The Anthrasteroid Rearrangement. X.[1a] Elucidation of the Stereochemistry of the C/D Ring Fusion from Chemical Transformation and N.m.r. Data

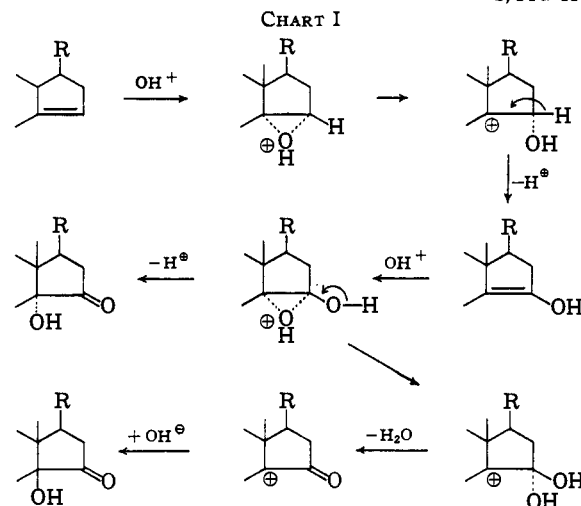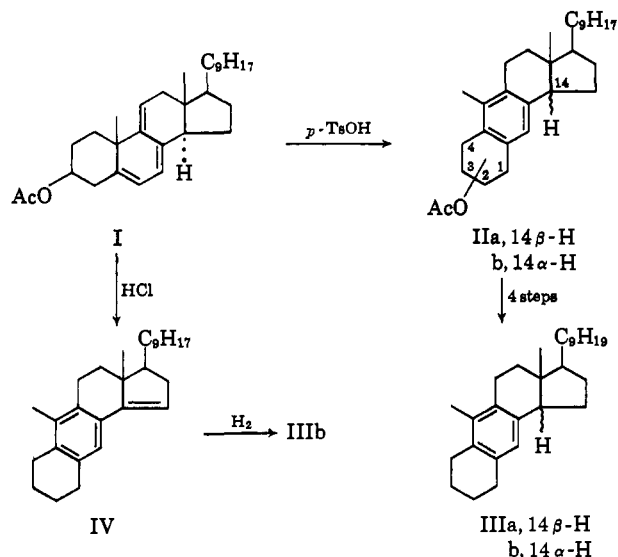By John A. Steele, Louis A. Cohen and Erich Mosettig[1b]

$\Delta^{5,7,9,14,22}$-Anthraergostapentaene (IV) is converted via several oxidation and reduction steps to 14β-$\Delta^{5,7,9}$-anthraergostatrien-15-one (VIII). The latter is reduced and dehydrated to the corresponding Δ^{14}-(XI) and Δ^{15}-(X) olefins which are hydrogenated to $\Delta^{5,7,9}$-anthraergostatrienes (IIIa and IIIb) differing only in their stereochemistry at C_{14}. The stabilities of the Δ^{15}-olefin and of the cis C/D ring fusion are demonstrated and interpreted. The analysis of n.m.r. spectra of the C_{18}-methyl group is shown to be a useful tool for elucidating C/D stereochemistry whenever ring B is aromatic. On such a basis, the trans C/D ring fusion for neoergosterol is confirmed.

In paper VIII of this series,[2] it was shown that the rearrangement of dehydroergosteryl acetate (I) (as well as of the analogous cholestatrienyl acetate), catalyzed by p-toluenesulfonic acid, leads to isomeric anthrasteroids (IIa, IIb) which have retained an oxygen function in ring A. Since IIa and IIb could be converted, respectively, into the hydrocarbons IIIa and IIIb, which were presumed to differ only in their stereochemistry at C_{14}, it is clear that analogous isomerism must also be assumed for IIa and IIb.[3] Whether IIa and IIb also differ, either in the position or orientation of the oxygen function in ring A (C_2 or C_3), remains undetermined. The nature of ring D in anthrasteroids has been elucidated both by degradation[4a] and by synthesis,[4b] and since anthraergostapentaene (IV) may be converted by hydrogenation into IIIb,[5] the anthrasteroid skeleton of IIIb is demonstrated. If one assumes that catalytic hydrogenation of IV proceeds by rear attack,[4b,6,7] IIIb may be assigned the C/D trans configuration and IIIa the C/D cis configuration. It remains to be demonstrated, however, that IIIa has, in fact, the expected anthrasteroid skeleton and that IIIa and IIIb differ only in their orientation at C_{14}.

When anthraergostapentaene (IV) is treated with monoperphthalic acid, the conjugated double bond disappears rapidly and a mixture of hydroxyketones Va and Vb is formed. As shown by subsequent transformations, the 14β-isomer appears to be the major product. Failure to realize stereochemical specificity is probably related to facile carbonium ion formation at C_{14}.[8] A proposed scheme leading to the two isomers is outlined in Chart I. Selective hydrogenation of the side-chain double bond of Va + Vb was effected with platinum in ethyl acetate to yield a mixture of the hydroxyketones VIa and VIb. Following extensive chromatography, VIb was obtained in crystalline form and is assigned the 14α-configuration on the basis of its n.m.r. spectrum (see below). The oily mixture of VI isomers was reduced with lithium aluminum hydride, whereupon crystalline VIIa could be isolated from the mixture of diols in ca. 50% yield; in this case, the n.m.r. spectrum indicates a 14β-structure. The diol VIIa was

(1) (a) Paper IX, O. Tanaka and E. Mosettig, J. Am. Chem. Soc., **85**, 1131 (1963). (b) Deceased, May 31, 1962.

