analytical sample exhibited m.p. 153–155°, $[\alpha]^{25}D$ −24.6° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.73; H, 10.60.

The reduction product (100 mg.) was hydrogenated in 10 ml. of redistilled dioxane over prereduced Pd–C (5%) (theoretical uptake 5.4 ml., actual uptake 7.0 ml.). After filtration, the solution was concentrated to dryness *in vacuo* and crystallization occurred spontaneously. The thick colorless needles, XIX, were recrystallized for analysis from methanol–acetone–ether, m.p. 165–166°, $[\alpha]^{25}D$ −10.5° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.42; H, 11.26. The melting point was not depressed when mixed with the product XIX of acidic Pd–C hydrogenation of XXII.

(c) **With Sodium–Amyl Alcohol.**—To a boiling solution of 200 mg. of compound XXII in 20 ml. of amyl alcohol, 1 g. of sodium was added in small pieces. After refluxing for an additional 0.5 hr. and cooling, 20 ml. of water was added, and the organic material was extracted with 100 ml. of ether. The ether solution was washed, dried (sodium sulfate) and concentrated to dryness *in vacuo*. The crude product was acetylated in the usual manner. The infrared spectrum of the resulting product exhibited a single very strong carbonyl maximum at 5.78 μ and no hydroxyl maximum. This product was combined with the product of a similar experiment. A total of 560 mg. was dissolved again in 40 ml. of ethanol and subjected to hydrogenation in the presence of 500 mg. of 5% Pd–C at atmospheric pressure. Chromatography of the hydrogenation product yielded about 10% of 8(14)-ergosten-3β-ol acetate, m.p. 103–107°.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.62; H, 11.37. Mixture with an authentic sample did not depress the melting point. The remainder of the product, which was eluted after the above compound, could not be characterized.

Reduction of 8-Ergosten-3β-ol-11-one Acetate (XXI) with Lithium–Ammonia.—Reduction of 403 mg. of XXI in 20 ml. of dimethoxyethane was carried out using 130 mg. of lithium in 100 ml. of liquid ammonia. (An unusually large amount of lithium was required to give a permanent blue color.) The product, isolated as described for compound XXII, consisted of 362 mg. of ivory-colored crystalline solid, m.p. 148–150°, $[\alpha]^{25}D$ +16.5° ($CHCl_3$), no ultraviolet absorption, infrared $\lambda\lambda_{max}$ 2.78 and 2.90 μ (strong) and 5.90 μ (weak). Chromatography on alumina separated the product into two parts. (a) By benzene elution a white solid (98 mg., m.p. 157–159°) was obtained which, when acetylated, gave 108 mg. of crude acetate, m.p. 130–132°. An analytical sample, obtained by recrystallization from methanol–acetone, melted at 137–140°, infrared $\lambda\lambda_{max}$ 5.79 and 5.90 μ.

Anal. Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.74; H, 11.27.

Another sample exhibited m.p. 138–139°, $[\alpha]^{25}D$ +33.5° ($CHCl_3$). The constants reported by Heusser, *et al.*,[14] were m.p. 134.5°, $[\alpha]^{25}D$ +32° ($CHCl_3$).

Anal. Found: C, 78.11; H, 10.86.

(b) Elution with 9:1 benzene–ether gave 141 mg. of white solid with melting points ranging from 154–159°. Acetylation gave 158 mg. of thick oil which was chromatographed on aluminae. Fractions eluted by 9:1 ether–benzene were combined (99 mg., m.p.'s 103 to 112°). Recrystallization from methanol–acetone gave thick flat prisms, m.p. 118–119°.

Anal. Calcd. for $C_{32}H_{54}O_4$: C, 75.86; H, 11.37. Found: C, 76.21; H, 10.89. Infrared $\lambda\lambda_{max}$ 5.79 and 8.0 μ and no other carbonyl band indicating that this was probably impure 3,11-diacetate of ergostane or of 8-ergostene.

Reduction of 8,22-Ergostadiene-3β,14α-diol-11-one Acetate (XVII) with Sodium Amalgam–Acetic Acid.—The reduction of 1 g. of compound XVII with sodium amalgam and acetic acid, as described for compound XXII, yielded a crude product which had practically no ultraviolet absorption. The infrared spectrum contained a strong doublet in the carbonyl region (5.79 and 5.84 μ). The product, purified by chromatography, was isolated in 67% yield, and a sample, recrystallized from methanol, exhibited m.p. 115.2–116.0°, $[\alpha]^{25}D$ +42.0° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.04, 79.00; H, 10.17, 10.24.

