[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

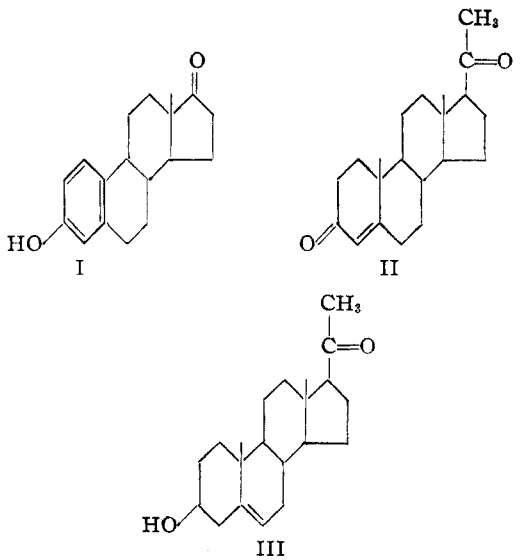
Steroids. XII.[1] Aromatization Experiments in the Progesterone Series[2]

BY CARL DJERASSI, G. ROSENKRANZ, J. IRIARTE, J. BERLIN AND J. ROMO

1,4,16-Pregnatriene-3,20-dione (VI), prepared[5] from allopregnane-3,20-dione (IV), has been converted by mineral oil vapor phase aromatization into 3-hydroxy-17-acetyl-1,3,5,16-estratetraene (VII). Some reactions of this unsaturated ketone are discussed including its transformation into the aromatic analogs (IX and XI) of the corpus luteum hormone, progesterone (II), and the adrenal hormone, 17α-hydroxyprogesterone. Progesterone (II) or 16-dehydroprogesterone (XV) on tri- or di-bromination, respectively, followed by collidine dehydrobromination lead to the same 1,4,6,16-pregnatetraene-3,20-dione (XIV), which undergoes the dienone–phenol rearrangement and on hydrogenation of the rearrangement product yields an aromatic analog (XVII) of progesterone bearing a methyl group at C-1.

The therapeutic effectiveness of Cortisone and other pregnane derivatives in a variety of diseases has greatly stimulated research on the *total* synthesis of such steroids. As one aspect of this problem, it was felt that the partial synthesis of aromatic analogs of steroid hormones might yield useful results, since the number of possible diastereoisomers would be materially reduced by aromatization of ring A and/or ring B thus simplifying eventual total synthesis if such an approach were warranted by the biological properties of such substances.

The present report deals with the partial synthesis of some aromatic analogs of the progesterone series starting with pregnane derivatives which are available in potentially unlimited amounts from steroidal sapogenins. It should be recalled that *both* female sex hormones, the follicular hormone estrone (I) and the corpus luteum hormone progesterone (II) are indispensable for the maintenance of the normal menstrual cycle of the female. Estrone (I) is characterized by an aromatic ring A and a 17-keto group, while progesterone (II) closely resembles the cortical hormones with its α,β-unsaturated keto function in ring A and an acetyl group at C-17. It appeared attractive to combine these structural features in one substance (IX) and to determine its physiological potentialities. Aside from its intrinsic interest, such an undertaking became particularly important in view of the report[3] that Δ^5-pregnen-3β-ol-20-one (III), a steroid with a hydroxyl group in ring A and an acetyl group at C-17, was effective in alleviating the symptoms of rheumatoid arthritis. Recently, Velluz and Muller[4] reported the synthesis of this aromatic analog (IX) in about 15% yield from estrone (I) by a method which in our hands proved unsatisfactory for large scale work. No biological properties were given.



A number of very readily available sapogenins, notably tigogenin and diosgenin can be converted in good yield in three to four steps to allopregnane-3,20-dione (IV), a substance which may be classed among the most available steroids at the present time. Rubin and co-workers[5] were able to show that tribromination of allopregnane-3,20-dione (IV) leads in high yield to a 2,4,17-tribromo derivative (V), which on short boiling with collidine affords 1,4,16-pregnatriene-3,20-dione (VI). Repetition of this work in our laboratory indicated that these steps were quite amenable to large scale operations and a substantial amount of the triene VI was prepared.

Aromatization of this triene (VI) in mineral oil solution[6,7] at 600° led in about 30% yield to an alkali-insoluble product, $C_{20}H_{24}O_2$, m.p. 247–248°, which exhibited ultraviolet absorption maxima at 230 mμ (log E 4.20) and 280 mμ (log E 3.47) and a minimum at 266 mμ (log E 3.29) (Fig. 1). Phenols in general exhibit a maximum at 280 mμ and a minimum at 250 mμ with high absorption around 220 mμ, but it is clear that super-imposition of a strong maximum at 240 mμ (Δ^{16}-20-keto grouping of VII) would result in a spectrum as observed. This is the second phenol[8] of the steroid series to be found insoluble in aqueous alkali, but the structure of the product was proved unequivocally as follows: the substance formed an acetate, m.p. 162–163°, whose infrared spectrum[9] showed bands at 1204 and 1766 cm.$^{-1}$ (phenolic acetate) and 1670 cm.$^{-1}$

(1) Paper XI, Djerassi, Yashin and Rosenkranz, THIS JOURNAL, **72**, 5750 (1950).