(2) K. Tsuda, R. Hayatsu, J. A. Steele, O. Tanaka and E. Mosettig, J. Am. Chem. Soc., **85**, 1126 (1963).

(3) Isomerism resulting from a difference in the skeletal system or in the structure of the side-chain was considered unlikely and is excluded in the sequel.
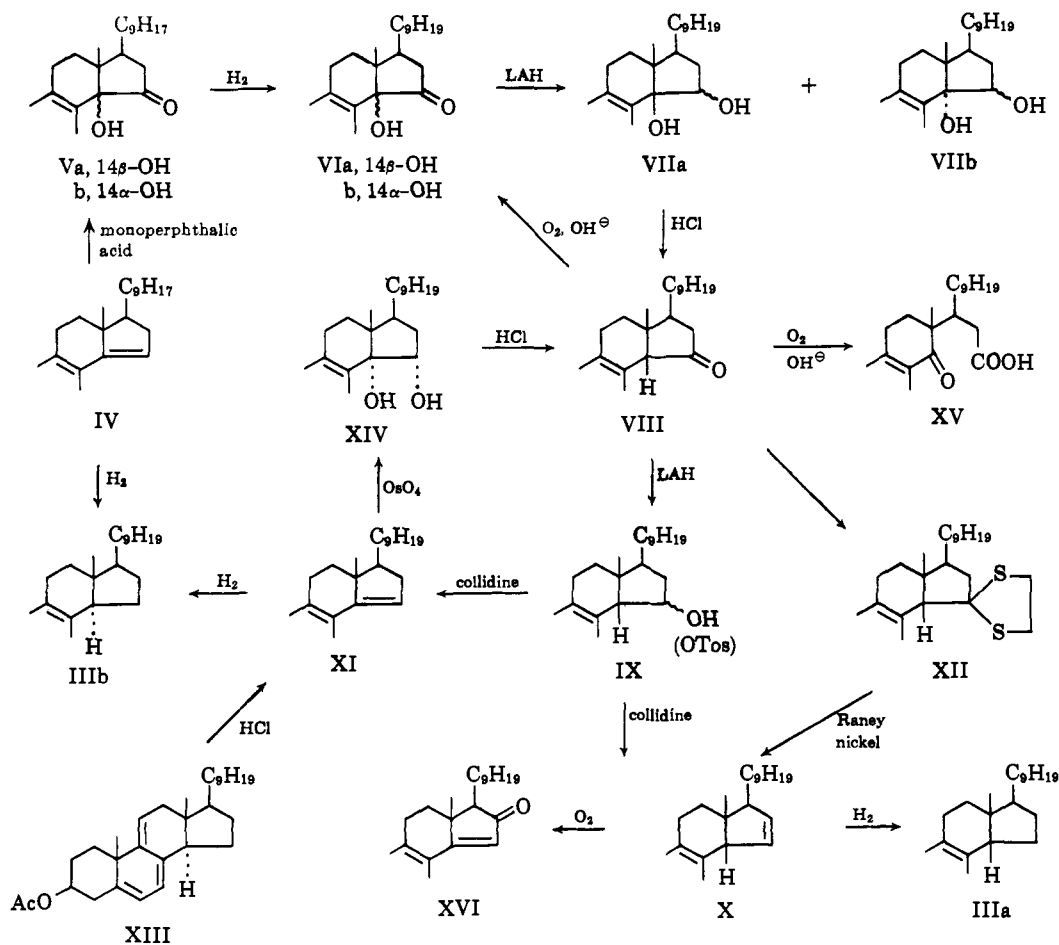
(4) (a) A. W. Burgstahler, J. Am. Chem. Soc., **79**, 6047 (1957); (b) A. W. Burgstahler and E. Mosettig, ibid., **81**, 3697 (1959).

(5) W. R. Nes and E. Mosettig, ibid., **76**, 3182, 3186 (1954).

(6) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, N. Y., 1959, p. 485.

(7) D. K. Banerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, J. Am. Chem. Soc., **78**, 3769 (1956).

(8) It should be noted that only the 14β-isomer is postulated to arise from the carbonium ion intermediate and is, therefore, the thermodynamically controlled product. Such differentiation is essential to subsequent arguments.

IIa, 14β-H
b, 14α-H

IIIa, 14β-H
b, 14α-H

Chart I

converted, by pinacol rearrangement with hydrogen chloride in dichloromethane, into the ketone VIII. Reduction of VIII with lithium aluminum hydride led to an oily mixture of C_{15}-carbinols (IX) which was directly tosylated. The mixture of IX-tosylates was heated with collidine in xylene and, following chromatography of the crude product, the Δ^{15}-olefin (X, oily) and the Δ^{14}-olefin (XI, crystalline) were isolated in a 2:1 ratio. The conjugated olefin XI was also prepared by direct rearrangement of the trienol acetate XIII with hydrogen chloride in chloroform. The location of double bonds in X and XI was readily established from ultraviolet and n.m.r. spectral data.

