no test for acetone (4 hours). The solvent was removed, and the residue was treated with dilute hydrochloric acid. The mixture was extracted with ether, and the ethereal solution was washed with sodium bicarbonate and dried over magnesium sulfate. A portion of the residue remaining after removal of the ether was recrystallized to give material melting at 116–117°. *Anal.* Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.03, 77.20; H, 7.13, 7.07.

Lactone of *cis*-1-Hydroxy-3-carboxy-4-phenyltetralin (XIII).—Saponification of the above crude hydroxy ester mixture afforded 1.9 g. (70%) of hydroxy acids, m.p. 150–158° dec. Upon recrystallization from a mixture of ethyl acetate (40 ml.) and petroleum ether (150 ml.), there was obtained 1.5 g. of product, m.p. 163–165° dec.

A sample of 0.716 g. of the hydroxy acid mixture, m.p. 163–165° dec., was heated for several minutes at 180°. The resulting glass was taken up in ether, and the *trans*-hydroxy acid was removed by sodium bicarbonate. Concentration of the dried ether solution gave 0.53 g. of crude lactone, m.p. 100–125°. This was recrystallized from 50% aqueous acetic acid to give a product which sintered at 120° and melted at 125–127°. Sublimation at 110° (0.01 mm.) afforded material melting at 126–128°. *Anal.* Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.93, 81.86; H, 5.93, 5.83.

***trans*-1-Hydroxy-3-carboxy-4-phenyltetralin.**—Acidification of the sodium bicarbonate extract obtained above afforded 0.09 g. of *trans*-hydroxy acid which melted at 191–193° after two recrystallizations from ethyl acetate–petroleum ether. *Anal.* Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.12, 75.92; H, 6.02, 6.13.

***cis*-1-Hydroxy-3-carboxy-4-phenyltetralin.**—Saponification of the lactone XIII produced the *cis*-hydroxy acid, m.p. 169–170° dec. *Anal.* Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.02, 76.04; H, 6.25, 6.23.

Ethyl α-Methyl-β-benzoylpropionate.—A solution of 21.1 g. of α-methyl-β-benzoylpropionic acid,[14] m.p. 138–142°, in 500 ml. of 1% ethanolic hydrogen chloride stood at room temperature for 24 hours. The residue remaining after removal of the ethanol was freed of acid and distilled. There was obtained 20.6 g. (85%) of the ethyl ester, b.p. 93° (0.1 mm.), $n^{25}D$ 1.5060, sp. gr. 25/25 1.0733. *Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; sapon. equiv., 220. Found: C, 71.19, 70.94; H, 7.36, 7.34; sapon. equiv., 219.

Acknowledgments.—We would like to express our thanks to Dr. Mary H. Aldridge and Miss Kathryn Gerdeman for performing the microanalyses. This work was supported in part by generous grants from the National Cancer Institute, National Institutes of Health, Bethesda, Maryland, and E. I. du Pont de Nemours and Co., Wilmington, Delaware, for which we are indebted.

(14) S. Dixon, H. Gregory and L. F. Wiggins, *J. Chem. Soc.*, 2139 (1949).

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

A Synthesis of Progesterone from Ergosterol[1]

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RECEIVED OCTOBER 27, 1954

A new and practical synthesis of progesterone from ergosterol, involving an improved method for the preparation of 4,22-ergostadien-3-one from 4,6,22-ergostatrien-3-one and conversion of the dienone to 3-ketobisnor-4-cholenaldehyde, is described.

The discovery[2a] and confirmation[2b] of a practical method for the conversion of progesterone to cortisone, *via* an 11-oxygenated intermediate produced biochemically, has emphasized the need for cheap progesterone in large quantities. Of the naturally-occurring sterols, ergosterol always has been an extremely attractive starting material because of its almost unlimited potential supply from fermentation processes. Only recently, however, has ergosterol served as the percursor of intermediates obviously useful in the preparation of steroid hormones,[3] and in these cases attention was centered on the preparation of 11-oxygenated *allo* compounds *via* reaction of the $\Delta^{7,9(11)}$ system.

This paper presents an efficient and practical synthesis of progesterone from ergosterol.