(2) Presented in part on the program of the Division of Medicinal Chemistry at the Chicago Meeting of the American Chemical Society, September 6, 1950.

(3) Freeman, Pincus, Johnson, Bachrach, McCabe and MacGilipin, *J. Am. Med. Assoc.*, **142**, 1124 (1950).

(4) Velluz and Muller, *Compt. rend.*, **226**, 411 (1948); details reported in *Bull. soc. chim. France*, 166 (1950).

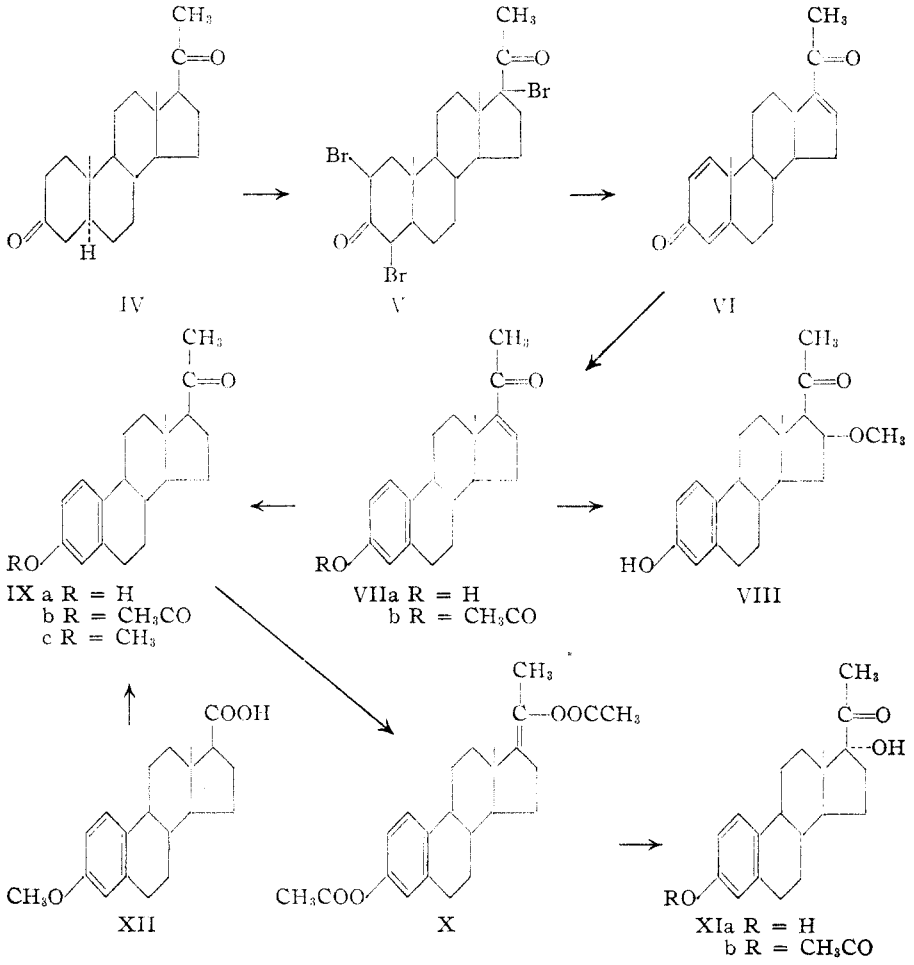
(5) Rubin, Wishinsky and Bompard, THIS JOURNAL, **73**, May (1951). We are grateful to Dr. Rubin for informing us of these results prior to publication.

(6) Hershberg, Rubin and Schwenk, *J. Org. Chem.*, **15**, 292 (1950).

(7) Rosenkranz, Djerassi, Kaufmann, Pataki and Romo, *Nature*, **165**, 814 (1950); Djerassi, Rosenkranz, Romo, Kaufmann and Pataki, THIS JOURNAL, **72**, 4534 (1950).

(8) Djerassi and Scholz, *ibid.*, **71**, 3962 (1949).

(9) Dr. K. Dobriner and Mrs. P. Humphries, Sloan-Kettering Institute for Cancer Research, kindly measured the infrared spectra.



