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

STEROIDAL SAPOGENINS. VIII.[1] STEROIDS. XVIII.[2] SYNTHESIS OF $\Delta^{7,9(11)}$-ALLOPREGNADIEN-3β-OL-20-ONE FROM DIOSGENIN AND FROM Δ^5-PREGNEN-3β-OL-20-ONE

CARL DJERASSI, J. ROMO, AND G. ROSENKRANZ

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As pointed out in an earlier communication (1), an attractive approach to the synthesis of C-11 oxygenated cortical hormones from steroids possessing *no substituents* in ring C (positions 11 and 12) appears to be by way of steroids with double bonds adjacent to or in ring C, and this was illustrated by the preparation of certain unsaturated key intermediates in the Δ^5-22-isospirosten-3β-ol[3] (diosgenin) series. The present paper deals with two synthetic approaches to similarly unsaturated derivatives in the pregnane series. In addition to providing valuable intermediates for the direct, chemical introduction of an oxygen function at C-11, these substances possess two other valuable features. Δ^5-Pregnen-3β-ol-20-one (Ia) is known to exhibit anti-arthritic properties (2) and the clinical evaluation of analogs with double bonds at or near position C-11 should prove to be of considerable interest. Furthermore, the biochemical introduction of a C-11 hydroxyl group (3) may well proceed *via* 9–11 dehydro steroids and the presently described pregnene derivatives are well-suited substrates for enzymatic and perfusion studies.

The first approach consisted of Wohl-Ziegler bromination (4) of Δ^5-pregnen-3β-ol-20-one acetate (Ib) or preferably the benzoate (Ic) exactly as described previously (5) in the diosgenin series. The resulting 7-bromo derivative II was dehydrobrominated with γ-collidine to yield a mixture of $\Delta^{5,7}$-pregnadien-3β-ol-20-one (III) and $\Delta^{4,6}$-pregnadien-3β-ol-20-one (IV). The former was separated in a pure state by crystallization of the free alcohol IIIa while the latter was isolated uncontaminated on chromatography of the mother liquors. The characteristic ultraviolet absorption spectra of the two new dienes IIIa and IV are shown in Figure 1 and are in excellent agreement with the values reported in the literature (5) for other steroids possessing the same chromophoric systems.[4] By analogy to earlier experiments in the diosgenin series (1), catalytic hydrogenation of the $\Delta^{5,7}$-diene III with platinum oxide in ethyl acetate solution led to the important Δ^7-allopregnen-3β-ol-20-one VI, which in turn on dehy-

[1] For paper VII see Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951).

[2] For paper XVII see Sandoval, Rosenkranz, and Djerassi, *J. Am. Chem. Soc.*, **73**, May (1951).

[3] For nomenclature of steroidal sapogenins see Rosenkranz and Djerassi, *Nature*, **166**, 104 (1950).

[4] Additional evidence in support of the structure assignments is provided by a calculation of the molecular rotation differences, which are in good agreement with the values reported by Barton, *J. Chem. Soc.*, 813 (1945); 512 (1946). It is interesting to note, however, that the Δ value (saturated minus unsaturated compound) of the Δ^7-allo derivative VI is not in agreement with the cited value for steroids possessing a hydrocarbon side chain (Barton, *loc. cit.*). It appears that in this type of compound acetyl or sapogenin side chains (ref. 1, footnote 3) exert a considerable vicinal effect.

drogenation at room temperature with mercuric acetate afforded the desired $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one (VII). Its ultraviolet absorption spectrum (Fig. 1) with maxima at 236 mμ and 242 mμ is consistent with that formulation (1). Similar dehydrogenation of the $\Delta^{5,7}$-dien III yielded a second pregnene derivative with a 9–11 double bond, $\Delta^{5,7,9(11)}$-pregnatrien-3β-ol-20-one (V), whose structure is further supported by the typical ultraviolet absorption spectrum (Fig. 1) and the large dextrorotatory shift in the molecular rotation (Δ^{Ac} +256) upon acetylation (1). Oppenauer oxidation of the $\Delta^{5,7}$-diene IIIa produced $\Delta^{4,7}$-pregnadiene-3,20-dione (7-dehydroprogesterone) (VIII), a valu-