The Δ^{15}-olefin showed no tendency to isomerize to the conjugated Δ^{14}-olefin, either in acid or alkaline

C_9H_{17} C_9H_{19} C_9H_{19} C_9H_{19}

Va, 14β-OH   VIa, 14β-OH   VIIa   +   VIIb
b, 14α-OH   b, 14α-OH

↑ monoperphthalic acid

C_9H_{17} C_9H_{19} C_9H_{19} C_9H_{19}

IV   XIV   VIII   XV

IIIb   XI   IX   XII

XIII   XVI   X   IIIa

media, or in refluxing collidine–xylene.[9] From a consideration of steric factors, we infer that the ease of proton abstraction from IX-tosylate by collidine varies thus: C_{16}–α-H > C_{14}–β-H > C_{16}–β-H. *trans*-Elimination between C_{16}–α-H and C_{15}–β-tosylate would then lead to the Δ^{15}-olefin. Steric considerations further suggest that hydride attack on the C_{15}-ketone would be favored from the rear, leading predominantly to the C_{15}–β-hydroxyl. The preponderance of the Δ^{15}-olefin is thus accounted for. Although the Δ^{14}-olefin is completely stable to oxygen in refluxing collidine–xylene, the Δ^{15}-olefin is fairly sensitive to oxidation and leads to a neutral product which we tentatively formulate as XVI.

Compound X was placed in the C_{14}-β series on the basis of its n.m.r. spectrum and its conversion to IIIa by hydrogenation. On the other hand, hydrogenation of the Δ^{14}-isomer XI led to the hydrocarbon IIIb as the sole product. Since X and XI were both derived from the same ketone VIII, it follows that IIIa and IIIb must differ only in orientation at C_{14}.

When the ethylenethioketal XII was treated with deactivated Raney nickel in ethanol, an oily mixture was obtained consisting largely of X (based on optical rotation and infrared spectrum) and a small amount of IIIa. Catalytic hydrogenation of the mixture led to IIIa as the sole product.

(9) The indifference of the Δ^{15}-olefin to acquire resonance stabilization by migrating to C_{14} follows from the thermodynamic stability of the C/D *cis* fusion and possibly from the limited accessibility of the C_{14}–β-H to alkali. Both factors are elaborated below; *cf.* W. S. Johnson, C. D. Gutsche, R. Hirschmann and V. L. Stromberg, *J. Am. Chem. Soc.*, **73**, 322 (1951). The facile $\Delta^{14} \rightleftarrows \Delta^{15}$ tautomerism observed in the equilenin series may be related to the enhanced acidity of the C_{14}–H resulting from the presence of the 17-keto group.

CHART II

Raney nickel
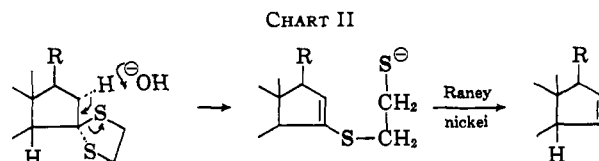
The rather unexpected formation of an olefin (X) from the thioketal XII may be due to inaccessibility of the β-C–S bond to catalyst. Evidently the inductive effect of two sulfur atoms at C_{15} is sufficient to permit proton abstraction at C_{16} by alkali present in the Raney nickel (Chart II). The formation of the Δ^{15}-olefin, to the exclusion of the Δ^{14}-isomer, may be considered the result of more facile removal of the C_{16}–α-H than of the C_{14}–β-H by hydroxide ion (*cf.* similar argument for the conversion of IX-tosylate to X).

The *cis*-α-diol XIV was prepared by hydroxylation of XI with osmium tetroxide (*cf.* ref. 4a). When subjected to a pinacol rearrangement, both the 14α-glycol XIV and the 14β-glycol VIIa formed the same ketone (VIII). Several attempts were made to effect the alkaline epimerization of VIII to its 14α-isomer. However, in the presence of alkali, the ketone is extremely sensitive to oxygen and is rapidly transformed to a mixture of the hydroxyketones VIa and VIb (predominantly the 14β-isomer) and to the keto-acid XV. When extreme care was taken to exclude oxygen from a solution of VIII in ethanolic alkali, no isomerization at C_{14} could be detected, VIII being recovered almost quantitatively. In those transformations in which thermodynamic control of stereochemistry at C_{14} is possible, *i.e.*, in the enolization of the C_{15}-ketone or in the solvolysis of the C_{14}-carbonium ion, the 14β-isomer is formed exclusively. It would appear, therefore, that
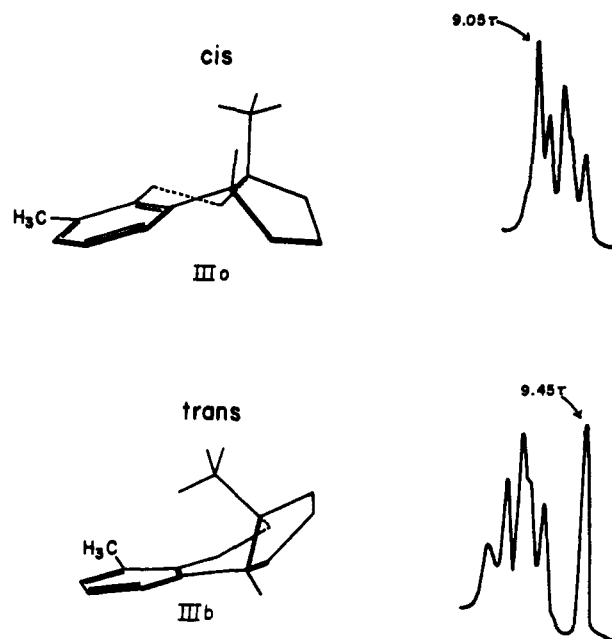
Fig. 1.—Partial Dreiding models and partial n.m.r. spectra of the isomeric anthrasteroid hydrocarbons IIIa and IIIb.

