[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

The Anthrasteroid Rearrangement. III. The Pathway in the Conversion of Dehydroergosterol to Anthraergostapentaene[1]

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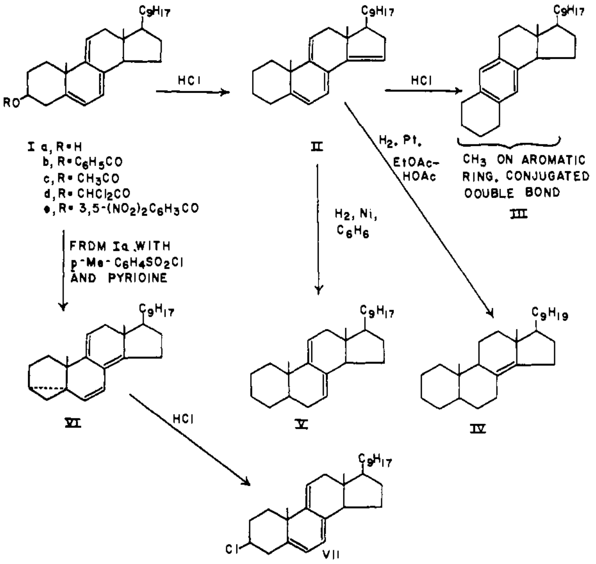
An intermediate hydrocarbon which is considered to be 5,7,9(11),14,22-ergostapentaene has been isolated from the reaction mixture when dehydroergosterol was treated with hydrogen chloride in chloroform. The hydrocarbon was convertible to anthraergostapentaene in 86% yield under the same conditions. That dehydration of dehydroergosterol precedes rearrangement and aromatization in the course of its conversion to anthraergostapentaene was also inferred from kinetic data as well as from the behavior of model compounds. 3,5-Cyclo-6,8(14),9(11),22-ergostatetraene has been prepared and shown not to participate in the acid-catalyzed reaction of dehydroergosterol. On treatment of the *i*-steroid with hydrogen chloride an addition reaction took place yielding dehydroergosteryl chloride. The *i*-steroid rearrangement of dehydroergosteryl *p*-toluenesulfonate in aqueous acetone is discussed.

Two general pathways are possible for the acid-catalyzed rearrangement of a $\Delta^{5,7,9(11)}$-sterol, *e.g.* I, to an anthrasteroid, *e.g.*, III, depending on whether ROH (in formula I) is eliminated prior to or following rearrangement and aromatization. This may be represented schematically as

$$\begin{tikzcd}
\mathrm{I} \arrow[r, "-\mathrm{ROH}"] \arrow[dr] & \mathrm{A} \arrow[r] & \mathrm{III} \\
& \mathrm{B} \arrow[ur, "-\mathrm{ROH}"'] &
\end{tikzcd}$$

in which A represents one or more steroidal, non-aromatic hydrocarbons and B represents a non-steroidal alcohol (or ester) containing an aromatic ring. Other work[2a] has shown that it is ring B which aromatizes, and, therefore, the RO-group in B would have to be in the position β to the aromatic ring. Since model compounds (β-tetralol, neoergosterol and 22-dihydroneoergosteryl acetate) were stable to the conditions of the rearrangement, this immediately suggested that the pathway through B did not apply.[2b]

The pathway through A was shown to be the correct one by interrupting the reaction of dehydroergosterol (Ia) with hydrogen chloride after only one-third of the starting material had reacted. A hydrocarbon (II, $C_{28}H_{40}$) was isolated which by further treatment with hydrogen chloride was converted to the anthrasteroid (III) in an 86% yield. Since II absorbed four moles of hydrogen (platinum, acetic acid–ethyl acetate) yielding 8(14)-ergostene (IV), it (II) must be a steroidal, non-aromatic hydrocarbon containing four double bonds in the nucleus. A 3,5-cyclo grouping can be excluded, because these conditions of hydrogenation are known either not to affect[3] this grouping or to cleave[4] it mainly to the 3β-methyl-A-nor derivative. Also, there was no band between 9.79 and 9.99 μ.[5] Selective hydrogenation of II using Raney nickel in benzene yielded a diene (V, λ_{max} 235.6, 243.0 and 251.3 mμ; ε 14,600, 17,900, 11,300; M_D +140°). The transoid[6] nature of the absorption together with the agreement of its molecular rotation with the calculated value[7] establish the structure of V as 7,9(11)-ergostadiene.[8] This in turn establishes the position of two of the four nu-



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(1) W. R. Nes and E. Mosettig, (a) Part I, THIS JOURNAL, **76**, 3182 (1954); (b) Part II, **76**, 3186 (1954).

(2) (a) See reference Ia and Part IV of this series (W. R. Nes, R. B. Kostic and E. Mosettig, THIS JOURNAL, in press); (b) *Added in Proof:* In a recent paper K. Tsuda and R. Hayatsu, THIS JOURNAL, **77**, 3089 (1955), have reported that under different conditions (particularly, strong irradiation) a rearrangement can be accomplished such that B is actually obtained. It is noteworthy, however, that the rearranged alcohol obtained by Tsuda and Hayatsu apparently did not undergo dehydration even in the presence of *p*-toluenesulfonic acid at 35–40°. This is in agreement with the present results relative to the behavior of such alcohols and supports our conclusion.

(3) (a) R. Heiz and P. Karrer, *Helv. Chim. Acta*, **36**, 1788 (1953); (b) H. Schmid and K. Kägi, *ibid.*, **35**, 2194 (1952); (c) J. J. Cahill, N. E. Wolff and E. S. Wallis, *J. Org. Chem.*, **18**, 720 (1953); (d) F. S. Prout and B. Riegel, THIS JOURNAL, **74**, 3190 (1952).