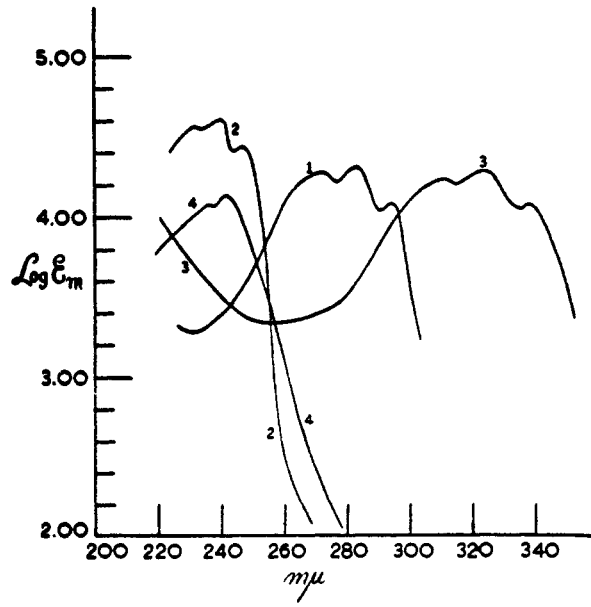
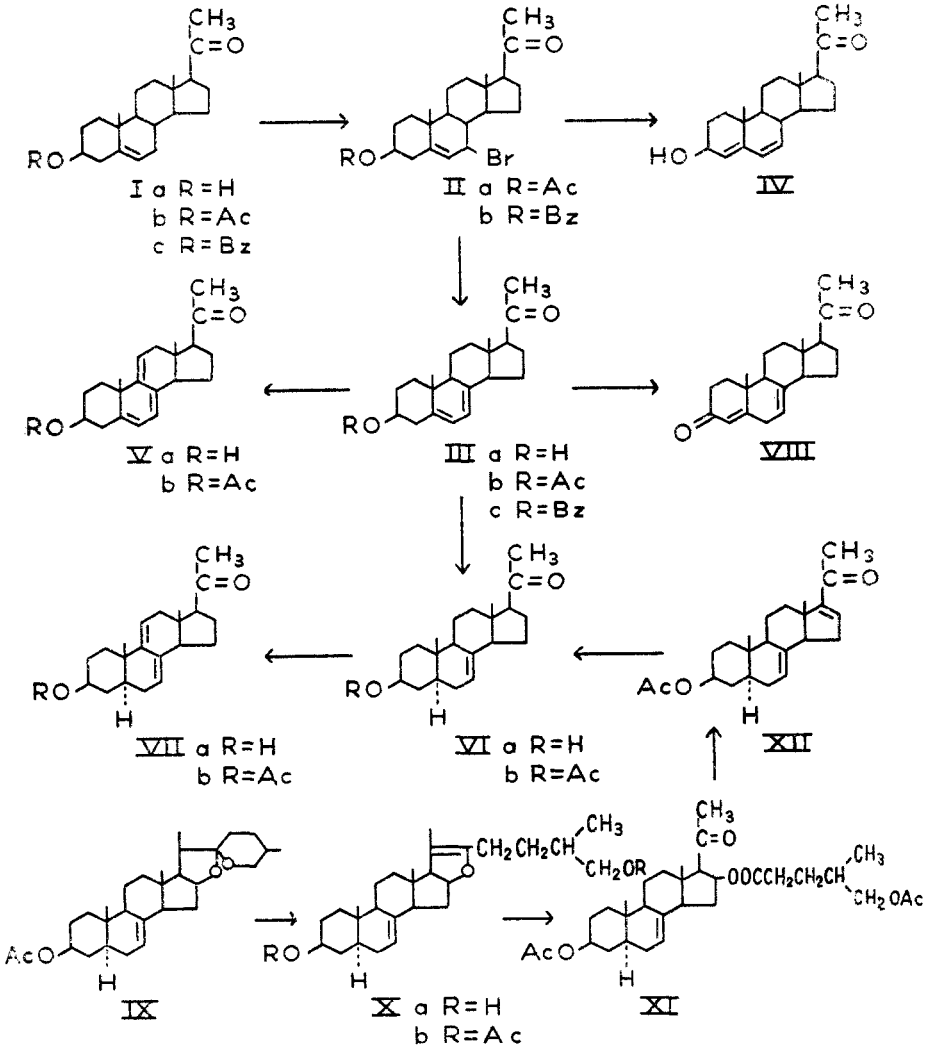