After treatment with phosphorous oxychloride and pyridine under the usual dehydrating conditions, the product was recovered unchanged. When the above reduction product was treated with either methanolic hydrochloric acid or methanolic potassium hydroxide, the crude new product exhibited λ_{max}^{ether} 244 mμ (log ϵ 3.60–3.78), infrared λ_{max} 5.8 (broad) and 6.02 μ (moderately strong).

14-Epi-8,22-ergostadien-3β-ol-11-one Acetate (XXIV).—A solution of 0.300 g. of XXII, m.p. 131–132°, $[\alpha]^{25}D$ +105° ($CHCl_3$), in 50 ml. of 5% ethanolic potassium hydroxide solution was heated at reflux for 3 hr. under a nitrogen atmosphere. The reaction mixture was diluted with water and the ethanol partially removed by evaporation *in vacuo*. The organic product was extracted with ether, washed to neutrality, dried over sodium sulfate and concentrated *in vacuo* to a mass of colorless, glistening plates, weight 0.303 g., λ_{max}^{ether} 244 mμ (log ϵ 3.85). The crude product was directly acetylated in 8 ml. of pyridine and 12 ml. of acetic anhydride, from which was recovered by the usual procedure 0.267 g. of nearly pure 14-epi acetate, m.p. 108°, $[\alpha]^{25}D$ +131.7° ($CHCl_3$). An analytical sample was obtained by twice recrystallizing from methanol; m.p. 114.0–114.4°, $[\alpha]^{25}D$ +133.2° ($CHCl_3$), λ_{max}^{ether} 244 mμ (log ϵ 3.98).

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.24; H, 10.20. Found: C, 79.21; H, 9.83.

Hydrogenation of the epi-ketone in ethanol over palladium catalyst resulted in absorption of 1 mole of hydrogen to afford a clear oil, λ_{max}^{ether} 243 mμ (log ϵ 3.99), which was not brought to crystallization.

BROOKLYN, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Corticosteroid Intermediates. V. Rearrangements of C-Ring Oxygenated Steroids[1]

BY E. J. AGNELLO, REX PINSON, JR., AND G. D. LAUBACH

RECEIVED APRIL 5, 1956

The rearrangement of 11α,14α-epidioxido-6,8,22-ergostatrien-3β-ol acetate to 8α(14α),9α(11α)-diepoxido-6,22-ergostadien-3β-ol acetate and the transformation of both of these compounds to 6,8(14),9(11),22-ergostatetraen-3β-ol-15-one acetate are described.

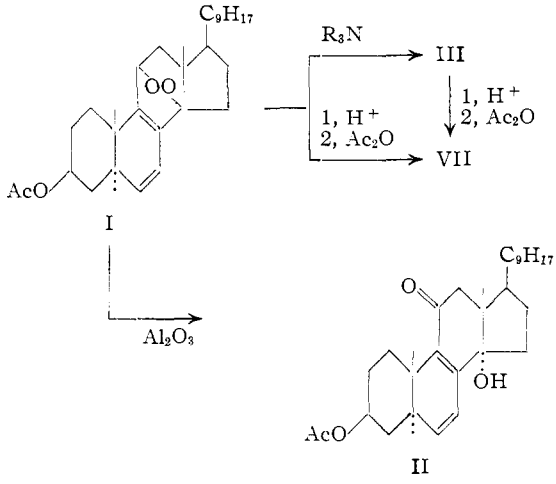
Previous communications[2,3] have described a number of transformations of 11α,14α-epidioxido-6,8,22-ergostatrien-3β-ol acetate (I). Among the reported reactions was the conversion of I to 6,8,22-ergostatrien-3β,14α-diol-11-one 3-acetate (II) by adsorption on basic alumina. The usefulness of II in the synthesis of corticosteroid intermediates,

(1) Presented before the Division of Organic Chemistry, 126th Meeting of the American Chemical Society, September, 1954.

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

(3) G. D. Laubach, E. C. Schreiber, E. J. Agnello and K. J. Brunings, *ibid.*, **78**, 4743 (1956).

e.g., 22-ergosten-3β-ol-11-one acetate, prompted a search for reagents which would effect the conversion of I to II or a related 11-keto derivative in homogeneous media.



Since the above reaction was found to occur only on *basic* alumina and similar conversions were known to be base catalyzed[4,5] the investigation included the reaction of I with a variety of inorganic alkaline reagents. Bases such as potassium bicarbonate, methoxide and *t*-butoxide did, indeed, isomerize the peroxide to II but in yields which were inferior to the original method. These results were not surprising in view of the fact that II itself rapidly deteriorated when in contact with the above reagents.