(4) (a) P. Karrer and H. Asmis, *Helv. Chim. Acta*, **35**, 1926 (1952); (b) H. Schmid and K. Kägi, *ibid.*, **33**, 1582 (1950).

(5) M. Fieser, W. E. Rosen and L. F. Fieser, THIS JOURNAL, **74**, 5397 (1952), and A. R. H. Cole, *J. Chem. Soc.*, 3807 (1954), have suggested that a band near 9.9 μ may not always be useful in the detection of cyclopropyl rings. Also V. A. Slabey, THIS JOURNAL, **76**, 3604 (1954), has shown that in 34 simple derivatives of cyclopropane the band is found at 9.54–9.82 μ. Nevertheless, a number of steroids and triterpenes containing a cyclopropyl group do exhibit a band near 9.9 μ (see, for instance, ref. 3a-c, 4a and D. H. R. Barton, *J. Chem. Soc.*, 1444 (1951), and ref. cited there), and for this reason the presence or absence of this band is reported in the present investigation. Although it may be coincidental, this information is in agreement with the other evidence relative to the structures of II and VI.

(6) D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.*, 257 (1951), and ref. cited there.

(7) D. H. R. Barton and W. Klyne, *Chemistry & Industry*, 755 (1948) report an average contribution (M_D) of −2° and −31° for the OH and AcO groups, respectively. Thus, based on the molecular rotations of ergosterol-D and its acetate (+119° and +101–146°, respectively) (R. C. Anderson, R. Stevenson and F. S. Spring, *J. Chem. Soc.*, 2901 (1952); W. V. Ruyle, *et al.*, THIS JOURNAL, **76**, 2604 (1953); G. Saucy, P. Geistlich, R. Helbling and H. Heusser, *Helv. Chim. Acta*, **37**, 250 (1954)) the calculated M_D for V is +143° ± 34°.

(8) I. M. Heilbron, F. S. Spring and E. T. Webster, *J. Chem. Soc.*, 1705 (1932).

clear double bonds in II, since hydrogenation using Raney nickel in neutral medium proceeds *via* 1,2-reduction without bond migration.[9] The ultraviolet spectrum of II (Fig. 1) indicates a cross-conjugated tetraene system which, therefore, allows only positions 5 and 14 for the remaining two nuclear double bonds. This leads to formulation of II as 5,7,9(11),14,22-ergostapentaene. Confirmation of this structure was afforded by the detection of the 5,7-isomer of V as a minor companion in the reduction of II.

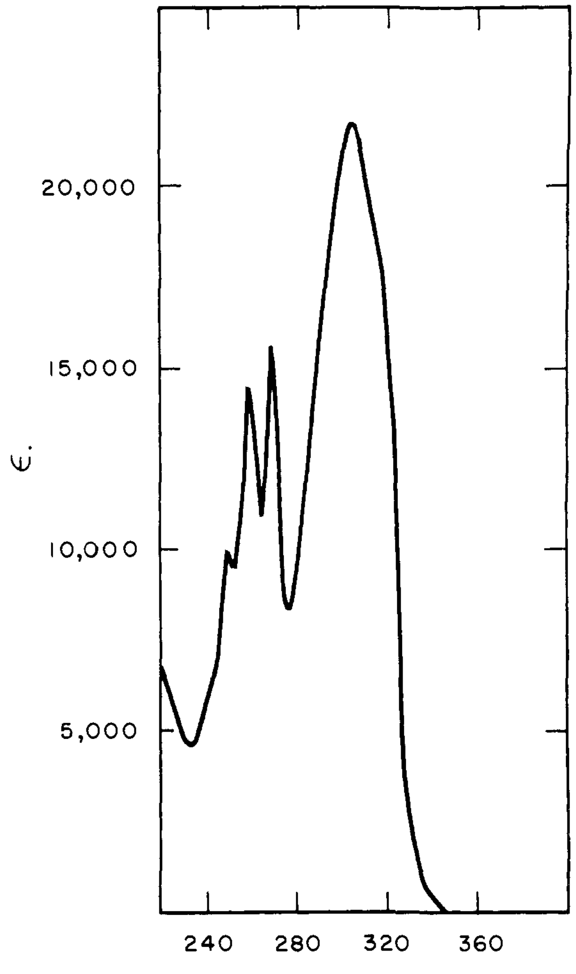

Fig. 1.—Ultraviolet absorption of 5,7,9(11),14,22-ergostapentaene (II) in isoöctane.

Measurements of the rates of disappearance of the 5,7,9(11)-triene system when Ia-e were treated with hydrogen chloride in chloroform revealed that the rate equation 1 (where the concentrations of I and hydrogen chloride are C_S and C_{HCl}, K is the rate constant, n is the order of reaction with respect to hydrogen chloride, and t is the time) could be used to about 50% reaction. The results are summarized in Table I and Fig. 2. There is approximately a twenty-fold difference in the rate constants in the series Ia-e. This suggests participation of the RO- group in the rate-determining step of the disappearance of the 5,7,9(11)-triene system and is in accordance with the general concept of 1,3-interactions.[10] The results are thus in agreement with the pathway through A (I → II → III) rather than through B, because the former involves the RO- group in the initial step while the latter does not. It is also of interest that the hydrocarbon II reacts at a rate faster than any of the esters of Ia but slower than Ia itself. This is seen in Fig. 2. As a result of these figures, II should not accumulate in the reactions of Ib-e. This was verified by comparing the rates of disappearance of the 5,7,9(11)-triene system of Id with the rate of appearance of the unsaturated system of the anthrasteroid III. The data are given in Fig. 3. There is no marked induction period in the formation of III. The situation was quite different with Ia, and the appearance of the spectrum of II always preceded that of III, the spectrum of II then disappearing as the absorption of III formed.

$$-\,dC_S/dt = K(C_{HCl})^n C_S \qquad (1)$$

TABLE I

	Compound I, R =	n	K^a
(a)	H	1.8	1.3
(b)	C_6H_5CO	1.7	0.14
(c)	CH_3CO	1.7	.13
(d)	$CHCl_2CO$	1.7	.074
(e)	$3,5\text{-}(NO_2)_2C_6H_3CO$	1.6	.050

[a] The values of K are given in units of seconds, moles and liters.