4,7,22-Ergostatrien-3-one (ergosterone, II)[4] was obtained in 77% yield by the Oppenauer oxidation of ergosterol (I) with cyclohexanone and aluminum isopropoxide in boiling toluene. The reaction proceeded with surprising rapidity, being essentially complete in 10 minutes as indicated by the rapid disappearance of the maximum (282 mμ) of ergosterol and the rapid rise of the maximum (242 mμ) of the Δ^4-3-ketone in the ultraviolet spectra of samples isolated consecutively from the reaction mixture.

Treatment of a hot solution of 4,7,22-ergostatrien-3-one in methanol with a small amount of concentrated hydrochloric acid caused the immediate precipitation of a white crystalline material. On the bases of its analysis, which showed the presence of a methoxyl group, and of its spectra typical of the $\Delta^{3,5,7}$- system, λ_{max} 321 mμ and maxima at 1571, 1620 and 1643 cm.$^{-1}$, this compound was assigned the

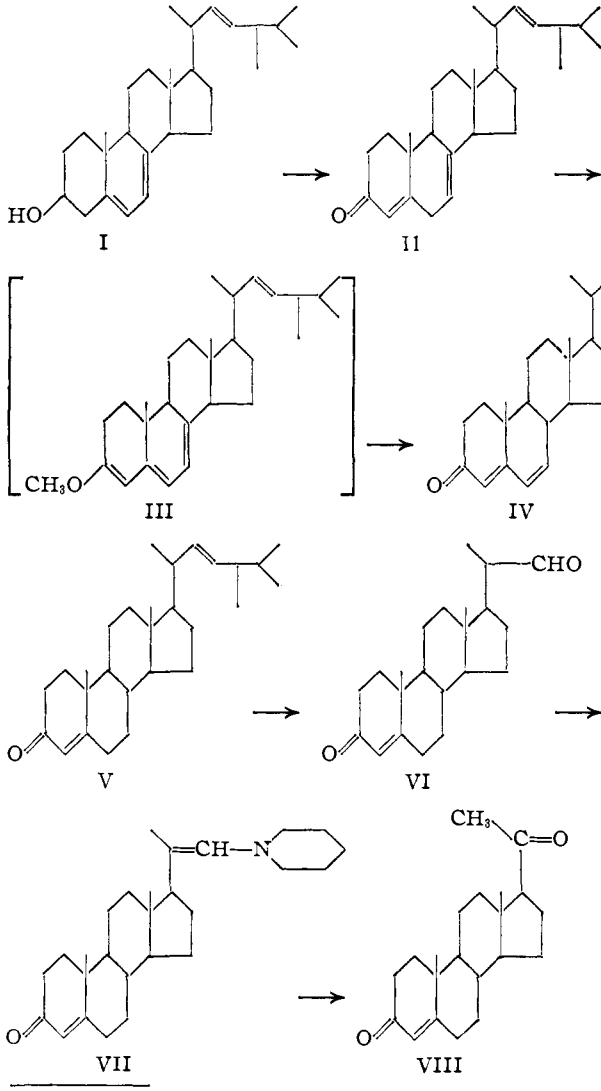
(1) Presented before the Division of Organic Chemistry at the 124th Meeting of the American Chemical Society, Chicago, Ill., September 6–11, 1953. A. F. Daglish, J. Green and V. D. Poole, *Chem. and Ind.*, **45**, 1207 (1953); *J. Chem. Soc.*, 2627 (1954), have since reported a synthesis of progesterone by a similar method. See also F. Johnson, G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1302 (1954).

(2) (a) D. H. Peterson and H. C. Murray, THIS JOURNAL, **74**, 1871 (1952); H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769; D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister and H. M. Leigh, THIS JOURNAL, **74**, 5933 (1952); (b) O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 3711 (1952); J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, *ibid.*, **74**, 3962 (1952).

(3) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *ibid.*, **73**, 2396 (1951); E. Schoenewaldt, L. Turnbull, E. M. Chamberlin, D. Reinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda and M. Tishler, *ibid.*, **74**, 2696 (1952); L. F. Fieser, J. C. Babcock, J. E. Herz, Wein-Yuan Huang and W. P. Schneider, *ibid.*, **73**, 4053 (1951); H. Heusser, K. Eichenberger, P. Kurath, H. R. Dällenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951); R. Budziarek, F. Johnson and F. S. Spring, *J. Chem. Soc.*, 3410 (1952); E. R. H. Jones, *et al.*, *ibid.*, 4883, 4890, 4894 (1952); 2009 (1953).