(typical of Δ^{16}-20-ketones) and no hydroxyl bands, while the free phenol exhibited the 1670 cm.$^{-1}$ band plus the hydroxyl band. The product formed an oxime and a semicarbazone, thus confirming the presence of the 20-keto group and the semicarbazone exhibited an ultraviolet absorption maximum at 266 mμ (log E 4.46 in chloroform), typical of semicarbazones of α,β-unsaturated ketones. We felt it important to prove rigorously the structure of this product, since on alkaline saponification (potassium hydroxide in methanol) the acetate VIIb yielded a product $C_{21}H_{28}O_3$, which could *not* be reacetylated to the starting material and exhibited a single ultraviolet absorption maximum at 280 mμ and a minimum at 248 mμ (Fig. 1); its infrared spectrum[9] showed a band at 1700 cm.$^{-1}$, typical of an *unconjugated* 20-ketone group. *It is thus clear that alkaline saponification in some manner affected the α,β-unsaturated Δ^{16}-20-keto system.* While this work was in progress, Marker[10] reported that alkaline saponification of a Δ^{16}-20-ketone derived from hecogenin results in direct introduction of a 17α-hydroxyl group, a result which would have been of considerable significance for the synthesis of cortical hormones. We were able to show that this was not the case in our analogous example, because the saponification product (after reacetylation) showed no free hydroxyl band in the infrared[9] and was clearly different from an authentic specimen of the 17-hydroxy-17-acetyl derivative (XI) prepared as shown below. In agreement with Fukushima and Gallagher,[11] who repeated Marker's work,[10] it was then found that the saponification product contained a methoxyl group (Zeisel determination) and hence is best formulated as 3-hydroxy-16-methoxy-17-acetyl-1,3,5-estratriene (VIII). Saponification of the acetate VIIb could be accomplished satisfactorily with bicarbonate in dilute methanol solution.

Hydrogenation of the unsaturated phenol VIIa in ethyl acetate solution with 5% palladium-on-charcoal catalyst smoothly yielded the desired 3-hydroxy-17-acetyl-1,3,5-estratriene (IXa), further characterized by the preparation of an acetate (IXb) and a methyl ether (IXc); the ultraviolet absorption spectrum (maximum at 280 and minimum at 250 mμ) (Fig. 1) and the infrared spectrum were fully compatible with the assigned structure IX. Direct comparison (mixed melting point and infrared spectrum) with a sample of IXa prepared from estrone[4,12] proved the identity of the two products. Finally, treatment of the acid chloride of 3-methoxy-1,3,5-estratriene-17-carboxylic acid (XII)[8] with dimethylcadmium yielded the methyl ether IXc, identical with a specimen prepared from the phenol IXa by means of dimethyl sulfate. Since the acid XII has been obtained from cholesterol[8] as well as from strophanthidin,[13] 3-hydroxy-17-acetyl-1,3,5-estratriene (IX) has now been correlated[4,8,13] with the estrogens, sterols, heart poisons and steroidal sapogenins.

3-Hydroxy-17-acetyl-1,3,5-estratriene (IXa) on slow distillation with acetic anhydride in the presence of *p*-toluenesulfonic acid[14] led to the enol acetate X, which on treatment with perbenzoic acid[15]

(10) Marker, THIS JOURNAL, **71**, 4149 (1949).

(11) Fukushima and Gallagher, *ibid.*, **73**, 196 (1951); we are indebted to Dr. Gallagher for informing us of his results prior to publication. For a similar case see Ruzicka, Hardegger and Kauter, *Helv. Chim. Acta*, **27**, 1165 (1944).

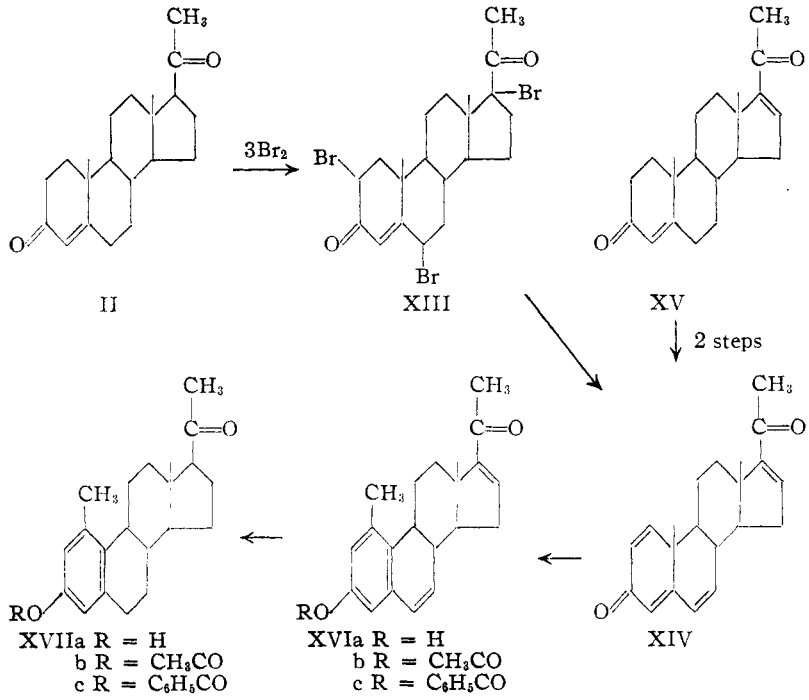
(12) We are greatly indebted to Prof. L. Velluz, Paris, for sending us a sample of his 3-hydroxy-17-acetyl-1,3,5-estratriene (IXa) prepared from estrone (I).