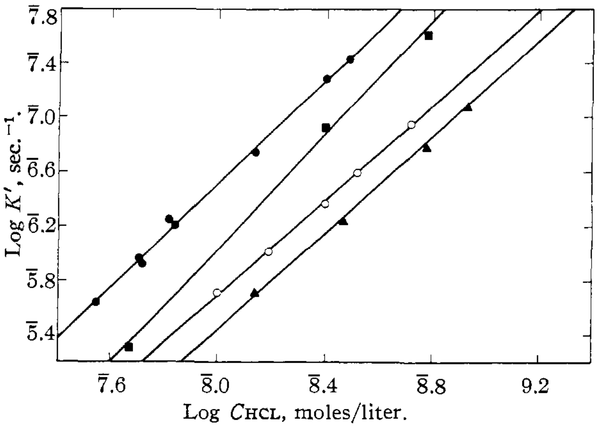

Fig. 2.—Reaction velocities at various concentrations of hydrogen chloride for 0.05 M solutions of the following steroids in chloroform: ●●, dehydroergosterol (Ia); ○○, its acetate (Ic); ▲▲, its dichloroacetate (Id); ■■, 5,7,9(11),-14,22-ergostapentaene (II). The curves for the benzoate Ib and the 3,5-dinitrobenzoate Ie are not shown, because the former is identical with that of the acetate Ic and the latter is approximately the same as that of the dichloroacetate Id.

The possibility that 3,5-cyclo-6,8(14),9(11),22-ergostatetrane (VI) was a transient intermediate between I and II was contraindicated by its behavior on treatment with hydrogen chloride at the

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(9) See for instance, (a) G. D. Laubach and K. J. Brunings, THIS JOURNAL, **74**, 705 (1952); (b) L. F. Fieser, J. E. Herz and W. Huang, *ibid.*, **73**, 2397 (1951); (c) P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch and G. W. Wood, *J. Chem. Soc.*, 2402 (1951); (d) W. R. Nes and E. Mosettig, *J. Org. Chem.*, **18**, 276 (1953); (e) Anderson, *et al.*, ref. 7. The behavior of platinum is different, particularly in the presence of acetic acid (see, for instance, ref. d above).

(10) M. Simonetta and S. Winstein, THIS JOURNAL, **76**, 18 (1954).

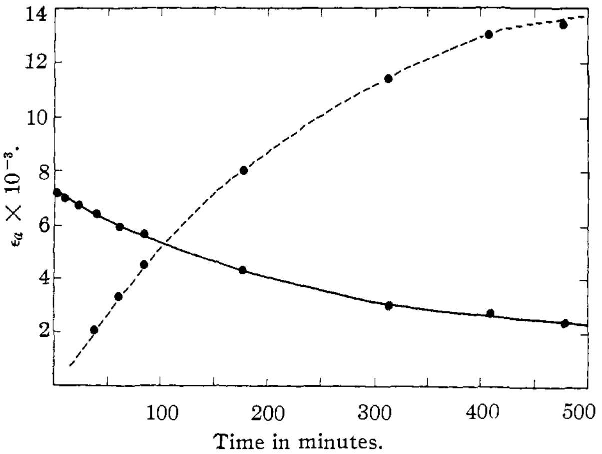

Fig. 3.—Change in absorption at 340 mμ (——) and 227 mμ (- - -) for a solution in chloroform which was initially 0.048 *M* with respect to dehydroergosteryl dichloroacetate (Id) and 0.014 *M* with respect to hydrogen chloride. The values at 227 mμ have been corrected for absorption at this wave length resulting from the 5,7,9(11)-triene ($\epsilon_{227}/\epsilon_{340} \times \epsilon_{a,340}$ = correction subtracted from $\epsilon_{a,227}$). ϵ_a is the extinction coefficient based on the number of moles of starting material as distinguished from ϵ which is based on the number of moles of absorbing material.

same concentration of acid (0.0056 *M*) as was used in the conversion of Ia to II. The *i*-steroid VI was converted to the chloro derivative VII; the 5,7,-9(11)-triene system was formed in the reaction mixture in 80–90% yield and the product VII was readily isolated.[11] At this concentration of acid the chloride VII was stable and the extent of reaction was directly dependent on the initial amount of hydrogen chloride present. This stoichiometric relationship did not exist with Ia-e. Since the addition reaction of VI was faster (half-time less than 12 min. in 0.0056 *M* acid) than the disappearance of Ia (half-time 130 min. at the same acid concentration), the presence of the *i*-steroid VI in the reaction of I to II would consume the hydrogen chloride and stop the reaction at an equivalent point. Nevertheless, regarding VII as the hydrochloric acid ester of Ia, it should be possible to convert VI to III *via* VII under the proper conditions. The results of Table I show that the dehydroergosteryl esters of the stronger acids react more slowly than the esters of the weaker acids. Accordingly by increasing the concentration of the hydrogen chloride tenfold and using an equivalent amount, the autocatalytic dehydrohalogenation of the intermediate VII took place and VI was converted to III.