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA (IN 95% ETHANOL); 1. $\Delta^{5,7}$ -Pregnadien-3β-ol-20-one (IIIa); 2. $\Delta^{4,6}$-Pregnadien-3β-ol-20-one (IV); 3. $\Delta^{5,7,9(11)}$-Pregnatrien-3β-ol-20-one 3-acetate (Vb); 4. $\Delta^{7,9(11)}$-Allopregnadien-3β-ol-20-one (VIIa).

able intermediate for hydrogenation studies leading to Δ^{7}-unsaturated pregnene derivatives with the *normal* configuration at C-5. The migration of only one double bond during the Oppenauer oxidation is amply supported by similar examples from the literature (6).

The other approach to the synthesis of VI and VII employs Δ^{7}-22-isoallospirosten-3β-ol 3-acetate (IX) (1) and is preferable, both with respect to yield, availability of starting material and especially, applicability to large scale operations. Conversion to $\Delta^{7,20(22)}$-allofurostadiene-3β,26-diol diacetate (Xb) was accomplished readily by heating IX with acetic anhydride at 200° for eight hours. Although the free diol Xa could be isolated in the crystalline state, from a practical standpoint it was preferable to oxidize the oily diacetate Xb directly with chromium trioxide to yield the crystalline Δ^{7}-allopregnen-3β,16β-diol-20-one 3-acetate 16-γ-methyl-δ-acetoxyvalerate (XI). Brief saponification with

bicarbonate led to $\Delta^{7,16}$-pregnadien-3β-ol-20-one 3-acetate (XII) in over 40% over-all yield based on the spirosten IX. This $\Delta^{7,16}$-dien XII, a useful intermediate for the elaboration of the cortical dihydroxyacetone side chain was smoothly hydrogenated with palladium-on-charcoal in the presence of piperidine[5] to Δ^{7}-allopregnen-3β-ol-20-one (VI), identical in all respects with the product obtained by the first route from Δ^{5}-pregnen-3β-ol-20-one (I).



Further transformations of the presently described unsaturated pregnene derivatives will be reported in subsequent papers.

[5] Palladium catalysts generally cause the migration of a Δ^{7}-double bond to the $\Delta^{8(14)}$-position, but this can be inhibited readily by the addition of a small amount of a base such as piperidine or pyridine (*cf.* ref. 1).

EXPERIMENTAL[6]

7″β″-Bromo-Δ⁵-pregnen-3β-ol-20-one (II). A solution of 30 g. of Δ⁵-pregnen-3β-ol-20-one 3-benzoate (Ic) (7) in 400 cc. of dry carbon tetrachloride was refluxed for five to eight minutes with 13 g. of N-bromosuccinimide, using two photospot lamps (GE No. RSP2) as sources of heat and illumination. At the end of this time, the succinimide was filtered, the filtrate washed well with water, dried over sodium sulfate, and concentrated *in vacuo* until crystallization commenced. Filtration and concentration of the filtrate yielded two crops of equal purity totalling 19.4 g. (54%); m.p. 141–144° (dec.), $[\alpha]_D^{20}$ −134°. The substance was labile and decomposed on standing. For analysis, a sample of *7″β″-bromo-Δ⁵-pregnen-3β-ol-20-one 3-benzoate* (IIb) was stirred with ether, filtered, dried at room temperature under a high vacuum for two hours and analyzed immediately; m.p. 148–150° (dec.) on rapid heating, $[\alpha]_D^{20}$ −141°.

