87 and 6.09 μ .

Anal.—Calcd. for $C_{21}H_{33}NO$: C, 79.94; H, 10.54; N, 4.44. Found: C, 79.40; H, 10.95; N, 4.16.

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