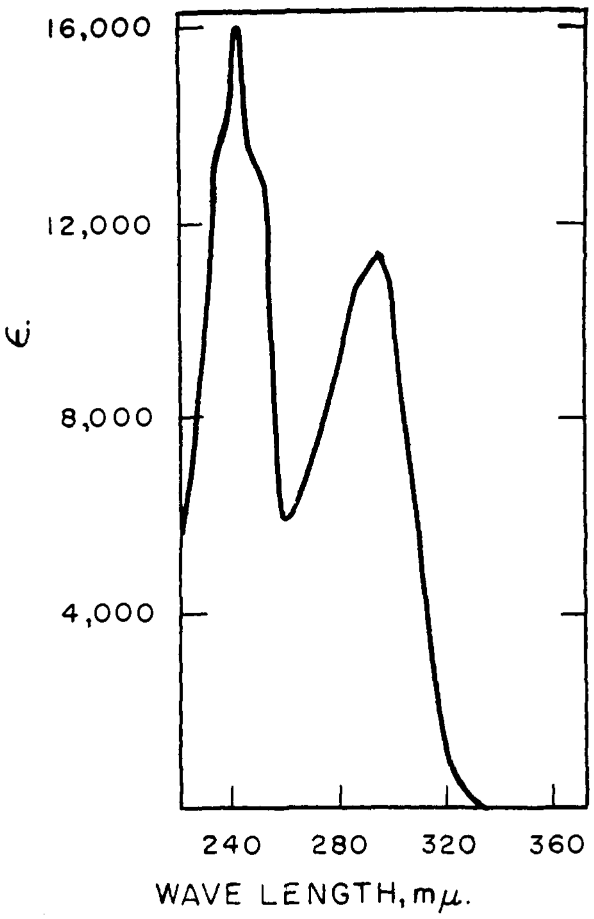

Fig. 4.—Ultraviolet absorption of 3,5-cyclo-6,8(14),9(11),22-ergostatetraene (VI) in isoöctane.

The *i*-hydrocarbon VI was prepared from Ia with *p*-toluenesulfonyl chloride in pyridine and its structure was shown by a comparison of its ultraviolet spectrum (λ_{max} 244 and 295 mμ; Fig. 4) with that of 6,8(14),9(11),22-ergostatetraenyl acetate[12] allowing for the bathochromic effect of the cyclopropyl group.[13] The hydrocarbon VI also possessed a band at 9.90 μ[5] and absorbed only three moles of hydrogen. Rees and Shoppee[14] have obtained a hydrocarbon (λ_{max} 252 mμ) as a by-product in the buffered hydrolysis of the tosylate of Ia. They have suggested formula VI for their compound. At the suggestion of Professor Shoppee the author repeated the buffered hydrolysis and found that the principal hydrocarbon constituent had maxima at 244 and 295 mμ and possessed the same infrared spectrum as the material obtained by the other procedure. It was, however, accompanied by another hydrocarbon (λ_{max} 252, 264 and 275 mμ) in smaller amount. Recrystallization from acetone enriched the precipitate in this material. Consequently, it may be the compound purified by Rees and Shoppee.[14,15] The hydrolysis of the tosylate of Ia took place very rapidly, and, when the reaction time was only one-tenth that used in the original work,[14] a sterol (λ_{max} 247 mμ) was isolated without chromatography. The compound had the same ultraviolet spectrum as the sterol isolated by Rees and Shoppee,[14] but the melting point was quite dif-

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[11] 3,5-Cyclo-6-cholestene and 3,5-cyclo-6,8(14),22-ergostatriene also undergo this addition reaction (B. Riegel, G. P. Hager and B. L. Zenitz, THIS JOURNAL, **68**, 2562 (1946), and Fieser, *et al.*, ref. 5, and the references cited there).

[12] G. D. Laubach, E. C. Schreiber, E. J. Agnello, E. N. Lightfoot and K. J. Brunings, THIS JOURNAL, **75**, 1514 (1953).

[13] A contribution of +8 mμ is found when the spectra of ergosterol-B_2 and the corresponding *i*-steroid are compared (Fieser, *et al.*, ref. 5). The calculated values for VI are, then, 241 and 296 mμ.

[14] R. W. Rees and C. W. Shoppee, *J. Chem. Soc.*, 3422 (1954).

[15] Professor Shoppee very kindly advised the author that their spectroscopic measurements ceased at 260 mμ. The other two maxima found in this work are not, therefore, a discrepancy.

ferent. Nevertheless, based on the same reasoning as used by these authors,[14] it would appear that the present sterol is also an *i*-dehydroergosterol.

Experimental[16]

Stability of β-Tetralol, Neoergosterol and 22-Dihydroneoergosteryl Acetate to the Rearrangement Conditions.[17]—Solutions of the three compounds in chloroform which were 0.05 *M* with respect to the organic material and 0.06 *M* with respect to hydrogen chloride were allowed to stand three to six hours at 20°. No changes in the ultraviolet spectra of the reaction mixtures were observed either qualitatively or quantitatively and the compounds were recovered unchanged by evaporation to dryness in a vacuum. The compounds were identified by melting point and/or infrared spectra.

Dehydroergosterol and its Esters.—The free alcohol Ia and its acetate Ic were obtained as previously described.[18] The following esters were prepared from the alcohol Ia and the appropriate acid chloride in pyridine by allowing the mixture to stand at room temperature overnight (Ib and Id) or by heating at 100° for one hour (Ie).