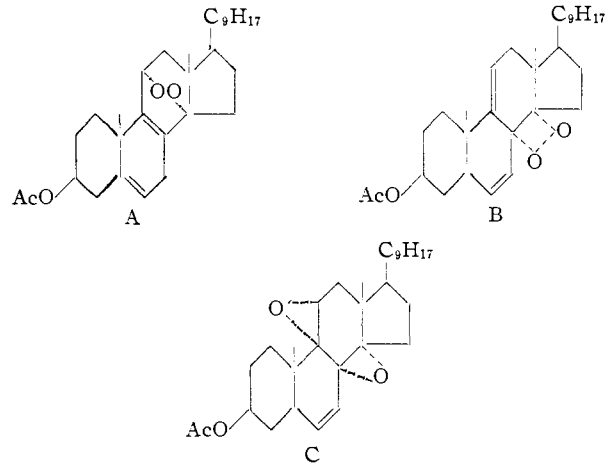
An unexpected result was observed when the peroxide I was heated with various organic bases. For example, when I was treated with refluxing triethylamine, the product, isolated in 70% yield, was an isomer of I which did not exhibit ultraviolet absorption. The new isomer III resembled its precursor in that it liberated iodine from potassium iodide solution and its infrared spectrum indicated the absence of ketone or hydroxyl functions. In contrast to I, however, the isomeric compound III was very stable to alumina and strong alkalies and was sensitive to acids. For example, III was recovered unchanged (except for removal of the acetate group) from treatment with refluxing methanolic potassium hydroxide, but reaction of III with dilute hydrochloric acid (0.025 *N* in aqueous acetone) resulted in its conversion to an amorphous product exhibiting ultraviolet absorption of undetermined origin (λ_{max} 256 mμ).

A consideration of possible structures for the isomer III included such formulations as A, B and C (below), all of which were consistent with its spectral properties and its ability to oxidize iodide to iodine.[6]

(4) N. Kornblum and H. E. DeLaMare, THIS JOURNAL, **73**, 880 (1951).

(5) R. J. Conca and W. Bergmann, *J. Org. Chem.*, **18**, 1104 (1953) and references cited therein.

(6) The reduction of cholesterol β-oxide benzoate by aqueous hydrogen iodide at room temperature reported by D. H. R. Barton, E. Miller and H. T. Young (*J. Chem. Soc.*, 2598 (1951)) is another example of the reactivity of oxides toward iodide.

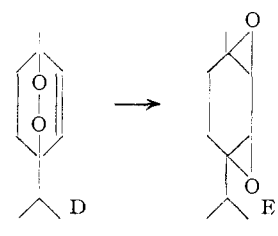


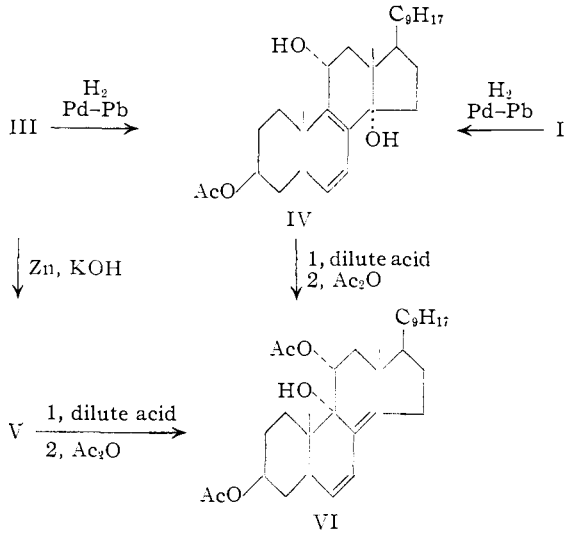
Although it was possible to envision the transformation of the peroxide I to any one of the three structures, there were strong arguments against formulations A[7] and B. The primary argument against them involved the lack of reactivity of compound III toward alkaline reagents, a property which is almost certainly incompatible with the strained four-membered cyclic peroxide B and one which would not be expected of a compound with structure A containing the identical peroxide function to that of the alkali-sensitive precursor I. Furthermore, when III was saponified and then oxidized under Oppenauer conditions to the corresponding 3-ketone, the product was a *saturated* ketone, a result inconsistent with the 5,8-diene formulation A.

