[Contribution from the Lederle Laboratories Division, American Cyanamid Company]

$\Delta^{5,7}$-STEROIDS. XIII. STEROIDAL CYCLIC KETALS. II[1,2] THE PREPARATION OF $\Delta^{4,7}$-PREGNADIENE-3,20-DIONE AND $\Delta^{4,7}$-PREGNADIENE-21-OL-3,20-DIONE-ACETATE

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The preparation of $\Delta^{4,7}$-pregnadiene-3,20-dione (IV) by means of an Oppenauer oxidation of $\Delta^{5,7}$-pregnadiene-3β-ol-20-one was described in a previous publication (1). The physical constants obtained were in disagreement with those reported by Djerassi, Romo, and Rosenkranz (2) for this compound which they prepared in an identical manner. In this paper, we wish to present an alternate method for the preparation of $\Delta^{4,7}$-pregnadiene-3,20-dione (IV) in order to resolve the discrepancy in the characterization of this compound.

Progesterone (I) was reacted with ethylene glycol in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid to give the Δ^{5}-3,20-di-ethylene-ketal (II) in 32% yield. Use of toluene as the solvent raised the yield of II to 67%; whereas xylene afforded only a 39% yield. The coincident rearrangement of the double bond to the C-5,6 position during ketal formation has been previously discussed.[1] The Δ^{5}-steroid so obtained was subjected to allylic bromination with NBS[4] and the bromo compound (not isolated) was dehydrobrominated with *s*-collidine in xylene to afford $\Delta^{5,7}$-pregnadiene-3,20-dione-di-ethylene ketal (III). Consistently higher yields were obtained in this reaction by the use of the 3-ethylene ketal derivative than have been obtained with Δ^{5}-pregnene-3β-ol-20-one-acetate (3). It was also noted, from an examination of the ultraviolet absorption spectrum, that in the case of the ethylene ketal derivative no $\Delta^{4,6}$-isomer was apparently obtained.[5] Acid hydrolysis converted compound III to the desired $\Delta^{4,7}$-pregnadiene-3,20-dione (IV). This hydrolysis may be carried out with dilute sulfuric acid in alcohol, or with aqueous acetic acid. The physical constants of IV, so obtained, were in excellent agreement with those previously reported by this Laboratory (1). In Table I, there are listed the physical constants of the samples of $\Delta^{4,7}$-pregnadiene-3,20-dione (IV) obtained by the two cited methods along with the results of the Syntex group. The discrepancy in the melting point with our material has been ascribed by the Syntex group to polymorphism, which may or may not be pertinent. Opinion must be reserved on

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[1] Paper XII, Antonucci, Bernstein, Littell, Sax, and Williams, *J. Org. Chem.*, **17**, this issue (1952).

[2] Presented in part before the Organic Group at the Fourth Annual Meeting of the New York Section, American Chemical Society, New York, N. Y., February 8, 1952.

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[4] NBS = N-bromosuccinimide.

[5] A more detailed discussion of the preparation of $\Delta^{5,7}$-from Δ^{5}-ketals will be forthcoming.

this explanation as these investigators have neglected to state the solvent or solvents used for the recrystallization of the compound. Moreover, one may question the purity of the Syntex material solely on the basis of ultraviolet absorption analysis. The recorded molecular extinction coefficient of 19,000 is unusually high for a $\Delta^{4,7}$-3-ketosteroid (1). We, therefore, believe that the properties of $\Delta^{4,7}$-pregnadiene-3,20-dione (IV) as described by us are correct. To further corroborate this conclusion, an infrared spectrum analysis showed that the samples of IV obtained by the two methods were identical (see Figure 1).