The dichloroacetate (Id) was obtained by evaporation of the pyridine solution to dryness in a vacuum. Extraction with benzene and treatment with decolorizing charcoal removed most of the color. The benzene was removed, and the residue was extracted with boiling petroleum ether (b.p. 30–60°). Evaporation of this solution to dryness left a residue which was crystallized twice from acetone–methanol. The ester formed in sheaves of colorless needles, m.p. 121.5–122.5°.

Anal. Calcd. for $C_{30}H_{42}Cl_2O_2$ (505.6): C, 71.26; H, 8.37; Cl, 14.02. Found: C, 71.15; H, 8.30; Cl, 14.35.

The benzoate Ib was obtained by pouring the reaction mixture onto ice and proceeding in the usual manner. The ester crystallized from benzene–ethanol as colorless needles, m.p. 149.5–150.5°.

Anal. Calcd. for $C_{35}H_{46}O_2$ (498.7): C, 84.28; H, 9.29. Found: C, 84.46; H, 9.44.

The 3,5-dinitrobenzoate (Ie) was obtained by pouring the reaction mixture onto ice and dissolving the washed and dried precipitate in benzene. This solution was passed through alumina. The ester so obtained was crystallized from benzene–methanol yielding a benzene solvate as bright yellow needles or elongated prisms, m.p. 193–194°. The compound was dried for analysis at room temperature and 0.1 mm. pressure for one hour.

Anal. Calcd. for $C_{35}H_{44}N_2O_6 \cdot {}^1/_2C_6H_6$: C, 72.70; H, 7.55; N, 4.46. Found: C, 72.88; H, 8.03; N, 4.20.

That benzene was really the solvate was proved by heating the material at 140° for 15 minutes and collecting the distillate.[19] The liquid so obtained had a spectrum which was identical with that of an authentic sample of benzene from 220–290 mμ. The benzene was difficult to remove completely by heating, however. Also, when the solvated yellow needles were recrystallized from ethyl acetate, the solvation was retained in the precipitate which was composed of yellow needles, m.p. 190–192°. For analysis they were dried as described above.

Anal. Calcd. for $C_{35}H_{44}N_2O_6 \cdot {}^1/_2C_6H_6$: C, 72.70; H, 7.55; N, 4.46. Found: C, 72.70; H, 7.74; N, 4.64.

If the solvated crystals were allowed to stand in the presence of ethyl acetate or acetone, the bright yellow needles changed to deep red, well-formed, hexagonal prisms, m.p. 195–196°, which turned bright yellow on heating to *ca.* 170° without change in crystal form. The thermochromism was not observed to be reversible on cooling or further heating. The red, hexagonal prisms were not solvated. They were dried as described above.

Anal. Calcd. for $C_{35}H_{44}N_2O_6$: C, 71.40; H, 7.53; N, 4.75. Found: C, 71.72; H, 7.57; N, 4.71.

The red, hexagonal prisms are apparently the ester previously described by Callow and Rosenheim[20] as "crimson leaflets," m.p. 186–189°, from ethyl acetate. Ando[21] has reported this ester without giving a C,H-analysis as "yellow small needles, m.p. 187.5–188.5°" from benzene–methanol. This would appear to be the solvated material obtained in the present investigation.

Kinetic Experiments.—All of the experiments were carried out at 19.8 ± 0.3° in commercial, reagent grade chloroform containing *ca.* 0.75% ethanol. The steroid concentration was 0.05 *M*. The hydrogen chloride concentration was as indicated below. The stock hydrogen chloride solutions were always prepared freshly and standardized just prior to use by titration with sodium hydroxide. The apparent first-order reaction rate constants (K') were evaluated from the slope of the straight lines (K' = slope × 2.30) produced by a plot of the logarithm of ϵ_a (see legend, Fig. 3) against time when 0.20-ml. aliquots were withdrawn, evaporated rapidly to dryness in a vacuum, dissolved in isooctane and the intensities of absorption measured at 340 mμ I and 304 mμ II. The orders of reaction with respect to hydrogen chloride (n) were evaluated from the slope of the straight lines (n = slope) produced when log K' was plotted against log C_{HCl} (Fig. 2). The values of K were obtained from the relation $K = K'/(C_{HCl})^n$. The values of both n and K which were calculated from the data below are given in Table I.

Derivative	$C_{HCl} \times 10^3$, moles/liter	$K' \times 10^4$, sec.$^{-1}$
Alcohol Ia	31	26
	26	19
	14	5.4
	6.9	1.6
	6.7	1.8
	5.3	0.84
	5.1	0.91
	3.5	0.43
Benzoate Ib	59	11
	31	3.5
	17	1.3
Acetate Ic	53	8.8
	34	3.8
	25	2.3
	15	1.1
	10	0.52
Dichloroacetate Id	85	12
	60	6.0
	29	1.7
	14	0.51
3,5-Dinitrobenzoate Ie	90	9.8
	59	5.0
	29	1.5
	19	0.91
	14	0.65
5,7,9(11),14,22-Ergostapentaene (II)	60	40
	25	8.4
	4.6	0.20

Isolation of 5,7,9(11),14,22-Ergostapentaene (II).—A solution of 9.9 g. of anhydrous dehydroergosterol (Ia) in *ca.* 470 ml. of chloroform was cooled to 19.8°. To this was added 10.0 ml. of 0.263 *M* hydrogen chloride in chloroform and the total volume was adjusted to 500 ml. This solu-

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[16] All melting points were determined on a Kofler block and are recorded as read. Rotations were determined at 20° in chloroform in *ca.* 1% solutions. All chloroform used in this investigation was a commercial, reagent grade containing approximately 0.75% ethanol. Ultraviolet spectra were determined in "spectro grade" isoöctane on a Cary recording spectrophotometer. Infrared spectra were determined in carbon disulfide (unless otherwise noted) on a Perkin-Elmer double beam spectrophotometer by Mrs. Alma Hayden, Mrs. Phyllis B. Smeltzer or Mr. H. K. Miller. Analyses were performed by the Analytical Service Laboratory of this Institute under the direction of Dr. William C. Alford.