The above-mentioned arguments against structures A and B, together with the observation that compound II possessed the properties commonly associated with oxido compounds (stability to alkalies and sensitivity to acids), strongly favored its formulation as 8α(14α),9α(11α)-diepoxido-6,22-ergostadien-3β-ol acetate (structure C).[8] The following transformations of III also were consistent with its formulation as the diepoxide. When III was hydrogenated in the presence of lead-poisoned palladium catalyst, the product was 6,8,22-ergostatriene-3β,11α,14α-triol 3-acetate (IV), the same product obtained from the original peroxide I under identical conditions.[2,3] The isolation of a known 11,14-dioxygenated compound from a hydrogenation reaction which is not prone to cause rearrangement supports the view that oxygen had not migrated from positions 11 and 14 during the triethylamine treatment of I.

(7) The preparation of a cholesterol derivative with the 5,8-diene system was reported recently by K. Tsuda, K. Arima and R. Hayatsu, THIS JOURNAL, **76**, 2933 (1954).

(8) A similar diepoxido structure (E) has been proposed recently by M. Matic and D. A. Sutton (*J. Chem. Soc.*, 349 (1953)) for the well-known isomerization product of ascaridole (D).



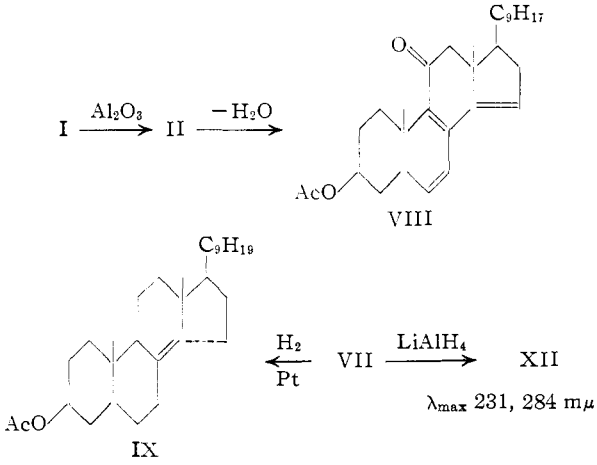


Another group of reactions lent additional support to the assignment of structure C to the isomer III. Reduction with zinc in alcoholic potassium hydroxide transformed III into a product V exhibiting λ_{max} 273 mμ, characteristic of the 6,8-diene system. When V was treated with dilute aqueous acid and acetylated, the product (isolated in 46% yield from III) was 6,8(14),22-ergostatriene-3β,9α,11α-triol 3,11-diacetate (VI) previously obtained[2] from the known monoacetate IV by dilute acid treatment and acetylation. The formation of the known rearrangement product VI by way of the above series of reactions could be explained satisfactorily presuming that the zinc–potassium hydroxide reduction product V was 6,8,22-ergostatriene-3β,11α,14α-triol (the free alcohol of IV) and that dilute acid treatment resulted in anionotropic rearrangement to a 3,9,11-triol, the 3,11-diacetate VI of which was finally isolated.

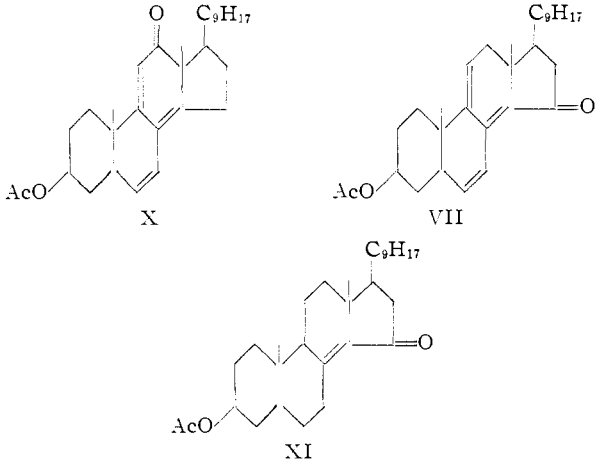
The isomerization of I to III could also be effected by another tertiary amine, pyridine, and also by refluxing toluene in the presence of zinc dust.[9] Treatment of the peroxide with most of the other reagents employed in this study[10] either produced no change in I or afforded an intractable mixture of products.

A crystalline product was isolated, however, when the peroxide was treated with concentrated hydrochloric acid in methanol—a product VII which could also be obtained in similar yield from the diepoxide III under identical conditions. The compound was a ketone, $C_{30}H_{42}O_3$, isomeric with the previously-prepared 11-ketone VIII but exhibiting important differences in properties.