(4) (a) R. J. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937); (b) F. Wetter and C. Dimroth, *Ber.*, **70B**, 1665 (1937); (c) I. M. Heilbron, T. Kennedy, F. S. Spring and G. Swain, *J. Chem. Soc.*, 869 (1938).

structure of the enol ether, 3-methoxy-3,5,7,22-ergostatetraene (III).[5] The rotations of chloroform solutions of this enol ether shifted progressively in the *dextro* direction when allowed to stand at room temperature, demonstrating an instability which has been noted previously in $\Delta^{3,5}$-3-enol ethers.[6] Addition of more acid to methanolic suspensions of the enol ether and continued heating converted it to 4,6,22-ergostatrien-3-one (isoergosterone, IV).[4b,4c] With sufficiently pure 4,7,22-ergostatrien-3-one, $[\alpha]_D - 10°$ ($CHCl_3$), the low conversions observed by Barton, Cox and Holness[7] for this reaction were not encountered in our experiments. The yields of 4,6,22-ergostatrien-3-one from 4,7,22-ergostatrien-3-one, without isolation of the enol ether intermediate, were 75–80%.



The catalytic reduction with hydrogen, in excess of one mole equivalent, of 4,6,22-ergostatrien-3-one in a non-selective system has been described by Barton, Cox and Holness.[7] Among the many products isolated by chromatography in that study was 4,22-ergostadien-3-one (V). Preliminary experiments on the catalytic hydrogenation of 4,6,22-ergostatrien-3-one indicated that the reactivity of the Δ^6-bond was not much greater than that of the Δ^4-bond of 4,22-ergostadien-3-one. However, the difficulty of separating the desired dienone V from the starting material and co-products required, for practical use, the formation of dienone in high conversion. Reductions of the trienone IV in the presence of palladium–carbon catalysts in a variety of solvents exhibited a fair degree of selectivity, and it was found that with these catalysts in alcoholic potassium or sodium hydroxide of proper concentration conversions of trienone to dienone were 80% or greater, permitting isolation of the dienone in yields of 70–75%. Optimum selectivity of the reduction system was found to be dependent on the reduction of the catalyst prior to addition of the steroid and on the concentration of alkali. Uniformly high conversions were observed in media 0.0010–0.010 *N* in potassium hydroxide; above and below this concentration range the yields of dienone were somewhat lower.

Preliminary kinetic studies of the reaction in this system indicate that the reductions of trienone to dienone and dienone to Δ^{22}-enone proceed stepwise, following heterogeneous reaction kinetics. Although reactions of added hydroxides with the catalyst are conceivable, it is currently believed that the increased selectivity observed in reduction in basic media is caused by base-catalyzed enolization of the various ketonic reactants involved, and that differences between the enolates in regard to rates of adsorption, reduction and desorption are greater than between the corresponding ketones.

Progesterone (VIII) was obtained from 4,22-ergostadien-3-one by a modification of the excellent method of Heyl and Herr[8] for the preparation of progesterone from stigmastadienone. Cleavage of the sidechain double bond of 4,22-ergostadien-3-one by ozonolysis proceeded surprisingly smoothly; the yields of 3-ketobisnor-4-cholenaldehyde (VI), identical with authentic samples, were greater than 90%. In the course of a study of the oxidation of the crude 22-(N-piperidyl)-bisnor-4,20(22)-choladien-3-one (VII), formed in 99% yield from the aldehyde, it was found that progesterone was obtained in improved yields (88%) by effecting the oxidation of the enamine in a sodium dichromate–benzene–acetic acid system.[9] Over-all, the yield of progesterone from ergosterol was 37%.

Acknowledgments.—The authors are indebted to Dr. J. L. Johnson and his staff for the determination and interpretation of absorption spectra,

(5) The m.p. of 3-methoxy-3,5,7,22-ergostatetraene was found to be 131–133°. Oppenauer[4a] has reported that 4,7,22-ergostatrien-3-one warmed with methanol occasionally formed an enol ether, m.p. 140–141°. We have recrystallized 4,7,22-ergostatrien-3-one from methanol many times and have never observed the formation of Oppenauer's compound.