[17] These three compounds were kindly supplied through the courtesy of Dr. Irving Scheer of this Laboratory.

[18] See, for instance, R. Antonucci, S. Bernstein, D. Giancola and K. J. Sax, *J. Org. Chem.*, **16**, 1159 (1951).

[19] Dr. William C. Alford kindly carried out this experiment on a semi-micro scale.

[20] R. K. Callow and O. Rosenheim, *J. Chem. Soc.*, 387 (1933).

[21] T. Ando, *Bull. Chem. Soc. Japan*, **13**, 371 (1938).

tion (0.050 M with respect to Ia and 0.0053 M with respect to hydrogen chloride) was placed in a constant temperature bath at 19.8°. The ensuing reaction was followed spectrophotometrically by removing aliquots (0.20 ml.) which were evaporated to dryness and dissolved in 50 ml. of isoöctane. When the intensity of the maximum at 340 mμ had fallen to 66% of its original value (83 minutes), the green solution was extracted with aq. sodium carbonate which changed the color to orange-red. After the solution had been washed with water, dried over sodium sulfate and evaporated to dryness, the residue was dissolved in 200 ml. of petroleum ether (b.p. 30–60°) and adsorbed on 200 g. of alumina (Woelm, "almost neutral"). The material was eluted with 145-ml. fractions of benzene–petroleum ether (5/1000). The weight of compound II was estimated spectrophotometrically at 304 mμ and the following was found (fraction no./wt. in mg.): $^1/_{382}$, $^2/_{980}$, $^3/_{298}$, $^4/_{141}$, $^5/_{65}$. Further fractions eluted very little material. Elution with 560 ml. of benzene yielded 0.56 g. of an oil, and 470 ml. of chloroform–ethanol ((1/1) eluted a highly colored fraction from which unchanged dehydroergosterol (Ia) was obtained by evaporation and crystallization. Fractions 1 and 2 were combined (fractions 3–5 contained an impurity absorbing near 250 mμ) and crystallized from 20 ml. of acetone, yielding 1.01 g. of colorless needles, m.p. 89–91°. Recrystallization several times from acetone raised the melting point to 94–95°, $[\alpha]_D$ + 164°; λ_{max} 250, 259, 269 and 304 mμ (ϵ 9,860, 14,400, 15,600 and 21,800). The infrared spectrum showed no band in the region 9.79–9.99 μ in carbon disulfide or chloroform. The compound turned yellow on exposure to air but was stable in a vacuum.

Anal. Calcd. for $C_{28}H_{40}$ (376.6): C, 89.29; H, 10.70. Found: C, 89.39; H, 10.86.

Hydrogenation of 5,7,9(11),14,22-Ergostapentaene (II) with Platinum.—A mixture of 70.0 mg. of platinum oxide, 7.0 ml. of ethyl acetate and 7.0 ml. of acetic acid was stirred magnetically in a hydrogen atmosphere. When the gas volume had become constant, 43.3 mg. of the pentaene II was allowed to fall into the solution in an aluminum boat. Within 30 min. 11.7 ml. of hydrogen was absorbed at 19° and 755 mm.; theory for 4.0 molecular equivalents of hydrogen is 11.2 ml. Stirring was continued for an additional 60 min. during which time 0.20 ml. of hydrogen was absorbed. The reaction mixture was filtered and evaporated to dryness. The residue was crystallized from acetone–ethanol to give 21 mg. of colorless needles, m.p. 74–75°, $[\alpha]_D$ +12°. Recrystallization raised the melting point to 78–79°. When mixed with an authentic sample[22] of 8(14)-ergostene (IV) of m.p. 75–76°, the melting point was 75–77°. The infrared spectra of the two samples confirmed their identity.

Hydrogenation of 5,7,9(11),14,22-Ergostapentaene (II) with Raney Nickel.—A mixture of 20 ml. of benzene and 1.5 g. of Raney nickel (wet with ethanol) was stirred magnetically in a hydrogen atmosphere. When the gas volume of the system had become practically constant, 92.4 mg. of the pentaene II was allowed to fall into the solution in an aluminum boat. Absorption of hydrogen began immediately and continued at 1.1 ml./min. until about one molecular equivalent had been absorbed after which the rate began to slow down. The reaction was interrupted when 2.18 molecular equivalents (12.8 ml. at 18.6° and 759 mm. pressure) had been absorbed at which time the rate of absorption was *ca.* one-fifth (0.20 ml./min.) of its original value. The catalyst was removed by decantation of the benzene solution. An aliquot of this solution after being evaporated and dissolved in isoöctane showed λ_{max} 235.0, 242.5 and 251.5 mμ (ϵ_a 10,500, 11,000 and 7,700) and λ_{infl} *ca.* 280 mμ (ϵ_a *ca.* 1,500), indicating 61% 7,9(11)-diene and 10–20% homoannular diene. The benzene solution was evaporated to dryness and the residue was crystallized from acetone giving 58 mg. (64%) of impure V melting at 120–123° with some previous softening near 100°. Three recrystallizations from acetone raised the melting point to 136–137° (20 mg.), but the ultraviolet spectrum indicated the presence of 6% homoannular diene, since three well-defined maxima occurred at 271, 282 and 293 mμ probably indicating the 5,7-isomer. In a larger batch the 7,9(11)-diene V was obtained pure by recrystallization from acetone a total of six times. It formed flat needles, m.p. 141–142°, $[\alpha]_D$ +37°; λ_{max} 235.6, 243.0 and 251.3 mμ (ϵ 14,600, 17,900 and 11,300); no absorption occurred above 270 mμ; lit.[3]: m.p. 134–135°, $[\alpha]_D$ +42.7°; λ_{max} 235, 243 and 252 mμ (ϵ not given).