TABLE I

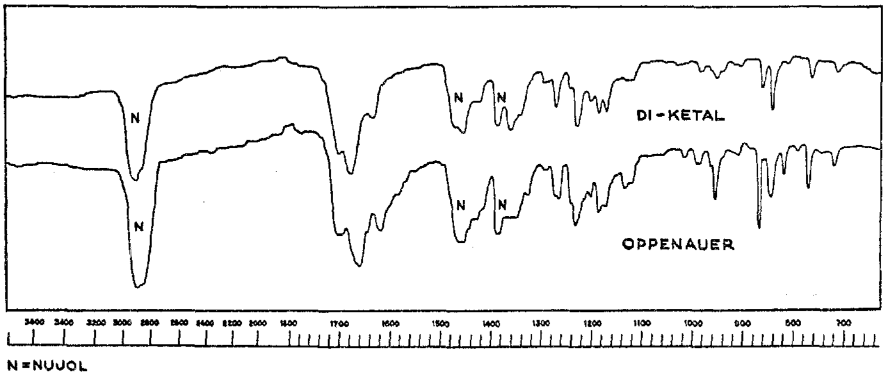
PHYSICAL CONSTANTS OF $\Delta^{4,7}$-PREGNADIENE-3,20-DIONE

SOURCE	M.P., °C.	λ_{max} (mμ)	ϵ	$[\alpha]_D^0$(CHCl$_3$)	$[\alpha]_{Hg}^0$ (CHCl$_3$)
Lederle (Oppenauer)	119–121	237.5–238.5 (abs. alc.)	14,100	+96.9	+120
Lederle (Ketal)	119–120.5	237–238.5 (abs. alc.)	14,800	+98.2	+125
Syntex (Oppenauer)	106–108	238 (alc.)	19,000	+102	—

FIG. 1

INFRARED SPECTRUM

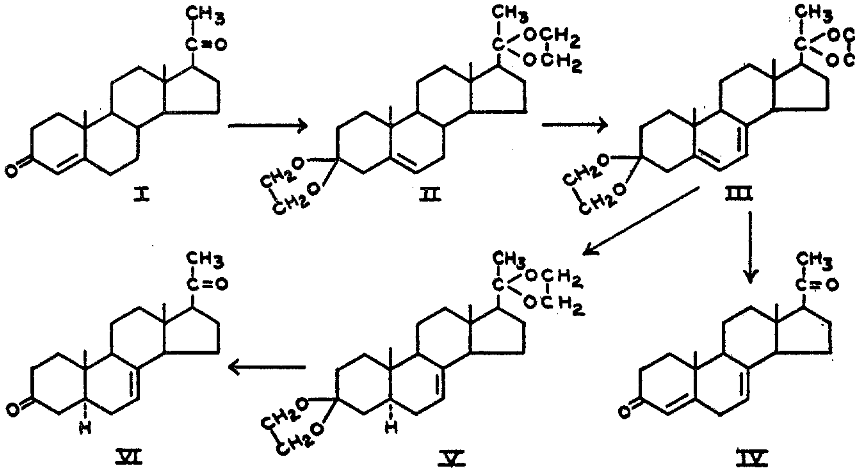
$\Delta^{4,7}$-PREGNADIENE-3,20-DIONE



In a previous publication (3), the conversion of a $\Delta^{5,7}$- to a Δ^{7}-ketal by hydrogenation with a Raney nickel catalyst was reported. In a similar manner, $\Delta^{5,7}$-pregnadiene-3,20-dione-di-ethylene ketal (III) yielded Δ^{7}-allopregnene-3,20-dione-di-ethylene ketal (V) in 80% yield. The reaction was also carried out with sodium and absolute alcohol. The products were identical. Hydrolysis of V with dilute acid (sulfuric acid or hydrochloric acid) gave Δ^{7}-allopregnene-3,20-dione (VI).