(6) E. Schwenk, G. Fleischer and B. Whitman, THIS JOURNAL, **60**, 1702 (1938).

(7) D. H. R. Barton, J. D. Cox and N. J. Holness, *J. Chem. Soc.*, 1771 (1949).

(8) (a) F. W. Heyl and M. E. Herr, THIS JOURNAL, **72**, 2617 (1950); (b) M. E. Herr and F. W. Heyl, *ibid.*, **74**, 3627 (1952).

(9) L. F. Fieser, *ibid.*, **73**, 5007 (1951), has employed sodium dichromate–benzene–acetic acid to convert cholesterol to Δ^4-cholestene-3,6-dione.

to Mr. William A. Struck and his staff for microanalyses, and to Dr. E. R. Garrett for the interpretation of certain preliminary rate studies.

Experimental[10]

Ergosterol (I).—The physical constants and analyses of a typical lot of commercial ergosterol used in this study were: m.p. 150–154°, $[\alpha]_D$ −123° (*c* 2.053 in $CHCl_3$), ϵ_{282} 11,300 mol. wt. calcd. for monohydrate). *Anal.* Calcd. for $C_{28}H_{44}O \cdot H_2O$: C, 81.10; H, 11.18; H_2O, 4.3. Found: C, 81.54, 81.42; H, 11.24, 11.18; H_2O, 3.5 (drying 60°, 0.1 mm.), 4.9 (drying 80°, 0.1 mm.), 2.9–3.1 (azeotropic distillation, toluene). Calcd. for $C_{28}H_{44}O$: C, 84.78; H, 11.18. Found: C, 83.82; H, 11.49 (after drying, 60°, 0.1 mm.); C, 83.31; H, 10.76 (after drying, 80°, 0.1 mm.). Comparison of these data with those cited by Callow,[11] Bills and Honeywell,[12] Bills, Honeywell and Cox,[13] and Huber, Ewing and Kriger[14] for purified ergosterol indicated the material to be approximately 95% ergosterol monohydrate or 90% ergosterol.

4,7,22-Ergostatrien-3-one (Ergosterone (II)).—The oxidation of ergosterol to 4,7,22-ergostatrien-3-one was conducted according to a modification of the method of Oppenauer.[4a] A solution of 296 ml. (280 g., 2.85 moles) of redistilled cyclohexanone in 1.7 l. of A. R. toluene, in a 5-l., three-neck, round-bottom flask equipped with a stirrer, Dean–Stark moisture trap and reflux condenser, was boiled under reflux with stirring until no more water collected in the trap (approximately 1 hour). To the dry solution was then added 100 g. (0.252 mole) of ergosterol, $[\alpha]_D$ −123° ($CHCl_3$), and again boiling under reflux with stirring was continued until the distillate deposited no water. Three milliliters of water from the ergosterol was collected in approximately 1 hour. After the rapid addition of 27.2 g. (0.133 mole) of aluminum isopropoxide, the orange-red reaction solution was stirred and boiled under reflux for 15 minutes. The solution was cooled to 15–20° and was then poured into 1.0 l. of 2 *N* hydrochloric acid at 5° in a 6-l. separatory funnel. The mixture was agitated and separated, and the aqueous layer wasb ack-washed twice with 700-ml. and 300-ml. portions of ether. The toluene solution and ether solution were washed separately with cold water and cold 1% aqueous sodium bicarbonate and were then combined and steam distilled for 70 minutes. The residue was cooled in ice-water, and the major portion of the residual water was separated by decantation through a filter. After being heated to 60° at 25 mm. to remove moisture, the yellow-orange organic cake was dissolved in 845 ml. of boiling acetone. The solution was allowed to cool slowly to −5°. The crystalline precipitate of 4,7,22-ergostatrien-3-one, collected on a filter, washed with two 50-ml. portions of cold acetone, and dried at 45° and 20 mm. amounted to 71.7 g. (74% of the theoretical yield based on anhydrous starting material), m.p. 129–132°, $[\alpha]_D$ −10° (*c* 1.10 in $CHCl_3$), ϵ_{242} 14,800. The combined mother liquor and washings, concentrated to 200 ml. and cooled for 24 hours at −5°, yielded a second crop of 4,7,22-ergostatrien-3-one, which, after being recrystallized from acetone, then from 30% methanol in Skellysolve B, and dried, amounted to 2.78 g. (2.8% of the theoretical yield), m.p. 128–130°, $[\alpha]_D$ −9° ($CHCl_3$), ϵ_{242} 14,000.