Anal. Calc'd for $C_{28}H_{35}BrO_3$: C, 67.33; H, 7.06.

Found: C, 66.91; H, 7.52.

From 10.7 g. of Δ⁵-pregnen-3β-ol-20-one 3-acetate (Ib) there was obtained in an analogous manner 3.61 g. (28%) of *7″ β″-bromo-Δ⁵-pregnen-3β-ol-20-one 3-acetate* (IIa), m.p. 137–140° (dec.), $[\alpha]_D^{20}$ −211°.

Anal. Calc'd for $C_{23}H_{33}BrO_3$: C, 63.15; H, 7.60.

Found: C, 62.90; H, 7.78.

Δ⁵,⁷-Pregnadien-3β-ol-20-one (III). A solution of 18 g. of the 7-bromo benzoate IIb in 72 cc. of γ-collidine and 720 cc. of dry xylene was refluxed for 1.5 hours, which resulted in the formation of 6.5 g. (89%) of collidine hydrobromide. After washing with dilute acid, dilute carbonate solution, and water, the solvent was removed by steam-distillation and the crude benzoate was filtered; yield, 13 g., m.p. 163–174°. Saponification was accomplished by boiling this material in a current of nitrogen for 2 hours with 16.5 g. of sodium hydroxide, 33 cc. of water, 225 cc. of dioxane, and 450 cc. of methanol. The usual work-up followed by recrystallization from methanol-chloroform or methanol-methylene chloride afforded 2.3 g. (20%) of *Δ⁵,⁷-pregnadien-3β-ol-20-one* (IIIa) of satisfactory purity for subsequent transformations; m.p. 195–205° (Kofler), $[\alpha]_D^{20}$ −65.5°, u.v. maxima at 240 mμ (log ε 3.68), 272 mμ (log ε 4.14), 282 mμ (log ε 4.17), and 292 mμ (log ε 3.95). Several recrystallizations yielded the analytical sample, m.p. 216–220° (Kofler), 232–234° (capillary with slight decomposition), $[\alpha]_D^{20}$ −66.8°, u.v. maxima (Fig. 1) at 272 mμ (log ε 4.28), 282 mμ (log ε 4.31), and 294 mμ (log ε 4.09).

Anal. Calc'd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62.

Found: C, 80.11; H, 9.68.

Four grams of the above alcohol IIIa upon heating with 15 cc. of pyridine and 15 cc. of acetic anhydride followed by recrystallization from methanol-chloroform gave 3.7 g. of *Δ⁵,⁷-pregnadien-3β-ol-20-one 3-acetate* (IIIb), m.p. 161–163°, $[\alpha]_D^{20}$ −28.7°. The analytical sample crystallized as glistening plates, m.p. 166–168° (Kofler), $[\alpha]_D^{20}$ −28.5°, u.v. maxima at 270 mμ (log ε 4.20), 282 mμ (log ε 4.23), and 294 mμ (log ε 3.99).

Anal. Calc'd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05.

Found: C, 77.47; H, 8.94.

The *benzoate* (IIIc) exhibited m.p. 226–229° (capillary), 213.5–215.5° (Kofler), $[\alpha]_D^{20}$ 0°, u.v. maxima at 230 mμ (log ε 4.22) (due to benzoyl group), 272 mμ (log ε 4.17), 282 mμ (log ε 4.20), and 294 mμ (log ε 3.96).