(13) Ehrenstein, Johnson, Olmsted, Vivian and Wagner, *J. Org. Chem.*, **15**, 264 (1950).

(14) Marshall, Kritchevsky, Liebermann and Gallagher, THIS JOURNAL, **70**, 1837 (1948).

(15) Kritchevsky and Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

(but not monoperphthalic acid[16]) followed by short saponification gave in good yield 3,17α-dihydroxy-17-acetyl-1,3,5-estratriene (XIa), an aromatic analog of the adrenal hormone 17α-hydroxyprogesterone. As was to be expected, the substance (XIa) showed a simple phenolic spectrum (maximum at 280 mμ and minimum at 248 mμ) and the infrared spectrum[9] of its acetate (XIb) indicated the presence of a free hydroxyl group (tertiary hydroxyl groups at C-17 are not acetylated under those conditions). Velluz and Muller[4] by hydration of 17-ethynylestradiol prepared the isomeric 17β-hydroxy derivative, which possesses the opposite configuration at C-17 from that of the natural 17-hydroxylated adrenal hormones (Cortisone, 17α-hydroxyprogesterone, etc.). Preliminary tests[17] indicated that the two aromatic progesterone analogs VIIa and IXa are inactive as estrogens when administered in one-hundred times the threshold dose of estrone (rats) and exhibited no progestational activity when injected into rabbits in five times the effective dose of progesterone. In concordance with earlier results[1,18] an α,β-unsaturated keto moiety in ring A appears to be essential for progestational activity. All three aromatic analogs (VII, IX and XI) are being subjected to a variety of biological tests, the results of which will be published elsewhere.



An alternate approach to aromatic progesterone analogs involves the bromination of Δ^4-3-ketosteroids which has recently been employed successfully[7] for the conversion of the androgens to the estrogens. *Tri*bromination of progesterone (II) in ether–acetic acid solution at low temperature afforded a tribromo derivative to which is assigned the structure of a 2,6,17-tribromo compound (XIII), since on collidine treatment it lost three moles of hydrogen bromide leading to 1,4,6,16-pregnatetraene-3,20-dione (XIV), identical with a specimen obtained by *di*bromination of 16-dehydroprogesterone (XV) followed by collidine dehydrobromination. This tetraene (XIV) thus contains the 1,4,6-trien-3-one structure which is required for aromatization of ring A with migration of the angular methyl group (dienone–phenol rearrangement). It has been shown previously[19] that the true 1-methylphenols of the steroid series can be obtained only by rearrangement of 1,4,6-trien-3-

