4-Aza-5ξ-hydroxypregnane-3,20-dione (IVb). IVb was prepared from 4-oxa-5-pregnen-3,20-dione[13] (IIIb) by the procedure of Uskoković and Gut.[7] The following data were obtained on this product after drying for 12 hr. at 25°/0.1 mm.[11]: m.p. 212–214° dec.; $[\alpha]_D^{28}$ + 171°; no peaks in the ultraviolet above 210 mμ; infrared 2.77 (OH stretching), 2.95 (OH, H-bond), 5.87 (ketone C=O), and 6.03 μ (lactam C=O); (reported m.p. 288–289°; $[\alpha]_D^{21}$ +173°).[7]

Anal. Calcd. for $C_{20}H_{31}O_3N$: C, 72.03; H, 9.37; N, 4.20. Found: C, 72.51; H, 9.25; N, 4.09.

Dehydration of IVb. IVb was dehydrated to IIb by the same procedures described above for IVa. The identity of the product, IIb, in each of these procedures was established by mixed melting point and a comparison of spectra.

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Steroids. III. Synthesis of Some 3-Aza-A-homocholestanes by the Beckmann and Schmidt Rearrangements in Polyphosphoric Acid[1,2]

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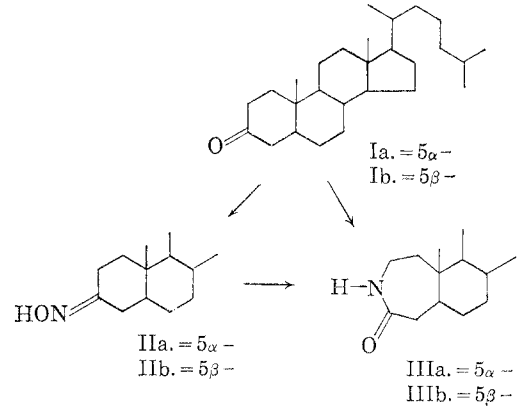
The great value of steroids in modern medicine and the interesting pharmacological properties of steroid alkaloids have brought about an increasing interest in aminosteroids and azasteroids. Over thirty papers and patents on azasteroids alone have appeared.[3]

The Beckmann and Schmidt rearrangements have offered two convenient methods for introducing a heterocyclic nitrogen into the steroid ring system. Many azasteroids have been prepared by the Beckmann rearrangement using a variety of solvents and such catalysts as tosyl chloride,[4–9] thionyl chloride,[10,11] phosphorus pentachloride,[4,5] *p*-acetylaminobenzenesulfonyl chloride,[7] and *p*-aminobenzenesulfonyl chloride.[12,13]

The Schmidt rearrangement has been applied to a few steroid ketones[4,5] with sulfuric acid being used as the catalyst in the presence of a suitable organic solvent.

The yields obtained by these methods have been variable and often below 60%. Recently Conley[14] reported polyphosphoric acid to be superior to other catalysts in the Beckmann and Schmidt rearrangements. Polyphosphoric acid is a mild catalyst and a good solvent for most organic compounds.

In 1957, a general study of heterocyclic steroids was begun in this laboratory. In order to obtain a preliminary evaluation of the usefulness of polyphosphoric acid for the synthesis of azasteroids, two azasteroids were synthesized by the Beckmann and Schmidt rearrangements using both polyphosphoric acid and more conventional methods. The azasteroids selected were 3-aza-A-homocholestan-4-one (IIIa) and 3-aza-A-homocoprostan-4-one (IIIb) since they may be prepared from readily available ketones. Shoppee and Sly[11] prepared these azasteroids by the Beckmann rearrangement of cholestan-3-one oxime (IIa) and coprostan-3-one oxime (IIb), using thionyl chloride as the catalyst and dioxane as the solvent. The crude yields, after purification by chromatography, were 63% for IIIa and 36% for IIIb. These chromatographed fractions were subjected to sublimation and repeated crystallizations in order to obtain analytically pure products. We obtained similar results with this procedure.



In this laboratory, it has been demonstrated that azasteroids may be prepared in high yield by either the Beckmann or Schmidt rearrangements, if polyphosphoric acid is used as the catalyst. No solvent was needed since polyphosphoric acid is a good solvent for cholestan-3-one (Ia) and coprostan-

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(2) (a) This work was supported by Research Grant CY-4132 from the National Cancer Institute, U. S. Public Health Service; (b) presented at the 1960 A.A.A.S. meeting in New York City, December 29.

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3-one (Ib) and their oxime derivatives, IIa and IIb. The yield of analytically pure product was at least 86% in each example. Analytical samples were obtained readily by one or two crystallizations.

Each azasteroid was prepared also by the Schmidt rearrangement with sulfuric acid as the catalyst. The yields were lower than those obtained with polyphosphoric acid. It is expected that polyphosphoric acid would offer even greater advantages in the Schmidt rearrangement of many of the steroids which contain functional groups sensitive to sulfuric acid.

EXPERIMENTAL[15]

Beckmann rearrangement of cholestan-3-one oxime (IIa). A mixture of 2.00 g. (0.005 mole) of cholestan-3-one oxime and 60 g. of polyphosphoric acid was heated with manual stirring at 120–130° for 30 min. The mixture was then poured onto 500 g. of crushed ice, neutralized with cold 50% sodium hydroxide, and extracted with ether (5 × 100 cc.). Removal of the solvent, after drying over magnesium sulfate, yielded 1.85 g. (93%) of 3-aza-A-homocholestan-4-one (IIIa), m.p. 270–274°. An analytical sample was prepared by crystallization from benzene-ether, m.p. 275.5–276.5° (reported[11] m.p. 268–271°).