The most outstanding difference between VII and VIII was the facile formation of a carbonyl derivative of VII (2,4-dinitrophenylhydrazone, λ_{max} 440 mμ). In view of the well-known nonreactivity of 11-ketosteroids to carbonyl reagents, the new ketone VII must have its carbonyl group in some position other than eleven or some fundamental change in the steroid skeleton must have occurred to allow derivatization of the ketonic function. The latter possibility (rearrangement of the steroid skeleton) was ruled out by hydrogenation of VII under acidic conditions to the known 8(14)-ergosten-3β-ol acetate (IX).



The similarity in the ultraviolet absorption spectra of VII (λ_{max} 237, 341 mμ) and VIII (λ_{max} 233, 326 mμ) suggested that a cross-conjugated triene system similar to that in VIII was present in the new ketone VII. Confirmation of this theory was obtained when reduction of VII with lithium aluminum hydride resulted in a non-ketonic product XII with an ultraviolet absorption spectrum (λ_{max} 231 284 mμ) associated with the 6,8(14),9(11)-triene.[2,11]



The combination of a 6,8(14),9(11)-triene and reactive carbonyl function could be accommodated by the two structures VII and X, which differed only in the location of the carbonyl group. The choice between these two structures was made on the basis of catalytic hydrogenation of the nuclear trienic ketone to a nuclear monoenic ketone, shown

(9) The treatment of I in refluxing toluene *without added zinc dust* did not cause any change in I.

(10) Among the reagents which produced no change in I were toluene (at reflux), glacial acetic acid (at room temperature) and potassium acetate in refluxing methanol. Treatment of I with refluxing dioxane (with or without added zinc dust) afforded a mixture of starting material and conversion products with lowered ultraviolet absorption from which neither III nor any other product could be isolated (synthetic mixtures of I and III could be separated by chromatography on Florisil). Intractable products were obtained from reactions of I with acetic–sulfuric acid, zinc dust–acetic anhydride, refluxing xylene or zinc–potassium hydroxide treatments.

(11) Attempts to prepare the known isodehydroergosterol acetate[2] by Wolff-Kishner reduction of VII were unsuccessful.

by mixed melting point and infrared spectral comparison to be the known 8(14),22-ergostadien-3β-ol-15-one acetate (XI).[12] The structure of the hydrochloric acid rearrangement product of the peroxide I or diepoxide III is formulated, therefore, as 6,8(14),9(11),22-ergostatetraen-3β-ol-15-one acetate (VII).[13]

Experimental[14]

Treatment of 11α,14α-Epidioxido-6,8,22-ergostatrien-3β-ol Acetate (I) with Refluxing Triethylamine.—A mixture of 5 g. of the peroxide I (ultraviolet assay 95%) and 250 ml. of freshly distilled triethylamine was heated under reflux for 3 hr. The triethylamine was removed by evaporation *in vacuo* and the residue was triturated with methanol. The ivory-colored crystalline product melted at 170–171° and did not exhibit absorption in the ultraviolet region above 220 mμ. Its infrared spectrum did not contain either hydroxyl or ketone carbonyl absorption bands. Upon recrystallization from 40 ml. methanol (ether) the product (3.0 g.) was isolated as platelets, m.p. 172–173°, $[\alpha]^{25}D$ −40.5° ($CHCl_3$). A second crop of 0.5 g., m.p. 171.6–172.4°, $[\alpha]^{25}D$ −40.8° ($CHCl_3$), raised the total yield to 70%. An analytical sample of III melted at 172–174°, $[\alpha]^{25}D$ −38.7° ($CHCl_3$).

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.9; H, 9.46. Found: C, 77.1; H, 9.72. The molecular weight of III (Rast method, using exaltone) was 403. A sample of III released iodine from potassium iodide in acetic acid solution under nitrogen.

Treatment of I with Pyridine.—Refluxing a small sample of peroxide I in pyridine for 3 hr. resulted in a tan solid (no ultraviolet absorption) which, after trituration with methanol, melted at 170–172°, m.p. on admixture with III, 169–170°. The infrared spectrum of this product was identical to III prepared with triethylamine.

Treatment of I with Zinc Dust and Toluene.—When 500 mg. of peroxide I (92% by spectral assay) was refluxed in 50 ml. of toluene with 2 g. of zinc dust, the ultraviolet absorption gradually decreased until after 22.5 hr. the intensity indicated about 25% of starting chromophore. Chromatography gave 20% of non-chromophoric material which, upon recrystallization from methanol (ether), melted at 166.8–168.0°, $[\alpha]^{25}D$ −27.2° ($CHCl_3$). The melting point was not depressed when the product was mixed with a sample of III prepared by the triethylamine method.