4,6,22-Ergostatrien-3-one (Isoergosterone (IV)).—The method was a modification of that of Wetter and Dimroth.[4b] In a 12-l., three-neck, round-bottom flask, equipped with a stirrer, reflux condenser and dropping funnel, a mixture of 74.8 g. (0.188 mole) of 4,7,22-ergostatrien-3-one, $[\alpha]_D$ −10° ($CHCl_3$), and 4375 ml. of methanol was boiled under reflux with stirring until solution occurred. Heating was discontinued, and when boiling had ceased 1 ml. of concentrated hydrochloric acid was added. The solution turned orange-red, and a thick white precipitate of 3-methoxy-3,5,7,22-ergostatetraene, *vida infra*, was formed with the evolution of heat. Heat was applied again, 185 ml. of concentrated hydrochloric acid was added over a period of 25 minutes, and stirring and boiling under reflux were continued for an additional 1.5 hours at which point the precipitate had been completely dissolved for at least 45 minutes. Approximately one-fourth of the methanol was removed by distillation under reduced pressure, and the remaining solution was cooled to room temperature. To the stirred solution was added 184 g. of sodium bicarbonate. The precipitated sodium chloride and a trace of insoluble organic matter were removed by filtration and washed with 50 ml. of methanol. The combined filtrate and washing was concentrated by distillation under reduced pressure until a thick slurry (approximately 500 ml.) remained. The slurry was mixed with 2 l. of water and 900 ml. of Skellysolve B. The mixture was separated, the aqueous layer being back-washed with 200 ml. and 100 ml. of Skellysolve B. The combined Skellysolve B solutions were washed with 1 l. of cold water and dried over magnesium sulfate. After removal of the drying agent, the solution was concentrated by distillation to 200 ml., cooled with stirring to −5°, and refrigerated for 12 hours. The light yellow precipitate of 4,6,22-ergostatrien-3-one collected on a filter, washed with three 20-ml. portions of Skellysolve B, and dried for 1 hour at 50° and 20 mm., weighed 56.8 g. The mother liquors were concentrated to one-fourth of the original volume, seeded and cooled in the refrigerator for 1 day. From the precipitate was obtained, by recrystallization from methanol, 2.8 g. of 4,6,22-ergostatrien-3-one of satisfactory quality. The total yield of 4,6,22-ergostatrien-3-one, m.p. 105–108.5°, ϵ_{286} 25,600, $[\alpha]_D$ −23° (*c* 1.047 in $CHCl_3$), was 59.6 g. (80% of the theoretical). A more nearly pure sample of 4,6,22-ergostatrien-3-one had the following constants: m.m.p.(K) 107–109°, $[\alpha]_D$ −25° (*c* 1.126 in $CHCl_3$), ϵ_{286} 26,900. *Anal.* Calcd. for $C_{28}H_{42}O$: C, 85.22; H, 10.73. Found: C, 85.05, 85.16; H, 10.56, 10.64. Heilbron, Kennedy, Spring and Swain[4c] have reported the following physical constants for 4,6,22-ergostatrien-3-one, m.p. 108°, $[\alpha]_D$ −30° ($CHCl_3$), λ_{max} 280, log ϵ 4.52, λ_{max} 335.