Conversion of 5,7,9(11),14,22-Ergostapentaene (II) to Anthraergostapentaene (III).—A solution in chloroform which was 0.050 M with respect to II and 0.060 M with respect to hydrogen chloride was allowed to react at 19.8° for 30 min. The ultraviolet spectrum of an evaporated aliquot exhibited all the maxima of III and the intensity of absorption indicated an 80–90% conversion. Evaporation of the dark green solution to dryness and crystallization of the residual oil from acetone–ethanol yielded 138 mg. (86% allowing for the removal of 1.0 ml. for ultraviolet determinations) of III, m.p. 93–98°, from 190 mg. of II. Two recrystallizations from acetone raised the melting point to 105–106°; λ_{max} 221.5, 227.0, 266.0, 296.5 and 308.0 mμ (ϵ 24,600, 25,900, 17,000, 2,560, 2,020). The infrared spectrum confirmed its identity with the material obtained directly from dehydroergosteryl acetate.[1a] Hydrogenation of III yielded anthraergostatriene which was identical in every respect with an authentic sample.[1a]

3,5-Cyclo-6,8(14),9(11),22-ergostatetraene (VI).—A solution of 18.5 g. of freshly crystallized and dried dehydroergosterol (Ia) and 30 g. of *p*-toluenesulfonyl chloride in 150 ml. of pyridine was allowed to remain at 27° for 30 hours in the dark. Water (2.0 ml.) was added and the solution was allowed to remain at 27° an additional 20 hours. The solution which had turned dark red was evaporated to dryness in a vacuum and the residue was extracted with *ca.* 200 ml. of hot petroleum ether (b.p. 85–100°). The cooled extract was filtered from much solid and evaporated to dryness in a vacuum. The residue was treated with *ca.* 50 ml. of warm petroleum ether (b.p. 30–60°), cooled and filtered from 6.5 g. of dehydroergosteryl *p*-toluenesulfonate (see below). The filtrate was chromatographed on 200 g. of alumina (Woelm, "basic"). Elution with low boiling petroleum ether (250-ml. fractions) gave 2.2 g. of colorless hydrocarbon, m.p. 94–98°, from the second fraction after crystallization from acetone. Further elution with petroleum ether gave less material. By recrystallization from acetone VI was obtained as long prisms, m.p. 98–100°, $[\alpha]_D$ +65°; λ_{max} 244 and 295 mμ (ϵ 16,300 and 11,700), $\lambda_{max}^{CHCl_3}$ 9.90 μ.

Anal. Calcd. for $C_{28}H_{40}$ (376.6): C, 89.29; H, 10.70. Found: C, 89.23; H, 10.72.

When 79.1 mg. of VI was hydrogenated with magnetic stirring in 20 ml. of ethyl acetate–acetic acid (1/1) in the presence of 135 mg. of platinum oxide at 755 mm. pressure and 18°, 17.3 ml. of hydrogen (2.9 molecular equivalents) was absorbed in 19 minutes. There was no further uptake of hydrogen in an additional 25 minutes. After three recrystallizations the product was obtained only as a semi-crystalline mass. The isolation of pure 3,5-cyclo-8(14)-ergostene from the analogous reduction of 3,5-cyclo-6,8(14),22-ergostatriene was also found by Wallis, *et al.*,[3c] to be very difficult. This is to be contrasted with the ready isolation of 8(14)-ergostene from the reduction of unsaturated steroids not containing the 3,5-cyclo group (see, for instance, the reduction of II; also Fieser, *et al.*, ref. 5).

Dehydroergosteryl tosylate, which was obtained prior to the chromatography of VI, had a variable melting point. When it was precipitated from a pyridine solution by a saturated aq. sodium bicarbonate solution, it melted at *ca.* 130° as reported by Rees and Shoppee,[14] but on recrystallization from acetone the melting point, while sharp, varied in the range 103–113°. Crystallization from isoöctane also gave material with a melting point in this range. Nace[23] has noted this type of behavior with α-cholestanyl tosylate. Dehydroergosteryl tosylate formed in large colorless prisms; λ_{max} 221.5, 311.0, 324.5 and 341.0 mμ (ϵ 17,700, 10,300, 12,000, 7,300); $[\alpha]_D$ +191°. When the compound was melted, a green color was produced which changed to greenish-black through a very transient red color.

Anal. Calcd. for $C_{35}H_{48}O_3S$ (548.8): C, 76.59; H, 8.82. Found: C, 76.51; H, 8.87.

Conversion of 3,5-Cyclo-6,8(14),9(11),22-ergostatetraene (VI) to 3-Chloro-5,7,9(11),22-ergostatetraene (VII).—To a solution of 194 mg. (0.51 mmole) of VI in 90 ml. of chloroform at 19.8° was added 2.0 ml. of 0.284 M hydrogen chlo-

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[22] This sample was obtained through the courtesy of Professor L. F. Fieser.