TABLE I

N.M.R. CHEMICAL SHIFTS FOR C_{18}-METHYL GROUPS[a]

IIIb, 9.45	9.42	IIIa, 9.05	9.00
VIb, 9.39	XIV, 9.38	VIII, 8.92	VIIa, 9.07
XVII, 9.40	XVIII, 9.11		X, 8.97

[a] Spectra were measured in CCl_4 solution with tetramethylsilane as internal reference; values given are τ-values.

the C/D *cis* fusion is thermodynamically the more stable. In earlier work on equilenin, the C/D *cis* fusion was found to be more stable than the *trans*.[6,10] It would seem that the preference for the *cis* fusion (under reversible conditions), in both the equilenin and anthrasteroid series, is related to the presence of an aromatic B ring. Indeed, examination of space-filling models reveals that the C_{18}-methyl group encounters serious van der Waals repulsion by the aromatic ring only in the C/D *trans* series.

Inspection of Dreiding models (perspective drawings of partial structures, Fig. 1) indicated that in the C/D *cis* series the C_{13}–C_{18} bond is oriented about 110° away from the aromatic plane, while in the C/D *trans* series the bond makes an angle of about 50° with the aromatic plane, bringing one of the protons of the C_{18}-methyl group into the field of the aromatic ring current. The geometrical fixation of a proton in a position partially perpendicular to the plane of the aromatic ring results in an anisotropic effect in the n.m.r. spectrum, its chemical shift increasing in τ-value.[11] The n.m.r. chemical shifts of the C_{18}-methyl groups in a variety of anthrasteroids were measured and were found to fall into two groups (Table I). Those compounds showing a relatively high τ-value for the C_{18}-methyl are assigned to the *trans* series, and those with lower values to the *cis* series. It may be noted that neoergosterol (XVII) falls into the first category in Table I, confirming its generally accepted C/D *trans* fusion.[12] On the other hand, the n.m.r. criterion cannot be used for estrone (XVIII), in which the aromatic ring is too far from the C_{18}-methyl to create an anisotropic shift, or for equilenin where the naphthalene ring system presumably diverts and dilutes the ring current excessively. The isomeric anthracholestatrienes previously prepared[2] show analogous chemical shifts for the C_{18}-methyl group (Table I) and have been assigned to the 14α- and 14β-series in the same manner as above.

We believe that the n.m.r. data and the chemical transformations outlined above provide reasonable evidence that the various anthrasteroids produced by a spectrum of rearrangement conditions belong to a common skeletal system; and, further, that the variable stereochemistry produced at C_{14} in the course of rearrangement merely reflects the extent to which unsaturation and planarity are realized at C_{14} during the transition period.

Experimental[13]

$\Delta^{5,7,9,22}$-Anthraergostatetraene-14-ol-15-one (Va, Vb).—To a solution of 12.0 g. of anthraergostapentaene (IV)[5] in 500 ml. of dry ether was added 500 ml. of ethereal monoperphthalic acid (containing approximately 13 g. of the peracid[14]) and the mixture was stored at room temperature for 1 hr. At that point, a starch–iodide test was only slightly positive and the ultraviolet spectrum indicated the disappearance of the ergostapentaene chromophore. The colorless, ethereal solution was divided into three portions, each portion extracted with two liters of 5% aqueous potassium carbonate and the combined extracts washed with water, dried and evaporated to dryness. The light brown, oily residue was dissolved in petroleum ether–benzene (1:1) and adsorbed on a column of 200 g. of Florisil. The first ten 250-ml. fractions were obtained by elution with petroleum ether–benzene (1:1), the following five 250-ml. fractions by elution with benzene and the final five 250-ml. fractions by elution with ethanol. Fractions 2–10 gave 9.5 g. of Va and Vb as a colorless oil, $[\alpha]_D$ +34°; λ_{max} 273, 282 and 300 mμ (ϵ 853, 674 and 186, respectively); $\lambda_{max}^{CS_2}$ 2.79, 5.72, 10.3, 11.1, 11.22, 11.36 μ.

Fractions 11–15 yielded 0.8 g. of oily material which showed infrared bands similar to those of the mixture of Va and Vb. Fractions 16–20 gave 3.0 g. of oily material which was not further investigated.

$\Delta^{5,7,9}$-Anthraergostatrien-14-ol-15-one (VIa, VIb).—To a solution of 9.5 g. of the mixture of Va and Vb in 500 ml. of ethyl acetate was added 20 ml. of glacial acetic acid and 2.0 g. of platinum oxide and the mixture shaken in a hydrogen atmosphere at room temperature. One mole-equivalent of hydrogen was adsorbed in 0.5 hr. Evaporation of the solvent left 9.6 g. of a colorless oil, $[\alpha]_D$ +34°; λ_{max} 273.5, 282 and 304 mμ (ϵ 808, 633 and 168, respectively); $\lambda_{max}^{CS_2}$ 2.79, 5.72, 11.02, 11.20 and 11.37 μ.