3-Methoxy-3,5,7-22-ergostatetraene (III).—In the course of one preparation of 4,6,22-ergostatrien-3-one, a sample of the initial transient precipitate was isolated. Recrystallized from petroleum ether the material was a white crystalline solid, m.m.p.(K) 129.5–130.5°, ϵ_{321} 16,000; infrared spectrum: strong conjugated carbon–carbon double bond (1643, 1620 and 1571 cm.$^{-1}$, indicative of the $\Delta^{3,5,7}$-system), weak isolated carbon–carbon double bond (972 cm.$^{-1}$), ether carbon–oxygen bond (1168 cm.$^{-1}$), no hydroxyl, no carbonyl. *Anal.* Calcd. for $C_{28}H_{41}OCH_3$: C, 85.23; H, 10.85; OCH_3, 7.59. Found: C, 85.13, 84.94; H, 10.87, 10.63; OCH_3, 6.92, 6.34. The $[\alpha]_D$ of the material in $CHCl_3$ (*c* 0.620) changed from an initial value of −51° to +33° after the solution had been at room temperature for 1.5 hours.

In another experiment, 3 ml. of concentrated hydrochloric acid was added to a solution of 1.00 g. (2.54 millimoles) of 4,7,22-ergostatrien-3-one in 70 ml. of boiling methanol. The solution was allowed to stand for 1 minute and was then cooled quickly. The crude crystalline precipitate, m.m.p.(K) 126–131°, was collected and reprecipitated with methanol from a chloroform solution at room temperature. The purified product, m.m.p.(K) 131–133°, $[\alpha]_D$ −99° initially, −0.8° and still changing after 1 hour at room temperature in solution (*c* 0.730 in $CHCl_3$), ϵ_{321} 17,800, infrared spectrum identical to that of the above described material, [*Anal.* Found: C, 85.48, 85.20; H, 11.03, 11.06] amounted to 0.57 g. (55% of the theoretical yield). A second crop of crystals, m.m.p.(K) 131–133°, 0.05 g. (4.8%), was isolated from the mother liquor.

4,22-Ergostadien-3-one (V).—A 2.5-gal. cylindrical bottle was fitted with a clamped rubber stopper carrying a gas-tight stirrer, a glass hydrogen inlet tube ending above the operating liquid level and connected to a mercury manometer, a glass sample solution inlet tube, and a capillary tube for periodic sampling.

To a solution of 1.4 g. of potassium hydroxide (Reagent

(10) Melting points: m.p.'s are recorded as observed on a Fisher–Johns block which had been checked against standard compounds; m.m.p.(K)'s are m.p.'s observed between crossed polaroids on a Kofler micro hot-stage checked against standard compounds. Molecular extinctions (ϵ) were determined with a Cary recording spectrophotometer on solutionsin 95% ethanol unless otherwise specified. Infrared spectra were determined with a Perkin–Elmer model 12C spectrophotometer equipped with NaCl prisms on mulls of the compounds in liquid petrolatum; $[\alpha]_D$'s were determined at temperatures of 22–26°.

(11) R. K. Callow, *Biochem. J.*, **25**, 79, 87 (1931).

(12) C. E. Bills and E. M. Honeywell, *J. Biol. Chem.*, **80**, 15 (1928).

(13) C. E. Bills, E. M. Honeywell and W. M. Cox, *ibid.*, **80**, 557 (1928).

(14) W. Huber, G. W. Ewing, and J. Kriger, THIS JOURNAL, **67**, 609 (1945).

Grade, 85%) in 2.0 l. of anhydrous methanol in the reaction bottle was added a slurry of 2.0 g. of 5% palladium–carbon catalyst in 400 ml. of methanol, rinsed in with 400 ml. of methanol. The bottle was stoppered, and the system was flushed three times with hydrogen. With vigorous stirring and hydrogen at approximately 11 inches (gage) the catalyst was completely reduced to constant hydrogen pressure. The bottle was then evacuated to a pressure slightly lower than atmospheric, and a warm solution of 25.0 g. (0.0635 mole) of 4,6,22-ergostatrien-3-one, m.m.p.-(K) 105–108.5°, in 600 ml. of methanol was drawn into the bottle through the sample inlet tube, with a rinse of 350 ml. of methanol. Then, with hydrogen at 11 inches (gage) and vigorous stirring, the trienone was reduced until 1.0–1.1 mole equivalents of hydrogen had reacted. The reaction suspension was then quickly withdrawn and filtered, the separated catalyst being washed with methanol. The filtrate and washings, acidified with 2 ml. of glacial acetic acid, was distilled under reduced pressure to remove solvent. The solid residue, containing 85% of 4,22-ergostadien-3-one and only a very small amount of trienone, was dissolved in 155 ml. of ethyl acetate, and the solution was filtered to remove potassium acetate. The 4,22-ergostadien-3-one which crystallized from the filtrate was recrystallized twice from 30 ml. of ethyl acetate. The yield of 4,22-ergostadien-3-one, m.m.p.(K) 128–132°, ϵ_{242} 16,400, was 17.5 g. or 70% of the theoretical.