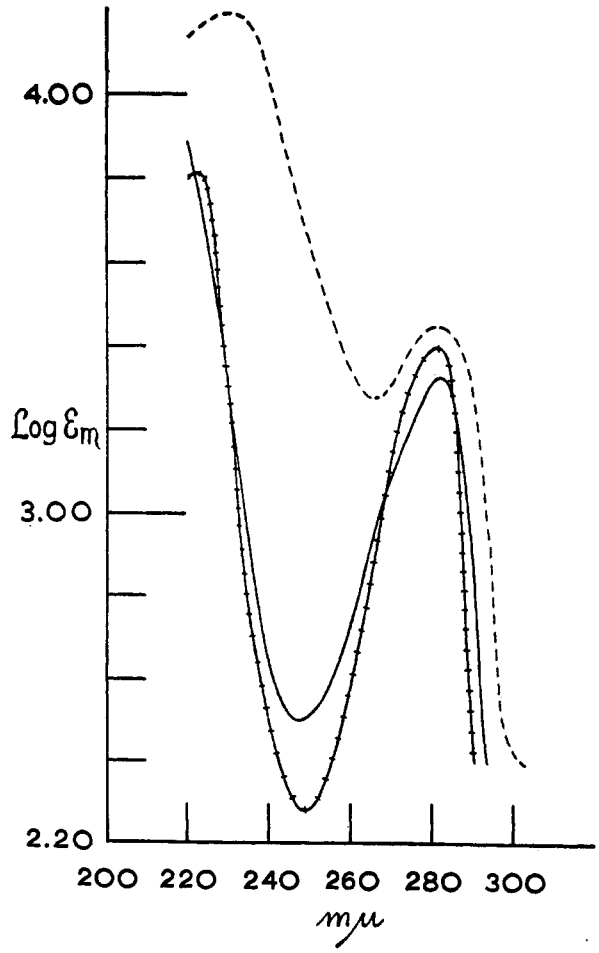


Fig. 1.—Ultraviolet absorption spectra (in 95% ethanol): – – – – –, 3-hydroxy-17-acetyl-1,3,5,16-estratetraene (VIIa); + + + +, 3-hydroxy-17-acetyl-1,3,5-estratriene (IXa); ————, 3-hydroxy-16-methoxy-17-acetyl-1,3,5-estratriene (VIII).

(16) Monoperphthalic acid generally works well with analogous pregnane derivatives (*cf.* Rosenkranz, Pataki, Kaufmann, Berlin and Djerassi, THIS JOURNAL, **72**, 4081 (1950)) and the lack of reaction in the present instance is a further example (*cf.* ref. 8) of the unexpected effect of an aromatic ring A upon a substituent at C-17.

(17) Kindly carried out by Dr. Elva G. Shipley of the Endocrine Laboratories, Madison, Wisconsin.

(18) Ehrenstein, *Chem. Revs.*, **42**, 457 (1948).

(19) Djerassi, Rosenkranz, Romo, Pataki and Kaufmann, THIS JOURNAL, **72**, 4540 (1950).

ones and not from 1,4-dien-3-ones (*e.g.*, VI) which lead to abnormal products.

Warming of the tetraene-3,20-dione XIV in acetic anhydride with *p*-toluenesulfonic acid for four hours resulted in smooth aromatization to 1-methyl-3-acetoxy-17-acetyl-1,3,5,6,16-estrapentaene (XVIb), characterized also by its benzoate (XVIc) and free phenol (XVIa). These compounds showed the typical negative rotation of 6-dehydrophenols of the steroid series observed previously[7,19] and on hydrogenation in ethyl acetate solution with palladium-on-charcoal catalyst were converted into the corresponding 1-methyl-3-hydroxy-17-acetyl-1,3,5-estratriene derivatives (XVII). The hydrogenation of the 6,7-double bond was accompanied by a large dextrorotatory change fully consistent with the earlier observations[7,19] on the reduction of steroidal 6-dehydrophenols. It is thus possible to convert progesterone in four steps into its ring A-aromatic analog possessing a 1-methyl group.

Experimental[20]

3-Hydroxy-17-acetyl-1,3,5,16-estratetraene (VIIa).—A solution of 80 g. of 1,4,16-pregnatriene-3,20-dione (VI)[5] (m.p. 210–211°, $[\alpha]^{20}D$ +118°) in 6 l. of mineral oil was dropped at a rate of 2 cc./sec. through a glass tube (32 × 3.0 cm.) filled with Pyrex helices and heated to 600°. After cooling for several days, the precipitate was collected, washed with hexane and recrystallized from acetone. The yield of material with m.p. 238–242° ranged from 22–30%. Approximately 10% of unreacted triene-dione VI could be recovered from the mother liquors on chromatography and recrystallization from ethyl acetate. The analytical sample of VIIa had a faintly yellowish tinge after recrystallization from acetone, which could not be removed on high vacuum sublimation; m.p. 247–248°, $[\alpha]^{20}D$ +118°, 145° (ethanol), ultraviolet maxima (Fig. 1) at 230 mμ (log *E* 4.20) and 280 mμ (log *E* 3.47) and minimum at 266 mμ (log *E* 3.29).

Anal. Calcd. for $C_{20}H_{24}O_2$; C, 81.04; H, 8.16. Found: C, 81.43; H, 8.25.

The oxime, prepared in ethanol–pyridine with hydroxylamine hydrochloride, crystallized from dilute methanol as colorless needles with m.p. 142–144°, resolidifying at *ca.* 156° and melting again at 176–180°.

Anal. Calcd. for $C_{20}H_{26}O_2N$: C, 76.88; H, 8.39. Found: C, 76.81; H, 8.02.

The semicarbazone was prepared by the sodium acetate method and after recrystallization from acetone–hexane melted at 251–253°, ultraviolet maximum at 266 mμ, log *E* 4.46 (chloroform).

Anal. Calcd. for $C_{21}H_{27}O_2N_3$: C, 71.36; H, 7.70. Found: C, 70.89; H, 8.05.

The acetate VIIb had m.p. 161–162°, $[\alpha]^{20}D$ +110°, when crystallized from hexane–acetone and was sublimed before analysis. The infrared spectrum[9] in carbon disulfide solution exhibited bands at 1204 and 1766 cm.$^{-1}$ (phenolic acetate), 1670 cm.$^{-1}$ (Δ^{16}-20-ketone), but no free hydroxyl bands.