Reaction of III with Alumina.—A sample of III was adsorbed on Brockman III alumina and eluted with 1:3 benzene–hexane after 28.5 hr. The crude product exhibited no ultraviolet absorption, and its infrared spectrum was identical to that of starting material. Trituration of the product with methanol gave a crystalline product, m.p. 165–167°. Admixture of the product with starting material did not lower its melting point.

Saponification of III.—A solution of 300 mg. of III in 15 ml. of benzene containing 3 ml. of 0.3 *M* sodium methoxide in methanol was allowed to stand 1 hr. at room temperature. The solution was diluted with 50 ml. of ether, washed thoroughly with water and concentrated to dryness *in vacuo*. Recrystallization of the residue from methanol yielded 275 mg. of fine colorless needles which melted at 153.5–155.0°, $[\alpha]^{25}D$ −45.5° ($CHCl_3$). Acetylation of 250 mg. of this product with acetic anhydride–pyridine yielded, after recrystallization, 185 mg. of III, which did not depress the melting point of an authentic sample.

The saponification of III could be accomplished equally satisfactorily in boiling 5% methanolic potassium hydroxide.

Oppenauer Oxidation.—A sample of the free alcohol of III (0.5 g.) was subjected to the usual Oppenauer oxidation conditions using 5 ml. of cyclohexanone, 1.0 g. of aluminum isopropoxide and 30 ml. of toluene. The product, isolated in the usual way and triturated with 90% methanol, was a white solid (225 mg.) with m.p. 193–194° dec., no ultraviolet absorption above 220 mμ, and infrared λ_{max} 5.82 μ. From the triturate there was isolated, by trituration of the residue with petroleum ether, 160 mg. of white solid, m.p. 158–160°, no ultraviolet absorption, infrared λ_{max} 5.82 μ. Refluxing of both of the above samples with 5% potassium hydroxide in methanol failed to produce a product with any ultraviolet absorption in the conjugated carbonyl region.

Hydrogenation of III.—A solution of 468 mg. (0.001 mole) of III in 40 ml. of ethyl acetate was added to 200 mg. of prereduced palladium–lead–calcium carbonate catalyst[15] in 15 ml. of ethyl acetate. Hydrogenation at atmospheric pressure with uptake of one molar equivalent of hydrogen gave the product (isolated from the filtered reaction mixture) as a white crystalline solid (455 mg.), m.p. 152–154°, $[\alpha]^{25}D$ −25.3° ($CHCl_3$), λ_{max}^{ether} 273 mμ (log ε 3.58). Recrystallization of 100 mg. from 2 ml. of ethyl acetate afforded 23 mg. of needles, m.p. 163–165°, $[\alpha]^{25}D$ −21.2° ($CHCl_3$), λ_{max}^{ether} 273 mμ (log ε 3.58).

Anal. Calcd. for $C_{30}H_{46}O_4$: C, 76.6; H, 9.86. Found: C, 76.2; H, 9.87. The infrared spectrum of this product was identical to that of an authentic sample of 6,8,22-ergostatriene-3β,11α,14α-triol 3-acetate (IV).

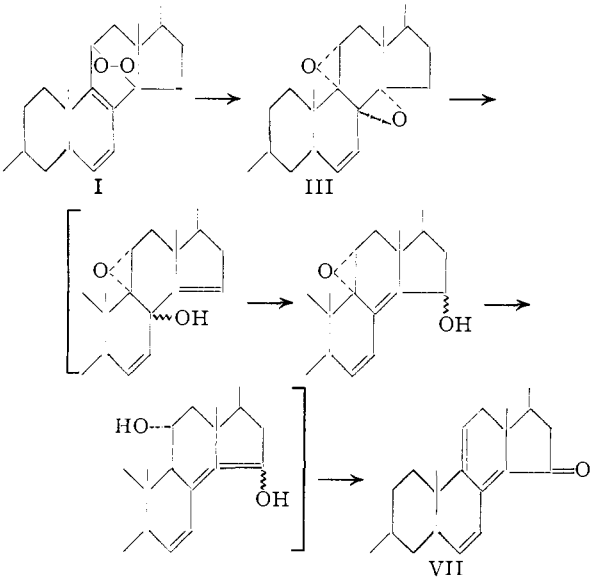
Treatment of III with Zinc–Potassium Hydroxide.—To a warm solution of 1.08 g. of III in 20 ml. of ethanol was added 2.4 g. of zinc dust and 0.3 g. of potassium hydroxide in 7 ml. of ethanol. After being refluxed for 3 hr. the mixture was filtered, the solution concentrated to a slurry and 50 ml. of water added. The white solid product was filtered and washed to yield 0.95 g. of white powder, m.p. 197–199°, λ_{max}^{ether} 275 mμ (log ε 3.38). A solution of the reduction product in 120 ml. of acetone was treated with 40 ml. of 0.1 *N* hydrochloric acid for 1.5 hr. at room temperature. The acetone was removed by distillation *in vacuo* and the product, isolated by filtration, was 870 mg. of white powder, m.p. 150–152°, λ_{max}^{ether} 248 mμ (log ε 4.36). Acetylation of this product gave 991 mg. of ivory-colored solid, m.p. 149–151°, which, upon methanol trituration, afforded 400 mg. of solid, m.p. 171–172°, $[\alpha]^{25}D$ −46.7° ($CHCl_3$), λ_{max}^{ether} 248 mμ (log ε 4.32). Recrystallization from 95% methanol gave an analytical sample, m.p. 171.2–172.0°, $[\alpha]^{25}D$ −50.4° ($CHCl_3$), λ_{max}^{ether} 248 mμ (log ε 4.45).