The properties determined for the dienone isolated in the above-illustrated procedure agreed well with those of a previously-purified sample which were: m.m.p.(K) 127–131°, $[\alpha]_D$ +43° (*c* 1.336 in $CHCl_3$), ϵ_{242} 16,600 (with no maximum at λ 286), infrared spectrum: –OH absent, conjugated ketone (1668 cm.$^{-1}$) and sidechain double-bond (967 cm.$^{-1}$) present. *Anal.* Calcd. for $C_{28}H_{44}O$: C, 84.79; H, 11.17. Found: C, 85.04, 85.33; H, 11.04, 11.20. These constants are in general agreement with those given by Barton[7] for 4,22-ergostadien-3-one: m.p. 127.5–128.5°, $[\alpha]_D$ +43° ($CHCl_3$), ϵ_{242} 18,200.

3-Ketobisnor-4-cholenaldehyde (VI).—4,22-Ergostadien-3-one was ozonized according to a modification of the procedure of Heyl and Herr.[8a] A solution of 21.0 g. (0.053 mole) of 4,22-ergostadien-3-one, m.p. 128–133°, in 950 ml. of methylene chloride and 6 ml. of pyridine in a tubular reactor equipped with a magnetic stirrer was cooled in a Dry Ice–acetone-bath. A stream of ozone-rich oxygen (0.43 millimole of ozone per minute) was passed into the stirred, cold solution through a sintered-glass sparger. After 5 minutes the cloudy solution developed a deep orange color which changed to red-brown as the reaction progressed. The cloudiness disappeared at about 90 minutes, and after 148 minutes (1.2 mole equivalents of ozone) the red-brown color began to fade rapidly, signaling completion of the reaction. After 163 minutes (1.32 mole equivalents of ozone) the color was nearly gone, and the ozonization was stopped. To a well-stirred suspension of 25.0 g. of zinc dust in this pale yellow reaction solution was added 111 ml. of glacial acetic acid, and stirring was continued for 1 hour at 0–10° and, finally, for 5 minutes at 35°. The bright yellow solution was removed from the zinc by filtration and was washed with two 500-ml. portions of water. It was then cooled by the addition of ice and washed with 75 ml. and 50 ml. of cold 10% sodium carbonate, 50 ml. of cold 10% sodium hydroxide, and four 300-ml. portions of cold water, all aqueous washes being back-washed with 75 ml. of methylene chloride. The fine white precipitates of sodium 3-ketobisnor-4-cholenate which formed at the interfaces during the extractions were separated with the aqueous phases and discarded. The combined methylene chloride solutions were dried over sodium sulfate in the refrigerator. The dry solution, separated from the drying agent and diluted with 100 ml. of isopropyl alcohol, was concentrated at 40° by distillation under reduced pressure to a volume of 125 ml. The crystalline precipitate was redissolved by warming, and the solution was seeded and refrigerated. The precipitate of 3-ketobisnor-4-cholenaldehyde, long white needles, collected, washed, and dried at 30 mm. over sulfuric acid at room temperature, amounted to 14.57 g. (83.8%), m.p. 154–156°, $[\alpha]_D$ +84° (*c* 1.930 in $CHCl_3$), ϵ_{242} 16,300, 0% bisnor acid. A second crop, 1.52 g. (8.7%), m.p. 152–154°, $[\alpha]_D$ +80° (*c* 1.753 in $CHCl_3$), <0.5% bisnor acid, was obtained by concentrating and cooling the mother liquors. The infrared spectrum of the ketoaldehyde prepared from 4,22-ergostadien-3-one was identical with that of an authentic sample of 3-ketobisnor-4-cholenaldehyde prepared from stigmastadienone, and their m.p.'s were not depressed by admixture.