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.75. Found: C, 78.31; H, 7.65.

Saponification of 3-Acetoxy-17-acetyl-1,3,5,16-estratetraene (VIIb).—Refluxing of the above acetate (100 mg.) with 10 cc. of methanol, 4 cc. of water and 200 mg. of potassium bicarbonate for one hour gave a nearly quantitative yield of the phenol VIIa. Substitution of 1 cc. of 20% sulfuric acid for the bicarbonate lowered the yield of phenol to *ca.* 50%.

When the saponification was carried out with boiling 5% methanolic potassium hydroxide solution, there was obtained a mixture with m.p. 183–190°. Repeated recrystallization from acetone–hexane, followed by high vacuum sublimation gave colorless crystals (30%) with m.p. 203–204°, $[\alpha]^{20}D$ +101°, ultraviolet maximum (Fig. 1) at 280 mμ (log *E* 3.33) and minimum at 248 mμ (log *E* 2.51). The ultraviolet absorption spectrum (no maximum at 230 mμ and hypsochromic shift of minimum) indicated the loss of the α,β-unsaturated ketone function, which was substantiated by its infrared spectrum[9] since a band at 1700 cm.$^{-1}$ (saturated 20-ketosteroid) was observed. The infrared spectrum after acetylation indicated the absence of a free hydroxyl group, thus excluding a 17-α-hydroxy-20-keto moiety. Insufficient material was available for a repetition of the methoxyl analysis (carried out on 4.0 mg.), but the above evidence clearly indicates the presence of 3-hydroxy-16-methoxy-17-acetyl-1,3,5-estratriene (VIII).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; methoxyl, 13.11. Found: C, 76.99; H, 8.64; methoxyl, 9.44.

3-Hydroxy-17-acetyl-1,3,5-estratriene (IXa).—A solution of 3.47 g. of the tetraene (once recrystallized) in 160 cc. of ethyl acetate was shaken in an atmosphere of hydrogen with 0.5 g. of 5% palladium-on-charcoal catalyst (American Platinum Works, Newark, N. J.) until the gas up-take stopped. Filtration and concentration afforded 81–89% (four experiments) of colorless crystals with m.p. 243–245°. Further recrystallization from ethyl acetate raised the m.p. to 247–249°, $[\alpha]^{20}D$ +159°, ultraviolet maxima (Fig. 1) at 280 mμ (log *E* 3.40) and 222 mμ (log *E* 3.82), and minimum at 248 mμ (log *E* 2.27); reported,[4] m.p. 254° (Maquenne block), $[\alpha]^{20}D$ +151°. In our hands, Prof. Velluz's sample[4,12] melted at 243–245°, but a mixed melting point gave no depression and the infrared spectra (after acetylation) of the two specimens were identical.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.61; H, 8.65.

The acetate IXb showed m.p. 107–109°, $[\alpha]^{20}D$ +126.5° after recrystallization from acetone–hexane; lit.,[4] 108° (no analysis given).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.62; H, 8.17.

3-Methoxy-17-acetyl-1,3,5-estratriene (IXc) (a) from 3-Hydroxy-17-acetyl-1,3,5-estratriene (IXa).—A boiling solution of 2.5 g. of the phenol IXa in 180 cc. of ethanol was treated four times alternately with 7 cc. of 50% potassium hydroxide solution and 7 cc. of dimethyl sulfate. After ten minutes, the mixture was cooled, diluted with water and the product collected. Recrystallization from hexane containing a small amount of acetone gave colorless prismatic needles with m.p. 134–136°, $[\alpha]^{20}D$ +160°.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.93; H, 9.25.

(b) From 3-Methoxy-1,3,5-estratriene-17-carboxylic Acid (XII).[21]—The acid chloride obtained from 0.3 g. of acid XII[8] (with thionyl chloride) in benzene was added to the cadmium Grignard solution[22] prepared from 0.12 g. of magnesium turnings, 0.5 cc. of methyl iodide, 0.68 g. of cadmium bromide and 20 cc. of ether. After stirring at room temperature for one-half hour and refluxing for two hours, acid was added and the organic layer was separated, washed, dried and evaporated. Recrystallization from hexane gave the methyl ether IXc in 27% yield, m.p. 134–136°, $[\alpha]^{20}D$ +163°; no depression in melting point was observed on admixture with a specimen prepared according to A. The optimum conditions for the Grignard reaction were not determined, since method A is obviously far superior, especially as far as availability of starting materials is concerned.