Anal. Calc'd for $C_{28}H_{34}O_3$: C, 80.34; H, 8.19.

Found: C, 80.17; H, 8.14.

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[6] Melting points are uncorrected unless marked "Kofler" or "capillary". All rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are indebted to Srta. Paquita Revaque for these measurements, and to Srta. Consuelo Amendolla for assistance with certain experiments described in this paper. The microanalyses were carried out in our Micronanalytical Department by the Srtas. Amparo Barba and Raquel Cervera.

$\Delta^{4,6}$-*Pregnadien-3β-ol-20-one* (IV). From the above mother liquors of the $\Delta^{5,7}$-dienolone IIIa there was obtained upon concentration and recrystallization from acetone 1.1 g. (10%) of crystals, m.p. 164–178° (Kofler), $[\alpha]_D^{20}$ + 56.1°, u.v. maxima at 232 mμ (log ε 4.43), 240 mμ (log ε 4.48), 248 mμ (log ε 4.29), 272 mμ (log ε 2.81), and 282 mμ (log ε 2.82). The small impurity of $\Delta^{5,7}$-isomer (maxima at 272 and 282 mμ) was removed on chromatography followed by recrystallization from acetone; shiny plates, m.p. 180–182° (Kofler), 191–193° (capillary), $[\alpha]_D^{20}$ +68.6°, u.v. maxima (Fig. 1) at 232 mμ (log ε 4.57), 240 mμ (log ε 4.60), and 248 mμ (log ε 4.42).

Anal. Calc'd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62.

Found: C, 80.35; H, 9.79.

$\Delta^{5,7,9,(11)}$-*Pregnatrien-3β-ol-20-one* (V). The dehydrogenation was carried out in the usual manner (1) with 3.7 g. of IIIb, 8.0 g. of C.P. mercuric acetate, 150 cc. of acetic acid, and 100 cc. of chloroform for 18 hours. Crystallization from methanol yielded 1.44 g. (39%) of $\Delta^{5,7,9,(11)}$-*pregnatrien-3β-ol-20-one 3-acetate* (Vb), m.p. 143–145° (Kofler), unchanged on further recrystallization; $[\alpha]_D^{20}$ +323.9°, u.v. maxima (Fig. 1) at 310 mμ (log ε 4.23), 324 mμ (log ε 4.27), and 338 mμ (log ε 4.07).

Anal. Calc'd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53.

Found: C, 77.57; H, 8.38.

$\Delta^{5,7,9,11}$ -*Pregnatrien-3β-ol-20-one* (Va), m.p. 201–203° (Kofler), $[\alpha]_D^{20}$ +284.5° was obtained on saponification of the above acetate and recrystallization from acetone.

Anal. Calc'd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03.

Found: C, 80.65; H, 9.14.

$\Delta^{4,7}$-*Pregnadiene-3,20-dione* (*7-dehydroprogesterone*) (VIII). A solution of 1.0 g. of $\Delta^{5,7}$-pregnadien-3β-ol-20-one (IIIa) in 170 cc. of toluene was dried by distilling 20 cc., and was then refluxed for three hours with 25 cc. of cyclohexanone and 2.0 g. of aluminum *tert*-butoxide. After addition of some ether, the solution was washed with water, Rochelle salt solution, and again water, steam-distilled, and the residue extracted with ether. Chromatography of the crude product on 25 g. of ethyl acetate-washed alumina and elution with hexane-benzene (1:1) afforded the desired ketone VIII in about 40% yield, m.p. 95–97°, $[\alpha]_D^{20}$ +173.8°, u.v. maximum at 238 mμ (log ε 4.29).

Anal. Calc'd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03.

Found: C, 80.46; H, 9.25.