(10) W. E. Bachmann, W. Cole and A. L. Wilds, *J. Am. Chem. Soc.*, 62, 824 (1940); W. E. Bachmann and A. S. Dreiding, *ibid.*, 72, 1323 (1950).

(11) *Cf.* J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 180; H. Conroy, in "Advances in Organic Chemistry," Vol. 11, Interscience Publishers, Inc., New York, N. Y., 1960, p. 281; J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, 80, 5121 (1958).

(12) Reference 6, p. 105.

(13) All melting points were determined on a Kofler block and are uncorrected. Rotations were determined in chloroform in approx. 1.0–1.5% solution at 20°. Ultraviolet spectra were determined on a Cary recording spectrophotometer, model 11, in ethanol; infrared spectra on a Perkin–Elmer double beam spectrophotometer, model 21; n.m.r. spectra were determined on a Varian model 4300-C spectrometer at 60 Mc. Microanalyses were performed by the Analytical Service Laboratory of this Institute under the direction of Mr. Harold G. McCann. Woelm neutral alumina, Grades I and II, was used for chromatography. Florisil (60/100 mesh) was used as purchased from Floridin Co., Tallahassee, Fla. Petroleum ether refers to the solvent of b.p. 30–60°, purified in the conventional manner.

(14) "Organic Syntheses," Coll. Vol. III, Ed., E. C. Horning, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 619.

In one experiment, when extensive chromatography was employed, VIb could be isolated in crystalline form in ca. 10% yield as prisms from ethanol, m.p. 107–108°, $[\alpha]$D +34°; λ_{max} 272.5, 283 and 300 mμ (ϵ 544, 458 and 48, respectively); $\lambda^{CS_2}_{max}$ 2.78, 5.70, 11.04, 11.23 and 11.38 μ.

Anal. Calcd. for $C_{28}H_{42}O_2$: C, 81.90; H, 10.31. Found: C, 82.13; H, 10.52.

$\Delta^{5,7,9}$-**Anthraergostatriene-14β,15ξ-diol (VIIa).**—To a solution of 9.6 g. of the mixture of VIa and VIb in 600 ml. of dry ether was gradually added 6.4 g. of powdered lithium aluminum hydride. The stirred mixture was allowed to reflux overnight, excess hydride destroyed by dropwise addition of ethyl acetate and the complex decomposed with water. Following addition of 1.5 liters of water, the ethereal layer was removed and the aqueous layer was exhaustively extracted with ether. The combined ether extracts were washed with water, dried, and evaporated *in vacuo* to yield 9.0 g. of partially crystalline material. Following trituration with petroleum ether–ether and crystallization from the same solvent pair, 4.8 g. of needles was obtained, m.p. 147–148°, $[\alpha]$D −35.2°; λ_{max} 273, 277 and 282 mμ (ϵ 505, 410 and 457, respectively), λ_{min} 247 (ϵ 95); $\lambda^{CS_2}_{max}$ 2.77, 10.95, 11.45 and 11.65 μ.

Anal. Calcd. for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.71; H, 10.70.

Evaporation of the mother liquors left 4.2 g. of a colorless oil which appeared to be a mixture of isomeric diols.

14β-$\Delta^{5,7,9}$-**Anthraergostatriene-15-one (VIII).**—A solution of 4.0 g. of VIIa in 200 ml. of dichloromethane was mixed with 150 ml. of dichloromethane which had been saturated with hydrogen chloride at room temperature. After 0.5 hr., the infrared spectrum indicated the complete disappearance of the hydroxyl band and the formation of a five-membered ring ketone. By removal of the solvent *in vacuo*, 3.95 g. of a colorless oil was obtained. Crystallization from ethanol gave 3.07 g. of prisms, m.p. 84–85°. The analytical sample melted at 86–87°; $[\alpha]$D +34.4°; λ_{max} 273, 282, and 302 mμ (ϵ 636, 616 and 328, respectively); $\lambda^{CS_2}_{max}$ 5.72 and 11.45 μ.

Anal. Calcd. for $C_{28}H_{42}O$: C, 85.22; H, 10.7⁷. Found: C, 84.90; H, 10.75.

2,4-Dinitrophenylhydrazone of VIII.—The derivative was prepared in the usual manner and crystallized from ethanol as light yellow needles, m.p. 207–208°.

Anal. Calcd. for $C_{34}H_{46}O_4N_4$: C, 71.05; H, 8.07; N, 9.75. Found: C, 71.03; H, 8.37; N, 9.82.

14β-$\Delta^{5,7,9}$-**Anthraergostatrien-15ξ-ol (IX).**—To a solution of 1.5 g. of VIII in 250 ml. of dry ether was added slowly 1.0 g. of powdered lithium aluminum hydride, and the stirred reaction mixture was heated under reflux overnight. The reduction product was isolated in the manner described for the reduction of VIa + VIb, and consisted of 1.55 g. of a colorless oil, probably a mixture of isomeric alcohols; $[\alpha]$D +65.5°; λ_{max} 282, 278 and 273 mμ (ϵ 627, 544 and 627, respectively); λ_{min} 247 (ϵ 111); $\lambda^{CS_2}_{max}$ 2.79 and 11.60 μ.