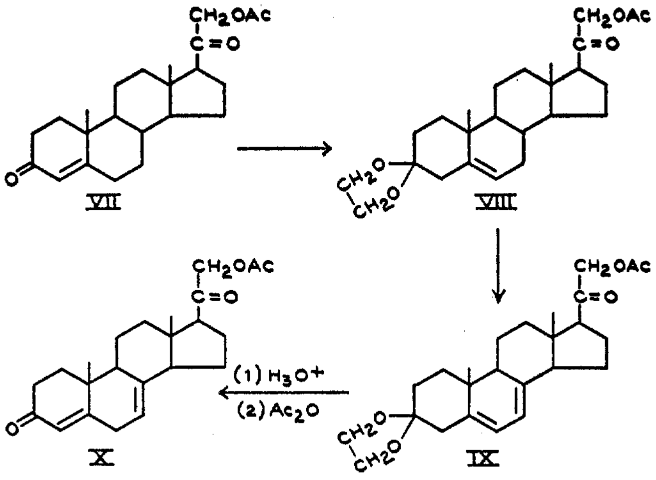
We have also extended the ethylene ketal and NBS reactions to desoxycorticosterone acetate (VII). The latter was treated with ethylene glycol, and the monoketal (VIII) was obtained. The structure of this compound was based on its ultraviolet absorption spectrum (no maxima) and elemental analysis. The non-reactivity of the C-20 ketone group in this reaction may be ascribed to the steric effects of the neighboring 21-acetoxy group.[6]

FLOWSHEET I



Compound VIII was readily converted into the $\Delta^{5,7}$-pregnadiene-21-ol-3,20-dione-21-acetate-3-ethylene ketal (IX), which on acid hydrolysis followed by acetylation, gave $\Delta^{4,7}$-pregnadiene-21-ol-3,20-dione-21-acetate (X), identical in all respects with the material previously prepared by Oppenauer oxidation of $\Delta^{5,7}$-pregnadiene-3β-21-diol-20-one-21-acetate (1).

FLOWSHEET II



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[6] The steric effect of the 21-acetoxy group on condensation reactions involving the C-20 carbonyl group has been previously noted; see Mancera, *J. Am. Chem. Soc.*, **72**, 5752 (1950); and Wendler, Huang-Minlon, and Tishler, *J. Am. Chem. Soc.*, **73**, 3818 (1951).

The utility of the above ketals as intermediates for the synthesis of corticoid hormones is being investigated.

EXPERIMENTAL

Absorption spectra. All spectra were determined with a Beckman quartz spectrophotometer (Model DU, mfg'd by the National Technical Laboratories, South Pasadena, California), and were determined in absolute alcohol.

Melting points. All m.p.'s are uncorrected, and were determined with uncalibrated Anschütz thermometers. Many of the m.p.'s were dependent on the rate of heating and on the temperature of the bath at which the sample was inserted.

Optical rotations. The sample was dissolved in chloroform to make a 2-ml. solution, and the rotation was determined in a 1-dm. semi-micro tube. The rotation, generally, was determined for two wavelengths, 5893 Å (D) and 5461 Å (Hg).

Petroleum ether. The petroleum ether fraction used had b.p. 64–66° and was purified with conc'd sulfuric acid and potassium permanganate.

Δ^5-Pregnene-3,20-dione-di-ethylene ketal (II). *A.* A mixture of 10 g. of progesterone (I), 80 ml. of freshly distilled ethylene glycol, 350 ml. of benzene, and 300 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the same manner as described in a previous publication in this series (3) (reflux 5 hours). Two recrystallizations of the crude product from acetone-methanol gave 4.15 g.; m.p. 178–181°. Yield, 32%. An aliquot was recrystallized three times more from acetone-methanol; m.p. 181–182°; λ_{max} none; infrared analysis (Nujol): no ketone present; $[\alpha]_D^{31}$ $-28.9°$, $[\alpha]_{Hg}^{31}$ $-31.3°$ (16.6 mg., α_D $-0.24°$, α_{Hg} $-0.26°$) α_{Hg}/α_D 1.08; $[M]_D$ $-116°$.

Anal. Calc'd for $C_{25}H_{38}O_4$ (402.55): C, 74.59; H, 9.51.
Found: C, 74.64; H, 9.71.

B. In another run which was carried out as above (*A*) with 2 g. of progesterone, 16 ml. of ethylene glycol, 65 mg. of *p*-toluenesulfonic acid monohydrate, and 70 ml. of toluene (reflux 4 hours), 1.34 g. of II was obtained; m.p. 178–182°. Yield, 67%.