[23] H. R. Nace, THIS JOURNAL, **74**, 5937 (1952).

ride in chloroform; the mixture was rapidly diluted to 100 ml. and maintained at 19.8° (final solution: 0.0051 *M* with respect to VI and 0.0056 *M* with respect to hydrogen chloride). The ultraviolet absorption was determined on evaporated aliquots in isoöctane solution at various times, and after 12 minutes the reaction was more than 50% complete based on the intensities of the maxima at 244 and 342 mμ for the starting material and product, respectively. After 64 minutes the spectrum was essentially that of the product isolated below except for a little extraneous absorption at 240–280 mμ. Based on the intensities of absorption at 311, 325.5 and 342 mμ, the conversion to the 5,7,9(11)-triene system was 80–90% of theory. After 71 minutes the pale greenish-yellow solution was evaporated to dryness and the residue was crystallized from acetone to give 78 mg. of slightly yellow crystals. Several recrystallizations from acetone yielded VII as colorless leaf-like prisms, m.p. 119–121°, $\lambda_{\max}$ 311.0, 325.3 and 342.0 mμ (ϵ 11,000, 12,100 and 7,300); $[\alpha]_D$ +181°.

Anal. Calcd. for $C_{28}H_{41}Cl$ (413.1): C, 81.41; H, 10.01; Cl, 8.58. Found: C, 81.32; H, 10.08; Cl, 8.49.

When the *i*-steroid VI was treated with one-half the equivalent amount of 0.02 *M* hydrogen chloride, the reaction stopped when half of VI had reacted and started again only when more 0.02 *M* hydrogen chloride was added. The chloro derivative VII was isolated by evaporation and crystallization.

When the *i*-steroid VI and hydrogen chloride were allowed to react at concentrations of 0.050 and 0.060 *M*, respectively, the absorption of the anthrasteroid III could be discerned after 22 minutes together with that of the 5,7,9-(11)-triene system (presumably of VII). After 1.5 hours there was very little 5,7,9(11)-triene system left; after *ca.* 3 hours the spectrum was no longer changing and indicated a 50–60% conversion to III.

The Buffered Hydrolysis of Dehydroergosteryl *p*-Toluenesulfonate.—The ester used in the following experiment was prepared according to the method of Rees and Shoppee.[14] It was, however, identical with that obtained in the preparation of VI.

A solution of 10.0 g. of dehydroergosteryl *p*-toluenesulfonate in 600 ml. of acetone and 300 ml. of water containing 20 g. of potassium acetate was refluxed 30 minutes. The ultraviolet spectrum of the reaction mixture showed that the starting material had been converted nearly completely to a compound with a single maximum at 247 mμ (D_{247}/D_{324} = 30). One hundred ml. was cooled to 0° yielding a compound melting at 119–121°. Three recrystallizations from acetone raised the melting point to 125–126°, $[\alpha]_D$ +126°, $\lambda_{\max}$ 247 mμ, ϵ 16,400 (no absorption 270–400 mμ), $\lambda_{\max}$ 2.78 μ.

Anal. Calcd. for $C_{28}H_{42}O$ (394.6): C, 85.22; H, 10.73. Found: C, 85.29; H, 10.56.

The remainder of the reaction mixture was refluxed an additional 5.5 hours and was concentrated in a vacuum. Benzene was added and partially removed by distillation at reduced pressure. The two layers were separated and the benzene solution was washed with water, dried and evaporated to dryness. The ultraviolet spectrum of the residue exhibited $\lambda_{\max}$ 247, 310, 324 and 340 mμ (D_{247}/D_{324} = 4.8). Ten per cent. of this was chromatographed on 30 g. of alumina (Woelm, "almost neutral"). Elution with 250 ml. of petroleum ether (b.p. 30–60°) in five fractions yielded crystals in each fraction having ultraviolet spectra nearly identical with that of VI (Fig. 4). More polar solvents failed to elute a compound with $\lambda_{\max}$ 247. Chloroform–ethanol (1/1) yielded a fraction composed principally of dehydroergosterol (spectroscopic). The remaining 90% of the residue from the benzene extract was chromatographed on 100 g. of alumina (Woelm, "basic"). Elution with 250 ml. of petroleum ether (b.p. 30–60°) yielded a crystalline hydrocarbon having an infrared spectrum in chloroform identical with that of VI. The ultraviolet spectrum ($\lambda_{\max}$ 244 and 295 mμ) was identical with that of VI (Fig. 4) except for slightly greater absorption at and near the minimum. Crystallization of the fraction from acetone yielded 91 mg. of elongated, flat prisms, m.p. 98–100°; $\lambda_{\max}$ 244.0, 251.5, 276.0 and 295.0 mμ (ϵ 15,600, 13,800, 8,700 and 9,900); $\lambda_{\min}$ 261 mμ (ϵ 7,600). Recrystallization from acetone gave prisms, m.p. 101–102°; $\lambda_{\max}$ 244.0, 251.5, 264.0, 275.0 and 295.0 mμ (ϵ 15,700, 14,900, 8,600, 9,100 and 9,900); $\lambda_{\min}$ 261 mμ (ϵ 8,600).

Anal. Calcd. for $C_{28}H_{40}$ (376.6): C, 89.29; H, 10.70. Found: C, 89.23; H, 10.72.

When 0.47 g. of VI ($\lambda_{\max}$ 244 and 295 mμ) was refluxed in 10 ml. of water and 60 ml. of acetone containing 0.51 g. of potassium acetate for 5.5 hours, no change in the ultraviolet spectrum of the reaction mixture was detected. The mixture was cooled to 0° and yielded 0.43 g. of elongated prisms, m.p. 100–101°, having an infrared spectrum in chloroform which was identical with that of the starting material.

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