14β-$\Delta^{5,7,9,15}$-**Anthraergostatetraene (X) and $\Delta^{5,7,9,14}$-Anthraergostatetraene (XI) from IX-Tosylate.**—To a solution of 1.35 g. of IX in 70 ml. of dry pyridine was added 1.6 g. of p-toluenesulfonyl chloride (freshly recrystallized from petroleum ether). The reaction mixture was stored overnight at room temperature and poured into 500 ml. of ice-cold 5% potassium bicarbonate solution. By extraction with ether and evaporation of the solvent, the tosylate was obtained as a colorless oil. Without further purification, it was dissolved in 20 ml. of dry xylene and added dropwise over 20 min. to a well stirred, refluxing mixture of 50 ml. of xylene and 20 ml. of collidine. Refluxing was continued for an additional hour, solvents were removed *in vacuo*, and the residue exhaustively extracted with hot petroleum ether (60–70°). The combined extracts were evaporated to dryness, taken up in a minimum amount of petroleum ether and placed on a column of 200 g. of Florisil. An automatic fraction collector was employed and 10-ml. fractions collected. The material was eluted with petroleum ether (30–60°) and fractions·pooled: Tubes 60–106 gave 0.324 g. (a); tubes 107–123, 0.019 g. (b); tubes 124–166, 0.069 g. (c); exhaustive elution of the column with benzene–ethanol (1:1) gave 0.727 g. of a mixture of IX and its tosylate. The latter material was again subjected to tosylation and detosylation as described above, and chromatographed. Tubes 71–115 (elution with petroleum ether) gave 0.157 g. (d); tubes 137–225 (eluted with petroleum ether–benzene, 19:1) gave 0.172 g. (e); final elution with benzene–ethanol (1:1) gave 0.234 g. of starting materials.

The combined fractions a and d gave 0.481 g. of X as a colorless oil, $[\alpha]$D +282°; λ_{max} 282.5, 277 and 273 mμ (ϵ 1006, 764 and 902, respectively), λ_{min} 247 mμ (ϵ 126); $\lambda^{CS_2}_{max}$ 3.29, 11.54, 12.29, 12.69 and 13.9 μ; n.m.r. 2 vinyl protons with multiplet centered at 4.40 τ (CCl$_4$) and C$_{14}$ proton (allylic-benzylic) multiplet centered at 6.62 τ.

The combined fractions c and e (oily) gave, by crystallization from acetone–methanol, 0.180 g. of XI as fine needles, m.p.

123–124°. The analytical sample melted at 125–126°, $[\alpha]$D −40°; λ_{max} 222, 227, 266, 296 and 308 mμ (ϵ 24,380, 25,090, 16,610, 2,297 and 1,943, respectively); $\lambda^{CS_2}_{max}$ 3.28, 12.3 μ; n.m.r., 1 vinyl proton with multiplet centered at 4.20 τ (CCl$_4$).

Anal. Calcd. for $C_{28}H_{42}$: C, 88.82; H, 11.18. Found: C, 88.75; H, 11.42.

14β-$\Delta^{5,7,9}$-**Anthraergostatriene (IIIa).**—A mixture of 0.4 g. of VIII, 0.2 ml. of ethandithiol, 0.2 ml. of boron trifluoride etherate and 4 ml. of glacial acetic acid was stored for 2 hr. at room temperature. Methanol was added slowly until the solution became turbid. When the mixture was cooled to 0°, a thick, colorless oil precipitated. The solvent was decanted and the residual oil triturated with ice-cold methanol and dried *in vacuo*. The product was devoid of carbonyl absorption in the infrared. To the ethylenethioketal thus obtained (0.5 g.) in 250 ml. of ethanol was added 12 g. of Raney nickel (deactivated by boiling in acetone) and the mixture heated at reflux for 20 hr. The reaction mixture was passed through a Celite mat and the filtrate concentrated to dryness. The oily residue, ca. 0.3 g., showed an ultraviolet spectrum typical of the simple anthrasteroid system (as in X), had an infrared spectrum very similar to that of X and $[\alpha]$D +214°, suggesting it to be predominantly X.

A mixture of 108 mg. of the above oil and 1.0 g. of 10% palladium-on-charcoal was hydrogenated to completion in 50 ml. of ethyl acetate. The crude hydrogenation product (90 mg.) melted at 64–65°. By recrystallization from acetone, the hydrocarbon IIIa was obtained as prisms, m.p. 70–71°, $[\alpha]$D +74.5°; λ_{max} 273, 278 and 282.5 mμ (ϵ 729, 629 and 793, respectively); λ_{min} 247 mμ (ϵ 82); $\lambda^{CS_2}_{max}$ 11.52 μ.

By direct comparison, this product proved to be identical with the hydrocarbon prepared from 14β-$\Delta^{5,7,9}$-anthraergostatrien-x-ol.[2] Catalytic hydrogenation of pure X, obtained from IX-tosylate, gave a quantitative yield of IIIa, m.p. 70–71°, $[\alpha]$D +75°. The hydrocarbon was identical in every respect with the samples prepared by the two alternative methods.