$\Delta^{7,16}$-*Allopregnadien-3β-ol-20-one 3-acetate* (XII). A solution of 100 g. of Δ^{7}-22-isoallospirosten-3β-ol 3-acetate (IX) (1) in 500 cc. of acetic anhydride was heated in a stainless steel autoclave for eight hours at 196° and then poured into ice-cold water. After allowing the excess acetic anhydride to hydrolyze, the oily acetate Xb was extracted with ether, washed well with water and bicarbonate, dried, and evaporated. In one experiment, a small amount of the acetate was saponified by boiling with 5% methanolic potassium hydroxide solution and diluted with water. Filtration and several recrystallizations from hexane-acetone gave the analytical sample of $\Delta^{7,20(22)}$-*allofurostadiene-3β,26-diol* (Xa) with m.p. 175–177° (Kofler), $[\alpha]^{20}$ +36° (dioxane).

Anal. Calc'd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21.

Found: C, 78.12; H, 10.16.

The above oily diacetate Xb was dissolved in a mixture of 1.6 l. of acetic acid and 300 cc. of water, and treated with stirring at 15° over a period of one-half hour with a solution of 60 g. of chromium trioxide in 80 cc. of water and 800 cc. of acetic acid. After 2 hours at room temperature, water was added and the mixture was extracted with chloroform, washed with water and bicarbonate solution, dried, and evaporated. Crystallization from methanol yielded 35 g. (30%) of Δ^{7}-*allopregnen-3β,16β-diol-20-one 3-acetate 16-γ-methyl-δ-acetoxyvalerate* (XI), m.p. 104–107°. Further recrystallization from methanol raised the m.p. of the colorless crystals to 113.5–115.5° (Kofler), $[\alpha]_D^{20}$ 0°, u.v. maximum at 276 mμ (log ε 1.62).

Anal. Calc'd for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74.

Found: C, 70.11; H, 8.87.

The filtrate was evaporated to dryness and the residue was refluxed for 35 minutes with a solution of 80 g. of potassium bicarbonate in 180 cc. of water and 1.5 l. of methanol. Dilu-

tion with water, extraction with ether, reacetylation of the product with acetic anhydride in pyridine solution (1 hour, 100°) followed by crystallization from methanol gave 7.3 g. of $\Delta^{7,16}$-allopregnadien-3β-ol-20-one 3-acetate (XII), m.p. 136–139°. Chromatography of the mother liquors afforded an additional 8.5 g. of dienolone acetate (XII), m.p. 134–138°. Since similar saponification of the ester XI gives between 80–90% of dienolone XII, the total yield of XII is 44–47% based on the spirosten IX. The analytical sample was obtained by recrystallization from methanol as colorless crystals, m.p. 145–147° (Kofler), $[\alpha]_D^{20}$ +58°, u.v. maximum at 238 mμ (log ε 4.11).

Anal. Calc'd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05.

Found: C, 77.71; H, 8.79.

Δ^7-Allopregnen-3β-ol-20-one (VI). (*a*) *By hydrogenation of $\Delta^{7,16}$-allopregnadien-3β-ol-20-one 3-acetate* (XII). A solution of 12.5 g. of $\Delta^{7,16}$-dienolone acetate (XII) in 150 cc. of ethyl acetate containing 0.6 cc. of piperidine[5] was shaken with 1.5 g. of prereduced 10% palladium-on-charcoal catalyst in an atmosphere of hydrogen for 30 to 40 minutes, which resulted in an uptake of one mole of gas. Filtration of the catalyst, evaporation of the solvent to dryness, and recrystallization from acetone yielded 10 g. (80%) of *Δ^7-allopregnen-3β-ol-20-one 3-acetate* (VIb), m.p. 170–172°. Further recrystallization gave glistening blades, m.p. 174–176° (capillary), 170–172° (Kofler), $[\alpha]_D^{20}$ +39°, u.v. maximum at 284 mμ (log ε 1.69).

Anal. Calc'd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56.

Found: C, 77.07; H, 9.52.