C. A third run was carried out with 2 g. of progesterone, 20 ml. of ethylene glycol, 65 mg. of *p*-toluenesulfonic acid monohydrate, and 70 ml. of xylene (reflux 2½ hours). Codistillation was extensive and it was necessary to add 20 ml. additional ethylene glycol during the reflux period. Recrystallization of the crude product from acetone-methanol gave 1.02 g.; m.p. 179–181°. Yield, 39%.

$\Delta^{5,7}$-Pregnadiene-3,20-dione-di-ethylene ketal (III). Δ^5-Pregnene-3,20-dione-di-ethylene ketal (II) (1.0 g.) in 17 ml. of carbon tetrachloride and 6 ml. of petroleum ether was brominated with 0.53 g. of NBS in the usual manner of this laboratory as described previously (3). Addition of 0.35 ml. of *s*-collidine to the refluxing mixture, evaporation, and dehydrobromination carried out in 25 ml. of xylene containing 0.12 ml. of *s*-collidine gave 0.53 g. of crude material. Two recrystallizations from acetone-methanol gave 0.39 g.; m.p. 186.5–188.5°; λ_{max} 271, 282, 294 mμ; ϵ10,800; 11,300; 6,500 respectively; $[\alpha]_D^{23}$ $-11.6°$, $[\alpha]_{Hg}^{28}$ $-20.6°$ (15.5 mg., α_D $-0.09°$, α_{Hg} $-0.16°$) α_{Hg}/α_D 1.77; $[M]_D$ $-46°$. Yield, 39%.

Anal. Calc'd for $C_{25}H_{36}O_4$ (400.54): C, 74.96; H, 9.06.
Found: C, 75.24; H, 9.24.

Concentration of the original mother liquor gave 0.11 g.; m.p. 153–155°; λ_{max} 240–242, 271–272, 282, 293–294 mμ; inflection 250–256 mμ; ϵ2,480; 5,000; 5,200; 3,200; 2,800 respectively (mixture of $\Delta^{4,7}$-3-ketone and $\Delta^{5,7}$-3-ketal?). The mother liquor of this fraction gave a syrup; λ_{max} 282–283 mμ ($\Delta^{4,6}$-3-ketone?).

$\Delta^{4,7}$-Pregnadiene-3,20-dione (IV). *A.* A solution of 220 mg. of $\Delta^{5,7}$-pregnadiene-3,20-dione-di-ethylene ketal (III) in 40 ml. of alcohol was treated with 4 ml. of dilute sulfuric acid (8.5%, v/v) and refluxed for 1 hour. The mixture was added to ice-water; the crystals were collected, dissolved in acetone, heated with Norit, and filtered. Addition of water to the filtrate gave 130 mg. of yellow crystals. A single recrystallization from dilute acetone, and two from acetone-petroleum ether gave 50 mg.; m.p. 119–120.5°; λ_{max} 237–238.5 mμ,

ϵ14,800; $[\alpha]_D^{30}$ +98.2°, $[\alpha]_{Hg}^{30}$ +125.3° (14.05 mg., α_D +0.69°, α_{Hg} +0.88°) α_{Hg}/α_D 1.27; $[M]_D$ +307°.

B. Acetic acid (50%) (5 ml.) was added to 300 mg. of $\Delta^{5,7}$-pregnadiene-3,20-dione-di-ethylene ketal (III); an additional 0.7 ml. of glacial acetic acid was added in order to obtain complete solution (hot) of the steroid. The mixture was heated on a steam-bath for ½ hour, water was added, and the product was collected. Recrystallization from aqueous acetone gave 140 mg.; m.p. 120–120.5°; λ_{max} 237 mμ, ϵ15,700. From the mother liquor an additional 40 mg. was obtained; m.p. 118–119°. Yield, 78%.

Δ^7-*Allopregnene-3,20-dione-di-ethylene ketal* (V). *A*. Sodium (45 g.) was added piecemeal to 0.97 g. of $\Delta^{5,7}$-pregnadiene-3,20-dione-di-ethylene ketal (III) in 800 ml. of ethanol over 5–6 hours. When all of the sodium was consumed, the solution was added to a large quantity of ice and water, and the product was extracted with ether. The extract was washed with water, dried, and concentrated with simultaneous addition of methanol. This gave crystals which were crystallized several times, 60 mg.; m.p. 192–194.5°; ϵ_{281} 710. From the mother liquor 30 mg. was obtained; m.p. 157–180°; ϵ_{282} 790.