14α-$\Delta^{5,7,9}$-**Anthraergostatriene (IIIb).**—A mixture of 0.230 g. of XI and 100 mg. of platinum oxide in 25 ml. of ethyl acetate absorbed one mole-equivalent of hydrogen rapidly. Following removal of the catalyst and crystallization from acetone–methanol, 0.180 g. of IIIb was obtained. A recrystallized sample melted at 108–109°, $[\alpha]$D +20.5°. By direct comparison, the hydrocarbon was found to be identical with the product obtained by hydrogenation of $\Delta^{5,7,9,14,22}$-anthraergostapentaene.[2]

$\Delta^{5,7,9,14}$-**Anthraergostatetraene (XI) by Rearrangement of $\Delta^{5,7,9(11)}$-Ergostatrien-3β-ol Acetate (XIII).**—The preparation of dehydroergosteryl acetate was carried out by a modification of the procedure of Antonucci, *et al.*[15] It was found advantageous to recrystallize the mercuric acetate from ethanol–glacial acetic acid (3:1), and to reduce both volume and reaction time. A solution of 60 g. of ergosteryl acetate in 300 ml. of carbon tetrachloride and 1 liter of ethanol was added to a hot solution of 140 g. of mercuric acetate in 100 ml. of acetic acid and 400 ml. of ethanol and the mixture refluxed for 1 hr. After additional stirring for 0.5 hr., the solution was filtered warm and the filtrate worked up as described.[15] Dehydroergosteryl acetate was converted to its maleic anhydride adduct,[16] which was obtained in two crystalline modifications, m.p. 203–204° and 228–229°. The corresponding 22,23-dihydrodehydroergosteryl acetate maleic anhydride adduct was prepared by hydrogenation of the unsaturated adduct with 10% palladium–charcoal.[16b]

Decomposition of the maleic acid adduct was carried out in hot dimethylaniline by modification of a published procedure.[17] A solution of 22 g. of the adduct in 100 ml. of dimethylaniline was added dropwise to 60 ml. of boiling dimethylaniline over 0.5 hr. and refluxing was continued for 4 hr. The solution was evaporated *in vacuo* and the dark oily residue dissolved in 800 ml. of benzene. The benzene solution was washed thoroughly with *N* hydrochloric acid, 5% potassium bicarbonate solution and water, dried over sodium sulfate and evaporated to dryness *in vacuo*. The dark, oily residue was dissolved in a minimum amount of benzene–petroleum ether (1:6), adsorbed on a column of 500 g. of Florisil and eluted exhaustively with benzene. A total of 10.8 g. of crystalline XIII was obtained. Recrystallization from acetone–methanol gave 9.9 g. of prisms, m.p. 126–127°, $[\alpha]$D +219° (lit.[16b] 128°, $[\alpha]$D +219°); λ_{max} 312, 325 and 340 mμ (ϵ 10,780, 12,320 and 7,700, respectively). The compound is stable indefinitely at −20°.

$\Delta^{5,7,9,14}$-**Anthraergostatetraene (XI) from XIII.**—A solution of 14.0 g. of XIII in 850 ml. of 0.053 *M* hydrogen chloride in chloroform was stored at room temperature for 16 hr. The solution was washed with 5% potassium bicarbonate solution and water,

(15) R. Antonucci, S. Bernstein, D. Ginacola and K. J. Sax, *J. Org. Chem.*, **16**, 1159 (1951).

(16) (a) A. Windaus and A. Lüttringhaus, *Ber.*, **64**, 850 (1931); (b) H. Honigmann, *Ann.*, **508**, 89 (1934).

(17) R. H. Levin, A. V. McIntosh, Jr., and G. B. Spero. U. S. Patent 2,577,777 (1951); *Chem. Abstr.*, **46**, 6166 (1952).

dried and evaporated to dryness *in vacuo*. The oily residue was dissolved in petroleum ether and adsorbed on a column of 400 g. of neutral alumina. By elution with petroleum ether (60–70°), twelve 250-ml. fractions were collected. The combined fractions 2–9 yielded 6.4 g. of crystalline material. Crystallization from methanol–acetone gave 4.4 g. of needles, m.p. 122–123°. A recrystallized sample melted at 126–127°. Direct comparison of this compound with a sample obtained from IX-tosylate showed complete identity.

$\Delta^{5,7,9}$-**Anthraergostatrien-14α,15α-diol (XIV).**—To a solution of 4.0 g. of XI in 400 ml. of dry ether and 8.5 ml. of dry pyridine was added 4.0 g. of osmium tetroxide. The reaction mixture was stored in the dark for 4 days. The precipitated osmate ester–pyridine complex was dissolved by the addition of 300 ml. of 95% ethanol. Hydrogen sulfide was passed through the solution, osmium sulfide filtered off through a Celite pad and the filtrate evaporated to dyness *in vacuo*. Crystallization of the oily brown residue from ether–petroleum ether gave 2.45 g. of needles, m.p. 118–119°. From the mother liquor there was obtained an additional 0.54 g., m.p. 104–108°. The higher melting fraction was decolorized with charcoal and recrystallized from ether–petroleum ether; m.p. 150–151°,[18] $[\alpha]$D +48.5°; λ_{max} 282, 277 and 272.5 mμ (ϵ 480, 431 and 549, respectively); $\lambda_{max}^{CS_2}$ 2.75, 2.79, 10.90, 11.13 and 11.35 μ.

Anal. Calcd. for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.39; H, 10.70.