Saponification with methanolic potassium hydroxide followed by recrystallization from acetone and from methanol produced *Δ^7-allopregnen-3β-ol-20-one* (VIa), m.p. 213–215° (capillary), 206–208° (Kofler), $[\alpha]_D^{20}$ +41°, u.v. maximum at 282 mμ (log ε 1.78).

Anal. Calc'd for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19.

Found: C, 80.00; H, 10.30.

(*b*) *By hydrogenation of $\Delta^{5,7}$-pregnadien-3β-ol-20-one 3-acetate* (IIIa) A solution of 2.0 g. of $\Delta^{5,7}$-dienolone acetate IIIa in 200 cc. of ethyl acetate was shaken in an atmosphere of hydrogen with 200 mg. of prereduced platinum oxide for three hours, at which time the hydrogen uptake corresponded to slightly more than one mole. After filtering the catalyst and evaporating to dryness, two recrystallizations from acetone afforded 0.4 g. (20%) of Δ^7-allopregnen-3β-ol-20-one 3-acetate (VIb), m.p. 171–173°, undepressed on admixture with a specimen prepared according to (a), $[\alpha]_D^{20}$ +40°, u.v. maximum at 284 mμ (log ε 1.72). The combined mother liquors were evaporated to dryness and subjected to a Girard separation, which produced almost exclusively ketonic material; upon recrystallization of this fraction, an additional 1.03 g. (50%) of VIb, m.p. 165–169° was isolated.

$\Delta^{7,9(11)}$-Allopregnadien-3β-ol-20-one (VII). The mercuric acetate treatment of VIb was carried out exactly as described for the diene IIIb above and led in 58% yield to *$\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one 3-acetate* (VIIb), which after recrystallization from methanol exhibited m.p. 139–141° (Kofler), $[\alpha]_D^{20}$ +78.9°, u.v. maxima at 236 mμ (log ε 4.00) and 242 mμ (log ε 4.03).

Anal. Calc'd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05.

Found: C, 77.52; H, 9.35.

$\Delta^{7,9(11)}$-Allopregnadien-3β-ol-20-one (VIIa), obtained on saponification of the above acetate, crystallized from acetone as brilliant prisms, m.p. 201–203° (Kofler), $[\alpha]_D^{20}$ +74.1°, u.v. maxima (Fig. 1) at 236 mμ (log ε 4.08) and 242 mμ (log ε 4.13).

Anal. Calc'd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62.

Found: C, 80.21; H, 9.90.

SUMMARY

The preparation of certain unsaturated pregnene derivatives, important for clinical work as anti-arthritic agents as well as representing key intermediates for the chemical and biochemical introduction of an oxygen function at C-11, is described.

The first synthesis consisted of Wohl-Ziegler bromination of Δ^5-pregnen-3β-

ol-20-one 3-benzoate (Ic) followed by collidine dehydrobromination of the intermediate 7-bromo derivative, yielding $\Delta^{5,7}$-pregnadien-3β-ol-20-one (III). This substance was converted by mercuric acetate dehydrogenation to $\Delta^{5,7,9(11)}$-pregnatrien-3β-ol-20-one (V), by Oppenauer oxidation to 7-dehydroprogesterone (VIII), and by catalytic hydrogenation to Δ^{7}-allopregnen-3β-ol-20-one (VI). An alternate synthesis of the latter was achieved by side chain degradation of Δ^{7}-22-isoallospirosten-3β-ol (IX) *via* the furostadien X and ester XI to $\Delta^{7,16}$-allopregnadien-3β-ol-20-one (XII) followed by hydrogenation of the 16,17-double bond. Mercuric acetate dehydrogenation produced $\Delta^{7,9(11)}$-allopregnadien-3β-ol-20-one (VII). It has thus been possible to introduce a double bond into the important 9–11 position of pregnane derivatives starting from ring-C unsubstituted steroids.

LAGUNA MAYRAN 413
MEXICO CITY 17, D.F.

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