The two fractions and mother liquors were combined and evaporated. To the 310 mg. of residue so obtained was added 50 ml. of acetone and a few crystals of potassium permanganate. Refluxing for ½ hour, addition of water, extraction with ether, and evaporation of the extract gave 250 mg.; ϵ_{281} 550. The procedure was repeated and the solution was allowed to stand overnight. This gave 210 mg.; ϵ_{281} 710. Four recrystallizations from acetone-methanol gave 18 mg.; m.p. 192–194.5°; λ_{max} none; $[\alpha]_D^{30}$ ±0 (11.0 mg., α_D −0.02°).

Anal. Calc'd for $C_{25}H_{38}O_4$ (402.55): C, 74.59; H, 9.51.

Found: C, 74.38; H, 9.77.

B. To a solution of $\Delta^{5,7}$-pregnadiene-3,20-dione-di-ethylene ketal (III) (1.0 g.) in 150 ml. of ether was added 50 ml. of alcohol and 0.85 g. of Raney nickel catalyst (W-2), and the mixture was shaken in a hydrogen atmosphere at room-temperature and atmospheric pressure for 2½ hours. Filtration and evaporation gave a crystalline residue which on recrystallization from acetone (containing a trace of pyridine) gave 0.80 g.; m.p. 193–195°; λ_{max} none; $[\alpha]_D^{30}$ ±0° (20.5 mg., α_D +0.01°).

Anal. Found: C, 74.40; H, 9.67.

Δ^7-*Allopregnene-3,20-dione* (VI). *A*. A solution of 0.11 g. of Δ^7-allopregnene-3,20-dione-di-ethylene ketal (V) in 50 ml. of alcohol was treated with 5 ml. of 10% sulfuric acid which was added in 1-ml. portions over a 15 minute interval. The solution was refluxed for 1¼ hours, diluted with water, and the crystals were collected. One recrystallization from acetone-methanol, followed by one recrystallization from methanol gave 50 mg.; m.p. 187.5–194.5°. Yield, 58%.

B. To 200 mg. of Δ^7-allopregnene-3,20-dione-di-ethylene ketal (V) in 35 ml. of ether and 3 ml. of methanol was added 1 ml. of concentrated hydrochloric acid. The mixture was shaken at room-temperature for 20 hours, neutralized with sodium bicarbonate solution, and extracted with ether. The extract was washed with water, dried, and filtered. Evaporation of the filtrate and crystallization of the residue from acetone-petroleum ether gave 83 mg.; m.p. 180–183°. Recrystallization from methanol and dilute acetone gave 30 mg.; m.p. 188.5–193°; $[\alpha]_D^{30}$ +66.6°, $[\alpha]_{Hg}$ +68.3° (12 mg., α_D +0.40°) α_{Hg}/α_D 1.02; $[M]_D$ +209°.

Anal. Calc'd for $C_{21}H_{30}O_2$ (314.45): C, 80.21; H, 9.62.

Found: C, 79.92; H, 9.57.

Δ^5-*Pregnene-21-ol-3,20-dione-21-acetate-3-ethylene ketal* (VIII). A mixture of 1 g. of Δ^4-pregnene-21-ol-3,20-dione-acetate (desoxycorticosterone acetate) (VII), 8 ml. of ethylene glycol, 35 ml. of benzene, and 30 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described. Two recrystallizations of the crude product from acetone gave 0.40 g.; m.p. 206–208°. Further recrystallizations did not alter the m.p. $[\alpha]_D^{29}$ +42.5°, $[\alpha]_{Hg}^{29}$ +56.4° (23.05 mg., α_D +0.49°, α_{Hg} +0.65°) α_{Hg}/α_D 1.33; $[M]_D$ +177°. Yield, 36%.