14β-$\Delta^{5,7,9}$-Anthraergostatrien-15-one (VIII) from XIV.—A solution of 0.31 g. of XIV in 50 ml. of dichloromethane previously saturated with hydrogen chloride was allowed to stand for 1 hr. Evaporation of the solution *in vacuo* gave 0.29 g. of colorless oil, which deposited from ethanol 0.25 g. of prisms, m.p. 79–81°. A second crystallization raised the m.p. to 85–86°. The product was compared with the ketone obtained from VIIa by means of ultraviolet, infrared and n.m.r. spectra, m.p. and mixture m.p. and optical rotation; the ketones were found to be identical in very respect. A mixture m.p. of the respective 2,4-dinitrophenylhydrazones showed no depression.

Stability of XI.—A solution of X in xylene–collidine was refluxed for 1.5 hr. with access to air (as in the conversion of IX-tosylate to a mixture of X and XI). After removal of solvents, the residue was found to be unchanged with respect to infrared and ultraviolet spectra. No indication of isomerization to X or sensitivity to oxygen was observed.

Stability of X.—A solution of X in xylene–collidine was refluxed as above in a stream of nitrogen. After removal of solvents, the oily residue was completely soluble in petroleum ether. Examination of infrared and ultraviolet spectra indicated a slight degree of oxidative decomposition, but no evidence of isomerization to XI. When the same reaction was run with access to air, extensive decomposition occurred. The infrared spectrum showed a carbonyl band at 5.95 μ and the ultraviolet spectrum, a new band at 308 mμ, suggesting the conjugated ketone XVI. The oxidation product was not investigated further.

Behavior of VIII in Alkaline Media.—A solution of VIII in ethanol was carefully deoxygenated by bubbling helium through it for 0.5 hr. A preparation of alcoholic alkali was similarly deoxygenated. The solutions were mixed in a stream of helium and the mixture examined by ultraviolet spectroscopy and polarimetry in tightly closed cells. No changes were observed after 16 hr. The same procedure was used on a larger scale, and,

(18) That the variation in melting point is the result of polymorphism was shown by the failure of the lower melting material to depress the m.p. of the higher.

after 16 hr., the ketone was recovered. It was found to be identical with VIII in every respect. The C_{14}-hydrogen, being both allylic and benzylic, is extremely sensitive to oxygen in alkaline solution. Only by working with *total* exclusion of oxygen can the ketone be recovered without some decomposition.

14,15-Seco-$\Delta^{5,7,9}$-anthraergostatrien-14-one-15-oic Acid (XV) and VI by Oxidation of VIII.—To a solution of 1.5 g. of VIII in 50 ml. of ethanol was added 50 ml. of 20% alcoholic potassium hydroxide and the mixture was stored at room temperature for 4 days in an open flask. The reaction mixture was reduced in volume and diluted with 1 liter of water. The mixture was extracted with three 200-ml. portions of ether, the ether extracts combined, washed with water, dried and evaporated to dryness; 0.571 g. The product was dissolved in petroleum ether–benzene (1:1) and adsorbed on 100 g. of Florisil. Elution of the column with benzene–petroleum ether followed by benzene gave 0.157 g. of oily material. Crystallization from ethanol gave 0.08 g. of VIb, m.p. 106–107°, $[\alpha]$D +34°; ultraviolet and infrared spectra identical with those of the compound previously obtained by chromatography. Stripping of the column with ethanol gave 0.271 g. of oily material which was identical with VIa on the basis of infrared and ultraviolet spectra.

The aqueous alkaline layer was acidified and extracted with three 200-ml. portions of ether. The combined ethereal extracts were washed with water, dried and evaporated to give 0.98 g. of XV as a colorless oil, $[\alpha]$D +17.8°; λ_{max} 219.5, 268 and 303 mμ (ϵ 27,000, 14,000 and 2,000, respectively); $\lambda_{max}^{CS_2}$ broad band between 3.0 and 4.65, 5.82, 5.93, 10.80, 10.98, 11.02 and 12.84 μ.

Reaction of the acid with diazomethane led to the formation of an oily ester (disappearance of broad hydroxyl absorption in the infrared) which could be saponified back to the acid readily.

14,15-Seco-$\Delta^{5,7,9}$-anthraergostatrien-14-one-15-oic Anhydride.—The alkali-soluble material obtained from VIII was first believed to be a stable enol of VIII, judging from its ultraviolet spectrum. Accordingly, an attempt was made to prepare an enol acetate by treatment with acetic anhydride. Following the demonstration that the alkali-soluble material was, in fact, the keto acid XV, it became obvious that the crystalline product obtained from the action of acetic anhydride was most probably the acid anhydride.

A sample of XV (0.29 g.) was stored for 4 days in 6 ml. of acetic anhydride. The solution was evaporated to dryness to give 0.28 g. of a colorless oil. Crystallization from ethanol gave 0.175 g. of the anhydride as needles, m.p. 149–150°. Additional material could be obtained from the mother liquor. A recrystallized sample melted at 150–151°, $[\alpha]$D +7.3°; λ_{max} 219.5, 268 and 301 mμ (ϵ 52,000, 27,300 and 4,000, respectively); $\lambda_{max}^{CS_2}$ 5.49, 5.70, 5.95, 10.84, 11.02, 11.15, 12.13 and 12.85 μ; molecular wt. by Rast method (camphor) calcd. 837, obsd. 878.

Anal. Calcd. for $C_{56}H_{84}O_5$: C, 80.33; H, 10.11. Found: C, 80.66; H, 10.09.

Saponification of the anhydride with 5% methanolic alkali afforded a colorless oil which was spectroscopically identical with XV.