22-(N-Piperidyl)-bisnor-4,20(22)-choladien-3-one (VII).—22-(N-Piperidyl)-bisnor-4,20(22)-choladien-3-one was prepared from 3-ketobisnor-4-cholenaldehyde by the method of Herr and Heyl[8b] modified to include the use of 1.00 g. of *p*-toluenesulfonic acid monohydrate per mole of steroid as an acid catalyst to increase the rate of condensation. From 32.8 g. of 3-ketobisnor-4-cholenaldehyde, m.p. 147–152°, $[\alpha]_D$ +83° (*c* 1.595 in $CHCl_3$), was obtained 39.3 g. (99%) of crude "enamine," m.p. 118–128°, $[\alpha]_D$ +86° (*c* 1.350 in $CHCl_3$), $\epsilon_{241}^{CH_3OH}$ 20,700. *Anal.* Calcd. for $C_{27}H_{41}NO$: C, 81.97; H, 10.45; N, 3.54. Found: C, 81.88; H, 10.52; N, 3.37.

Progesterone (VIII).—The oxidizing reagent was prepared by dissolving 35.8 g. (0.12 mole) of sodium dichromate dihydrate in 180 ml. of glacial acetic acid in a 2-l. flask equipped with an efficient stirrer and an addition tube. When solution of the dichromate salt was complete, 120 ml. of thiophene-free benzene was added, and the resulting solution was cooled to 0–5° by means of an ice–salt-bath. A solution of 23.8 g. (0.06 mole) of the "enamine" in 180 ml. of benzene was added over a period of 1 hour, keeping the temperature below 5°. Stirring of the dark reaction mixture was continued for an additional 2 hours. At this point 60 ml. of methanol was added, and after stirring for 30 minutes the cooling bath was removed, and the reaction mixture was diluted with 720 ml. of water. The layers were separated; the dark brown aqueous phase was extracted once with 300 ml. of benzene. The extract and the original benzene solution were combined, and the resulting benzene solution was washed successively with 100 ml. of water, two 100-ml. portions of cold 10% sodium hydroxide solution, 100 ml. of water, 100 ml. of 10% hydrochloric acid solution, and four 100-ml. portions of water. The colorless benzene solution was concentrated to dryness under reduced pressure, leaving 18.2 g. (96.5%) of crude progesterone, m.p. 125–127° (s. 123°), $[\alpha]_D$ +173° (*c* 1.830 in dioxane), ϵ_{241} 16,600.

The crude progesterone was dissolved in 20 ml. of boiling methylene chloride. The solution was diluted with 80 ml. of cyclohexane, and the solution was concentrated by slow distillation to approximately 60 ml. While stirring rapidly the hot solution was seeded with progesterone (m.p. 128–130°) and was allowed to cool from 81–82° to room temperature over a period of 6–8 hours. The yield of recrystallized progesterone was 15.7 g. (83%), m.p. 126–129°, $[\alpha]_D$ +175° (*c* 1.932 in dioxane). Concentration of the liquors yielded an additional 1.0 g. (5.4%) of progesterone, m.p. 125–128°, $[\alpha]_D$ +174° (*c* 1.361 in dioxane). Thus, the total yield of progesterone was 16.7 g. (88%). Progesterone is polymorphic: "α-progesterone," m.p. 128–129°; "β-progesterone," m.p. 121°.[15]

Isolation of the enamine in the above transformations is not obligatory. The benzene solution of enamine at a suitable concentration may be treated directly with the sodium dichromate–acetic acid–benzene solution. In a typical experiment 19.7 g. (0.06 mole) of 3-ketobisnor-4-cholenaldehyde yielded 16.0 g. (84.6%) of progesterone, m.p. 124–127°, $[\alpha]_D$ +174° (*c* 1.884 in dioxane), ϵ_{241} 16,300 in the first crop. An additional 0.8 g. (4.2%) of progesterone, m.p. 117–125°, $[\alpha]_D$ +171° (*c* 1.264 in dioxane), was isolated from the mother liquors.

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(15) A. Butenandt and J. Schmidt, *Ber.*, **67**, 2088 (1934); E. Fernholz, *ibid.*, **67**, 2027 (1934).