Anal. Calc'd for $C_{25}H_{36}O_5$ (416.54): C, 72.08; H, 8.71.

Found: C, 72.01; H, 8.63.

$\Delta^{5,7}$-*Pregnadiene-21-ol-3,20-dione-21-acetate-3-ethylene ketal* (IX). The bromination and dehydrobromination of 2.0 g. of Δ^5-pregnene-21-ol-3,20-dione-21-acetate-3-ethylene ketal (VIII) was carried out in the manner described with 1.03 g. of NBS, 35 ml. of carbon tetrachloride, and 13 ml. of petroleum ether for the bromination, and 0.31 ml. of *s*-collidine in 50 ml. of xylene for the dehydrobromination. Evaporation of the xylene, and addition of acetone gave 0.92 g.; m.p. 209–216°; λ_{max} 240–241, 272, 282, 294 mμ; ϵ3,160; 9,700; 10,500; 6,250, respectively. Recrystallization from acetone-methanol-carbon tetrachloride, and acetone gave 0.30 g.; m.p. 218.5–222.5°; λ_{max} 272, 282, 294 mμ; ϵ11,700; 12,600; 7,500, respectively; $[\alpha]_{\mathrm{D}}^{29}$ +56.2°, $[\alpha]_{\mathrm{Hg}}^{29}$ +65.9° (18.5 mg., α_{D} +0.53°, α_{Hg} +0.61°) $\alpha_{\mathrm{Hg}}/\alpha_{\mathrm{D}}$ 1.15; $[\mathrm{M}]_{\mathrm{D}}$ +233°. Yield, 15%.

Anal. Calc'd for $C_{25}H_{34}O_5$ (414.52): C, 72.43; H, 8.27.
Found: C, 72.33; H, 8.44.

$\Delta^{4,7}$-*Pregnadiene-21-ol-3,20-dione-acetate* (X). $\Delta^{5,7}$-Pregnadiene-21-ol-3,20-dione-21-acetate-3-ethylene ketal (IX) (89 mg.) in 16 ml. of alcohol was treated with 2.0 ml. of dilute sulfuric acid (8.5%, v/v) and the mixture was refluxed for ½ hour. After neutralization with sodium bicarbonate solution, it was evaporated *in vacuo*. Water was added and the product was extracted with benzene and ethyl acetate. The extract was washed with water, dried, filtered, and the filtrate was evaporated *in vacuo*. The residue was acetylated at room-temperature with 3 ml. of pyridine and 0.3 ml. of acetic anhydride. The mixture was allowed to stand overnight. Addition of water gave crystals; wt. 70 mg.; m.p. 138.5–142°. Several recrystallizations from dilute methanol, and dilute acetone gave white needles, m.p. 147–147.5°; λ_{max} 237–238 mμ, ϵ13,800; $[\alpha]_{\mathrm{D}}^{30}$ +94.5°, $[\alpha]_{\mathrm{Hg}}^{30}$ +123° (5.5 mg., α_{D} +0.26°, α_{Hg} +0.34°) $\alpha_{\mathrm{Hg}}/\alpha_{\mathrm{D}}$ 1.31. $[\mathrm{M}]_{\mathrm{D}}$ +350°.

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SUMMARY

1. A new synthetic route for the conversion of progesterone and desoxycorticosterone acetate to $\Delta^{4,7}$-pregnadiene-3,20-dione and $\Delta^{4,7}$-pregnadiene-21-ol-3,20-dione-acetate, respectively, has been described.

2. The following new compounds have been prepared and characterized: Δ^5-pregnene-3,20-dione-di-ethylene ketal, $\Delta^{5,7}$-pregnadiene-3,20-dione-di-ethylene ketal, Δ^7-allopregnene-3,20-dione-di-ethylene ketal, Δ^7-allopregnene-3,20-dione, Δ^5-pregnene-21-ol-3,20-dione-21-acetate-3-ethylene ketal, and $\Delta^{5,7}$-pregnadiene-21-ol-3,20-dione-21-acetate-3-ethylene ketal.

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