Anal. Calcd. for $C_{27}H_{47}ON$: C, 80.73; H, 11.79; N, 3.50. Found: C, 80.80; H, 11.62; N, 3.43.

The infrared spectrum was identical with that of a sample prepared by Shoppee's method[11] and a mixed melting point gave no depression.

Beckmann rearrangement of coprostan-3-one oxime (IIb). A mixture of 700 mg. (0.0017 mole) of coprostan-3-one oxime and 21 g. of polyphosphoric acid was heated, with manual stirring, to 120° and maintained at this temperature for 10 min. Then the mixture was poured onto 200 g. of crushed ice, neutralized with cold sodium hydroxide, and extracted with ether (4 × 100 cc.). Removal of the solvent, after drying over sodium sulfate, gave a solid residue. This residue was crystallized from ether to yield 630 mg. (90%) of 3-aza-A-homocoprostan-4-one (IIIb), m.p. 173–175° (reported[11] m.p. 166–174°).

Anal. Calcd. for $C_{27}H_{47}ON$: C, 80.73; H, 11.79; N, 3.50. Found: C, 80.32; H, 11.58; N, 3.37.

The infrared spectrum was identical with that of a sample prepared by Shoppee's method[11] and a mixed melting point gave no depression.

Schmidt rearrangement of cholestan-3-one (Ia). Sodium azide (0.68 g., 0.011 mole) was added with slow agitation to a mixture of 3.86 g. (0.01 mole) of cholestan-3-one and 100 g. of polyphosphoric acid at 50–60°. This temperature was maintained by means of a water bath for 10 hr. Then the mixture was poured onto crushed ice, made alkaline with cold 50% potassium hydroxide, extracted with chloroform (4 × 100 cc.), and washed with water. Removal of the solvent, after drying over sodium sulfate, yielded 3.46 g. (86%) of 3-aza-A-homocholestan-4-one (IIIa), m.p. 275–277°.

Schmidt rearrangement of coprostan-3-one (Ib). The Schmidt rearrangement of coprostan-3-one (Ib) in polyphosphoric acid was carried out using the procedure outlined above for Ia. 3-Aza-A-homocoprostan-4-one (IIIb) was obtained in 88% yield, after one crystallization from ether, m.p. 172–174°.

(15) Melting points were taken on a Fisher-Johns block and are uncorrected. Analyses were performed by Sterling-Winthrop Research Institute and Drs. Weiler and Strauss, Oxford, England. Steroid intermediates were furnished by the National Service Center for Cancer Chemotherapy, National Institutes of Health.

Schmidt rearrangement of cholestan-3-one (Ia) (*sulfuric acid method*). Twelve cubic centimeters of a 4.7% solution of hydrazoic acid (0.013 mole) was added slowly with stirring at room temperature to a solution of 3.86 g. (0.01 mole) of cholestan-3-one and 5 cc. of sulfuric acid in 30 cc. of benzene. After 1 hr. the solution was poured into ice water. The benzene layer was separated and washed with dilute sodium hydroxide and water. Removal of the solvent, after drying over sodium sulfate, yielded 3.25 g. (81%) of 3-aza-A-homocholestan-4-one (IIIa), m.p. 270–273°. Two crystallizations from ether-methanol yielded an analytical sample, m.p. 275–276.5°.

Schmidt rearrangement of coprostan-3-one (Ib) (*sulfuric acid method*). The Schmidt rearrangement of coprostan-3-one (Ib) in sulfuric acid was carried out using the procedure outlined above for Ia. 3-Aza-A-homocoprostan-4-one (IIIb) was obtained in 72% yield, m.p. 164–170°, after one crystallization from ether. Two recrystallizations from ether raised the m.p. to 171–174°.

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Cycloethylene Ketals of $\Delta^{4,6}$-3-Ketosteroids

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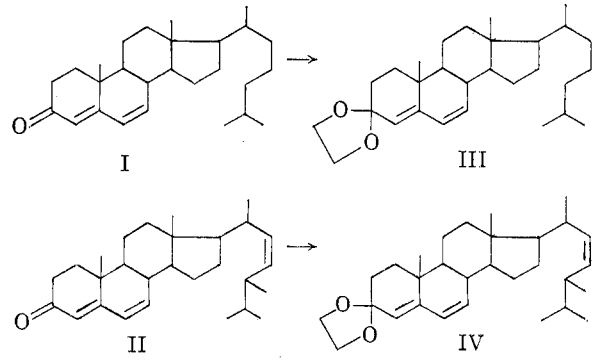
In the course of another investigation, the cycloethylene ketal derivatives of $\Delta^{4,6}$-cholestadiene-3-one, I, and $\Delta^{4,6,22}$-ergostatriene-3-one, II, were prepared. In contrast to the well established rearrangement of the Δ^4-double bond to the Δ^5-position on formation of the cycloethylene ketals of Δ^4-3-ketosteroids,[1] the $\Delta^{4,6}$-3-ketosteroids give rise to ketal derivatives in which the double bonds remain in their original position. Thus, I forms $\Delta^{4,6}$-cholestadiene-3-one-3-cycloethylene ketal, III and II gives rise to the corresponding $\Delta^{4,6,22}$-ergostatriene-3-one-3-cycloethylene ketal, IV.



I III

II IV

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