Enol Acetate of 3-Acetoxy-17-acetyl-1,3,5-estratriene (X).—A mixture of 4.0 g. of 3-hydroxy-17-acetyl-1,3,5-estratriene, 1.7 g. of *p*-toluenesulfonic acid and 250 cc. of acetic anhydride was concentrated to *ca.* 25–30 cc. by slow distillation over a period of five hours. After addition of 0.5 cc. of pyridine and 100 cc. of ether, the solution was

(20) All melting points are corrected and were determined on the Kofler block. Unless noted otherwise, rotations were carried out in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are indebted to the Srtas. Paquita Revaque and Maria Eugenia Frontana for these measurements, and to Srta. Amparo Barba of our Microanalytical Department and Mr. Joseph F. Alicino, Metuchen N. J., for the analyses. Srta. Josefina Gatica and Sr. Hector Martinez assisted with certain phases of the experimental work.

(21) This experiment was carried out for the first time by one of us (C. D.) in the Ciba Research Laboratories.

(22) Cason, *Chem. Revs.*, **40**, 15 (1947).

filtered and washed five times with ice-cold 1% sodium hydroxide solution and water, dried and concentrated. The crystals, thus obtained (3.76 g.), were combined with a second crop isolated from the mother liquors by chromatography and recrystallized once from ether–hexane; yield 4.14 g. (78%), m.p. 154–158°, $[\alpha]^{20}D$ +42°. The melting point range was not narrowed by further recrystallization.

Anal. Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.65; H, 8.10.

3,17α-Dihydroxy-17-acetyl-1,3,5-estratriene (XIa).—A solution of 4.13 g. of the above enol acetate in 100 cc. of chloroform was allowed to stand at room temperature for two days with 40 cc. of a chloroform solution of perbenzoic acid (0.066 g./cc.) and then washed successively with aqueous solutions of sodium iodide, sodium thiosulfate, sodium carbonate and finally water. The residue obtained on evaporation of the solvent was refluxed for 15 minutes with 1.7 g. of potassium hydroxide, 12 cc. of water and 340 cc. of methanol. Neutralization with acetic acid followed by concentration gave three crops of crystals of nearly equal purity totalling 2.72 g. (80%) with m.p. 234–240°. Recrystallization from ethyl acetate afforded the analytical sample with m.p. 240–242° (inserted at 225°), $[\alpha]^{20}D$ +83.7° (dioxane), ultraviolet maximum at 280 mμ (log *E* 3.29) and minimum at 248 mμ (log *E* 2.35).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.39. Found: C, 76.60; H, 8.59.

The 3-monoacetate XIb was obtained on heating the phenol XIa with acetic anhydride–pyridine for one hour on the steam-bath; m.p. 128–129°, $[\alpha]^{20}D$ +29.3, +73.3° (dioxane) after recrystallization from hexane-acetone. The infrared spectrum[9] showed the presence of a free hydroxyl group, phenolic acetate and non-conjugated 20-keto group (1709 $cm.^{-1}$).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.19; H, 7.94.

Tribromination of Progesterone (II).—An ice-cold suspension of 10 g. of progesterone in 350 cc. of ether was treated with 3 drops of hydrogen bromide–acetic acid solution followed by slow addition of a solution of 15.28 g. of bromine in 150 cc. of glacial acetic acid. At the end of the addition, all the solid had gone into solution and after an additional one-half hour 6.5 g. of colorless crystals with m.p. 173–175° (dec.) was collected. The filtrate was washed well with water, dried and concentrated whereupon a second crop (3.8 g.) of solid, m.p. 170–173° (dec.), was obtained, raising the yield to 59%. The analytical sample of 2,6,17-tribromoprogesterone (XIII) was obtained from methanol–chloroform with m.p. 174–176° (dec.), $[\alpha]^{20}D$ +2.3°, ultraviolet maximum at 250 mμ, log *E* 4.21.

Anal. Calcd. for $C_{21}H_{27}O_2Br_3$: C, 45.73; H, 4.93; Br, 43.52. Found: C, 45.93; H, 5.08; Br, 44.02.

1,4,6,16-Pregnatetraene-3,20-dione (XIV) (a) From Tribromoprogesterone (XIII).—Ten grams of the tribromo derivative XIII was refluxed with 40 cc. of collidine for 30 minutes resulting in the loss of three moles of hydrogen bromide (11.3 g. of collidine hydrobromide). After addition of ethyl acetate, the collidine was removed by washing with dilute acid and the product was isolated by evaporation, chromatographing on alumina and elution with benzene. Recrystallization from acetone or methanol afforded colorless plates (2.1 g., 37%) of the tetraene with m.p. 239–240°, $[\alpha]^{20}D$ +112°, ultraviolet maxima at 234 mμ (log *E* 4.34) and 298 mμ (log *E* 4.19).

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.77; H, 7.80.