Anal. Calcd. for $C_{32}H_{48}O_5$: C, 75.0; H, 9.44. Found: C, 74.7; H, 9.45. The melting point of this product was not depressed on admixture with an authentic sample of 6,8-(14),22-ergostatriene-3β,9α,11α-triol 3,11-diacetate (VI).

Reaction of I or III with Hydrochloric Acid in Methanol.—To a suspension of 500 mg. of I or III in 30 ml. of methanol was added 4 ml. of concentrated hydrochloric acid, and the mixture was refluxed on a steam-bath for 10 minutes, cooled in an ice-bath and neutralized with saturated sodium bicarbonate solution. The yellow precipitate was removed by filtration and washed to yield 380 mg. of light tan powder,

(12) D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954). A sample of XI was kindly furnished by Prof. D. H. R. Barton for comparison purposes.

(13) The formation of the ketone VII from the peroxide I or the diepoxide III might occur by a sequence of steps depicted as follows:



(14) All melting points are uncorrected.

(15) H. Lindlar, U. S. Patent 2,681,938 (June 16, 1950).

λ_{max}^{ether} 230 mμ (log ε 4.02) and 335 mμ (log ε 3.98), infrared λ_{max} 5.75 μ (weak), 5.96 μ (intense), 6.10 and 6.22 μ (weak) and 6.4 μ (intense). The product was reacetylated and chromatographed. Most of the product (184 mg.) was eluted from Florisil in 20:1 benzene–ether as light yellow crystals. A fraction recrystallized from methanol–acetone–water gave clusters of short needles, m.p. 186–188°, $[\alpha]^{25}D$ −145.6° ($CHCl_3$), λ_{max}^{ether} 237 mμ (log ε 4.04) and 341 mμ (log ε 4.06). The infrared spectrum was unchanged.

Anal. Calcd. for $C_{30}H_{42}O_3$: C, 79.9; H, 9.39. Found: C, 79.9; H, 9.38. The product formed a deep red 2,4-dinitrophenylhydrazone, $\lambda_{max}^{CHCl_3}$ 440 and 326 mμ.

Hydrogenation of Ketone VII under Acid Conditions.—A 50-mg. sample of VII in 10 ml. of acetic acid was subjected to hydrogenation overnight in the presence of platinum catalyst. The reaction mixture was filtered, and the product was precipitated by addition of water to the filtrate. The white solid, m.p. 96–98°, was recrystallized from ethyl acetate to give 15 mg. of plates, m.p. 106–107°, $[\alpha]^{25}D$ +17° ($CHCl_3$). The melting point on admixture with an authentic sample of 8(14)-ergostenol 3-acetate (m.p. 110–111°) was 109–110°. The infrared spectrum also was identical to that of the known compound.

8(14),22-Ergostadien-3β-ol-15-one Acetate (XI).—A solution of 168 mg. (0.37 mmole) of ketone VII in 20 ml. of ethyl acetate was added to 1 g. of Raney nickel pre-reduced in 40 ml. of ethyl acetate and subjected to hydrogenation at room temperature and atmospheric pressure. The rate of hydrogen uptake slowed down considerably after 18 ml. had been absorbed (30 minutes). The hydrogenation was stopped after 2 hr. (total uptake 22.6 ml.). The catalyst was removed by filtration and the colorless solution concentrated to dryness to give 168 mg. white solid, m.p. 130–135°, $[\alpha]^{25}D$ +81.5° ($CHCl_3$), λ_{max}^{EtOH} 257 mμ (log ε 4.00). Trituration of the crude product with methanol yielded 23 mg. of white crystalline solid, m.p. 166–168°. Recrystallization from 1 ml. of methanol gave the product (13 mg.) as short needles, m.p. 176–177°, $[\alpha]^{25}D$ +72.5° ($CHCl_3$), λ_{max}^{EtOH} 259 mμ (log ε 4.16). Comparison of this product with an authentic sample of 8(14),22-ergostadien-3β-ol-15-one acetate[13] by mixed melting point and infrared spectra showed them to be identical.

