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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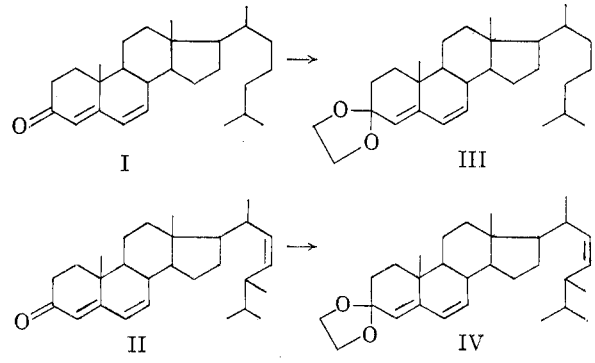
In the course of another investigation, the cycloethylene ketal derivatives of $\Delta^{4,6}$-cholestadiene-3-one, I, and $\Delta^{4,6,22}$-ergostatriene-3-one, II, were prepared. In contrast to the well established rearrangement of the Δ^4-double bond to the Δ^5-position on formation of the cycloethylene 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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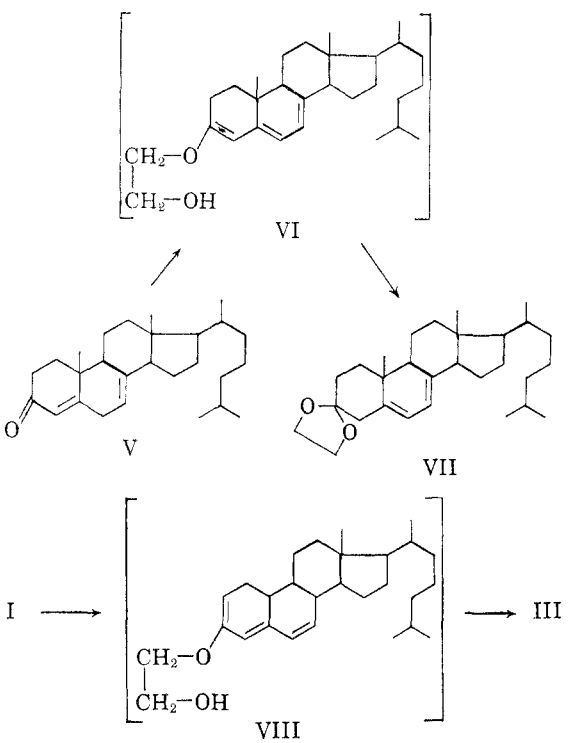
The same ketal derivatives were obtained by both the acid catalyzed reaction of the ketones with ethylene glycol and by the exchange dioxolanation method.[2]

The proposed mechanism of ketal formation[3] suggests that double bond isomerization in the course of cycloethylene ketal formation of a Δ^4-3-ketosteroid results from the formation of an intermediate $\Delta^{3,5}$-dienol ether species. Thus, $\Delta^{4,7}$-cholestadiene-3-one, V, forms $\Delta^{5,7}$-cholestadiene-3-one-3 cycloethylene ketal VII *via* the probable intermediate VI.



In the case of the $\Delta^{4,6}$-3-ketosteroids, the process may involve the intermediate $\Delta^{2,4,6}$-trienol ether VIII rather than the isomeric species VI. The intermediate trienols VI and VIII apparently are not capable of interconversion under the reaction conditions employed and examination of the mother liquors from the preparation of III by ultraviolet spectroscopy gave no indication of the isomeric cycloethylene ketal VII.

The structural assignments of the cycloethylene ketals were verified by reversion of each ketal to its parent $\Delta^{4,6}$-3-ketosteroid precursor upon acid hydrolysis and by the characteristic ultraviolet absorption of each derivative. The $\Delta^{4,6}$-cholestadiene-3-one-3-cycloethylene ketal III exhibited λ_{max} 236 mμ (ϵ = 18,700) and the corresponding $\Delta^{4,6,22}$-ergostatriene-3-one-3-cycloethylene ketal IV had λ_{max} 235 mμ (ϵ = 19,200) which is characteristic of the $\Delta^{4,6}$-diene system ascribed.[4] The isomeric $\Delta^{5,7}$-cholestadiene-3-one-3-cycloethylene ketal VI,[1c] absorbs at λ_{max} 271, 282, 293 mμ. The ergosterol analog exhibits similar absorption.[1c] Hydrolysis of the $\Delta^{5,7}$-3-keto-3-cycloethylene ketals yields the $\Delta^{4,7}$-3-ketosteroids.[1c]

EXPERIMENTAL

$\Delta^{4,6}$-Cholestadiene-3-one-3-cycloethylene ketal. A solution of 200 mg. (0.523 mmole) of $\Delta^{4,6}$-cholestadiene-3-one, 10 mg. of *p*-toluenesulfonic acid, 10 ml. of ethylene glycol, and 50 ml. of benzene was allowed to reflux for 5 hr. The water which separated was collected in a Dean-Stark phase separator. When the reflux period had ended, the solution was poured into 100 ml. of a 5% aqueous sodium carbonate solution and the mixture was extracted with two 100-ml. portions of ether. The ether extracts were washed with water, combined and dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure. The residual pale yellow oil crystallized upon trituration with acetone and there was obtained 193 mg. of pale yellow needles, m.p. 112–114.5°. Two recrystallizations from acetone afforded 142 mg. (64%) of colorless needles, m.p., 116–117.5°, $[\alpha]_D^{25}$ + 57° ($CHCl_3$) λ_{max}^{CasOH} 236 mμ (ϵ = 18,700).

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.69; H, 11.04.

$\Delta^{4,6,22}$-Ergostatriene-3-one-3-cycloethylene ketal. A solution of 800 mg. (2.01 moles) of $\Delta^{4,6,22}$-ergostatriene-3-one, 40 mg. of *p*-toluenesulfonic acid, 30 ml. of ethylene glycol, and 100 ml. of benzene was allowed to reflux for 6 hr. The water which separated was collected in a Dean-Stark separator. Upon completion of the reflux period, the cooled mixture was poured into 300 ml. of a 5% aqueous sodium carbonate solution. The benzene layer was separated and the aqueous phase was extracted with 100 ml. of ether. The combined benzene and ether extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness at reduced pressure. The yellow residual oil crystallized upon trituration with acetone. The crude crystalline product was twice recrystallized from acetone and afforded 672 mg. (77%) of colorless leaflets, m.p. 129–130°, $[\alpha]_D^{25}$ ± 0.0° ($CHCL_3$), λ_{max}^{CasOH} 235 mμ (ϵ = 19,200).

Anal. Calcd. for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57. Found: C, 82.30; H, 10.41.

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Conformational Analysis. XV. The Dipole Moment of 2-Fluorocholestanone[1,2]

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Since various biologically active steroids have been found to have their activity increased by the

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