(b) **From 16-Dehydroprogesterone (XV).**—16-Dehydroprogesterone (6.2 g.) was dibrominated exactly as described for the above tribromination, but since the product crystallized very poorly, the ether–acetic acid solution was washed very well with water, the ether evaporated and residue refluxed directly with collidine. Judging from the amount of collidine hydrobromide isolated (9.0 g.; calcd., 8.02 g.), a small amount of tribromo (2,6,15-?) derivative also was formed. The usual work-up gave 1.17–1.57 (19–25% over-all yield based on XV) of 1,4,6,16-pregnatetraene-3,20-dione (Found: C, 81.66; H, 7.50) with m.p. 238–240°, undepressed on admixture with a specimen prepared according to (a); the rotations and ultraviolet absorption spectra were identical.

Dienone–Phenol Rearrangement of 1,4,6,16-Pregnatetraene-3,20-dione (XIV).—A solution of 1.40 g. of the tetraenedione and 0.4 g. of *p*-toluenesulfonic acid in 50 cc. of acetic anhydride was heated on the steam-bath for 4.5 hours, then cooled and the anhydride hydrolyzed with water. The product was extracted with ether, washed free of acid, dried and evaporated. Crystallization was induced by trituration with ether–hexane; yield 0.81 g. (51%), m.p. 119–126°. Additional material was isolated from the mother liquors *via* the insoluble benzoate (*vide infra*). Repeated crystallization from ether–hexane and high-vacuum sublimation led to practically colorless crystals of **1-methyl-3-acetoxy-17-acetyl-1,3,5,16-estrapentaene (XVIb)** with m.p. 128–130°, $[\alpha]^{20}D$ −100°.

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48. Found: C, 78.81; H, 7.62.

The filtrate from the first crop of acetate was saponified by boiling for one hour with 350 mg. of sodium bicarbonate, 15 cc. of ethanol and 3.5 cc. of water and the resulting oil was benzoylated with pyridine–benzoyl chloride. Crystallization from methanol afforded an additional 0.26 g. (14%) of **1-methyl-3-benzoyloxy-17-acetyl-1,3,5,6,16-estrapentaene (XVIc)** with m.p. 200–203°. The analytical sample crystallized as needles with m.p. 210–212°, $[\alpha]^{20}D$ −101°.

Anal. Calcd. for $C_{28}H_{28}O_3$: C, 81.52; H, 6.84. Found: C, 81.55; H, 6.83.

1-Methyl-3-hydroxy-17-acetyl-1,3,5,6,16-estrapentaene (XIVa) was obtained by sodium bicarbonate saponification of the pure acetate and recrystallized from hexane–acetone; m.p. 187–188.5°, $[\alpha]^{20}D$ −101.4°, ultraviolet maxima at 228 mμ (log *E* 4.53), 266 mμ (log *E* 3.91), and 306 mμ (log *E* 3.25).[7,19]

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.94; H, 8.11.

1-Methyl-3-hydroxy-17-acetyl-1,3,5-estratriene (XVIIa).—A solution of 0.38 g. of the acetate XVIb in 20 cc. of ethyl acetate absorbed two moles of hydrogen in 45 minutes in the presence of 5% palladium-on-charcoal catalyst. Filtration of the catalyst, evaporation of the solvent to dryness and trituration of the residue with hexane gave 0.31 g. (81%) of **1-methyl-3-acetoxy-17-acetyl-1,3,5-estratriene (XVIIb)** with m.p. 128–130°. The analytical sample was once recrystallized and then sublimed in high vacuum, m.p. 129–131°, ultraviolet maximum at 268 mμ (log *E* 2.59) and minimum at 252 mμ (log *E* 2.42) typical of a phenolic acetate.

Anal. Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53; Found: C, 78.14; H, 8.75.

1-Methyl-3-benzoyloxy-17-acetyl-1,3,5-estratriene (XVIIc) was obtained in analogous fashion by hydrogenation of the benzoate XVIc and crystallized from ethyl acetate as colorless needles with m.p. 181.5–183°, $[\alpha]^{20}D$ +200°.

Anal. Calcd. for $C_{28}H_{32}O_3$: C, 80.73; H, 7.75. Found: C, 80.74; H, 7.96.

Saponification of the benzoate XVIIc with 2% methanolic potassium hydroxide solution followed by recrystallization from hexane–acetone produced **1-methyl-3-hydroxy-17-acetyl-1,3,5-estratriene (XVIIa)** with m.p. 250–251.5°, $[\alpha]^{20}D$ + 200° (dioxane), ultraviolet maximum at 284 mμ (log *E* 3.31) and minimum at 252 mμ (log *E* 2.49).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.60; H, 9.02.

LAGUNA MAYRÁN 413
MEXICO CITY, D. F.

RECEIVED OCTOBER 27, 1950