Reduction of Ketone VII with Lithium Aluminum Hydride.—Reduction of a sample (80 mg.) of acid-rearrangement product VII in 50 ml. of ether with 5 ml. of 0.5 *M* lithium aluminum hydride solution overnight gave a crude product XII, λ_{max}^{ether} 231 mμ (log ε 4.02) and 284 mμ (log ε 3.65).

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Synthesis of 2-Hydroxy-8-keto-5-methoxy-4a-methylperhydrophenanthrene

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2-Hydroxy-8-keto-5-methoxy-4a-methylperhydrophenanthrene (IX) and 2,5,8-trihydroxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XIX), potential C-11 oxygenated steroid intermediates, have been synthesized.

The synthesis of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (I), a potential intermediate for the synthesis of C–11 oxygenated steroids, has been reported.[1] Its conversion into two of the isomeric 2-hydroxy-8-keto-5-methoxy-4a-methylperhydrophenanthrenes (IXA) and (IXB) is described in the present paper. In addition, some reactions of these and related compounds are reported.

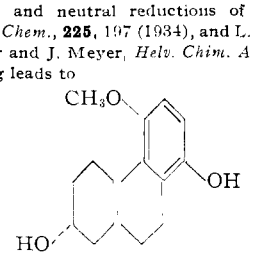
The reduction of the hexahydrophenanthrene I to give the hydroxyphenol IV was accomplished in two ways. Hydrogenation over a palladium catalyst gave a quantitative yield of one isomer of the ketophenol II. Subsequent reduction of the ketophenol II over Raney nickel yielded a single crystalline hydroxyphenol IV. This product was also obtained by hydrogenation of the hexahydrophenanthrene I in one step using Raney nickel as a catalyst.[2]

2-Acetoxy-8-hydroxy-5-methoxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VI) could be prepared directly by monoacetylation of the hydroxyphenol IV. Better yields were obtained, however, by selectively hydrolyzing the diacetoxy derivative V with an aqueous solution of potassium bicarbonate.

Numerous methods for hydrogenation of the aromatic ring of the acetoxyphenol VI were studied. In general, conditions satisfactory for obtaining complete reduction of the ring also brought about varying amounts of hydrogenolysis of the oxygen functions. Early in this work the only satisfactory system for obtaining the desired result was the palladium-catalyzed reaction described by Cornforth and Robinson[3] for the reduction of 2-acetoxy-8-hydroxy-4a-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene. It was later found that hydrogenation at about 15,000 p.s.i. over a ruthenium–Darco catalyst was more satisfactory. Almost

(1) W. F. Newhall, S. A. Harris, F. W. Holly, E. L. Johnston, J. W. Richter, E. Walton, A. N. Wilson and K. Folkers, THIS JOURNAL, **77**, 5646 (1955).

(2) An A/B-*cis* structure is postulated for these reduction products by analogy to neutral hydrogenations of cholestenone (H. Grashof, *Z. physiol. Chem.*, **223**, 249 (1934)) and of 2-keto-10-methyl-$\Delta^{1(9)}$-octalin (R. P. Linstead, A. F. Millidge and A. L. Walpole, *J. Chem. Soc.*, 1140 (1937); V. C. E. Burnop and R. P. Linstead, *ibid.*, 720 (1940); E. C. du Feu, F. J. McQuillan and R. Robinson, *ibid.*, 53 (1937)). In addition, a closer analogy may be drawn to the neutral reduction of 8-hydroxy-2-keto-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene to yield the corresponding A/B-*cis* octahydrophenanthrene (J. W. Cornforth and R. Robinson, *ibid.*, 676 (1946); *Nature*, **160**, 737 (1947)). The neutral reduction of the 2-keto function probably gives rise to a secondary hydroxyl having a *trans* relation to the angular methyl; *cf.* acidic and neutral reductions of coprostanone: H. Grassoff, *Z. physiol. Chem.*, **225**, 197 (1934), and L. Ruzicka, H. Brunger, E. Eichenberger and J. Meyer, *Helv. Chim. Acta*, **17**, 1407 (1934). The above reasoning leads to



as a tentative stereochemical representation of the hydroxyphenol IV.

(3) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).